Withdrawal Assessment Report

FLUAD PAEDIATRIC

Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1

Prodedure No. **EMEA/H/C/002299**

Day 180 Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

An agency of the European Union

TABLE OF CONTENTS

1. RECOMMENDATION 4

2. EXECUTIVE SUMMARY 4

2.1. Problem statement 4
2.2. About the product 5
2.3. The development programme/Compliance with CHMP guidance/Scientific advice 5
2.4. General comments on compliance with GMP, GLP, GCP 8
2.5. Type of application and other comments on the submitted dossier 18

3. SCIENTIFIC OVERVIEW AND DISCUSSION 20

3.1. Quality aspects 20
3.2. Non clinical aspects 27
3.3. Clinical aspects 37

4. ORPHAN MEDICINAL PRODUCTS 120

5. BENEFIT RISK ASSESSMENT 121

5.1. Conclusions 128

LIST OF ABBREVIATIONS

CHMP	Committee for Human Medicinal Product
CBER	Center for Biologics Evaluation and Research
HI	Haemagglutination Inhibition
SRH	Single Radial Hemolysis
RR	Relative Risk
VE	Vaccine Efficacy
AE	Adverse Event
BMI	Body Mass Index (calculated)
CI	Confidence Interval
CSR	Clinical Study Report
HA	Hemagglutinin
ICH	International Conference on Harmonisation
IM	Intramuscular
ISS	Integrated Safety Summary
MedDRA	Medicinal Dictionary for Regulatory Affairs
MPH	Monovalent Pooled Harvest
NA	Not applicable
NS	Not solicited
PO	per os (oral)
PT	Preferred Term
RMP	Risk Management Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
WHO	World Health Organization

1. RECOMMENDATION

Based on the review of the data and the Applicant response to the CHMP Day 180 LoQs on quality, safety and efficacy, the CHMP considers that the application for Fluad paediatric, for active immunization against influenza in infants and children (6 months to less than 9 years of age), is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Questions to be posed to additional experts

NA

Inspection issues

A GCP inspection was carried out at the request of the CHMP to verify the conduct of the clinical pivotal Phase III trial on efficacy and safety study in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC. Results of the inspection revealed three critical findings and several major findings the details of which are summarised in section 2.4 of this assessment report.

2. EXECUTIVE SUMMARY

2.1. Problem statement

The influenza virus is a globally important infectious agent. Among high-risk groups (the very young, elderly or chronically ill), influenza illnesses may result in hospitalizations and deaths. Annual seasonal influenza epidemics result in about 3 to 5 million cases of severe illness and about 250000 to 500000 deaths worldwide. In industrialized countries, the majority of deaths associated with influenza occur among people age 65 or older (WHO 2005).

Influenza A and B are the two types of influenza viruses that cause epidemic human disease, with A influenza strains, especially A/H3N2, being predominant in non-elderly and elderly adults while the B influenza viruses are more epidemiologically relevant in children.

In an average year, 20% of children will be infected with influenza virus; this attack rate may be substantially higher during certain epidemic years and among certain populations, such as children in day care. In children aged <2 years, influenza may lead to hospitalizations for lower respiratory tract disease, nonspecific febrile illness, or central nervous system complications. Furthermore, young children shed larger quantities of influenza virus for longer periods of time than do older children and adults, and this may contribute to the spread of influenza within a community or household.

All the available literature results indicating that antibody responses are substantially higher when young children are given 2 doses, are the basis for the recommendation that all children aged 6 months to <9 years who are being vaccinated for the first time should receive 2 vaccine doses separated by ≥4 weeks.

Although conventional vaccines have a long track record of use in children, they do not appear to induce satisfactory protective antibodies in unprimed children, especially the very young ones. This trend is particularly evident for the B influenza strain, where conventional non-adjuvanted vaccines generally show lower immunogenicity for A influenza antigens. Moreover, influenza B frequently occurs

in late-season spring outbreaks, so a greater persistence of HI antibodies and the maintenance of vaccine efficacy through the end of the influenza season is needed.

The use of an adjuvanted vaccine may cover this relevant medical need as adjuvants have been used to increase the immunogenicity of vaccines especially those containing purified antigens (e.g., subunit).

2.2. About the product

Fluad paediatric is a trivalent influenza-virus vaccine, presented as suspension for injection in prefilled syringe, containing the surface antigens of influenza viruses type A (Taiwan H1/N1, Beijing H3/N2) and B, adjuvanted with MF59C.1. Its Anatomical Therapeutic Classification (ATC) is J07BB.

Fluad paediatric contains purified haemagglutinin (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 WHO and CHMP for the Northern 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 potency of the vaccine is expressed as the amount of the HA protein per dose.

The presence of the MF59C.1 adjuvant increases the immune response to vaccination with the influenza antigens.

The vaccine was developed in late 90's and since the year 2000 is used in many EU countries following a Mutual Recognition Procedure with Italy as reference member state. So far, the use of the adjuvanted seasonal vaccine has been limited in EU to elderly population.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

No formal scientific advice was given by the CHMP or by any Member State for this medicinal product.

All relevant CHMP guidelines have been followed.

According to the CHMP Note for Guidance on the Harmonization of Requirements for Influenza Vaccines, CPMP/BWP/214/96 and in compliance with the European Pharmacopoeia requirement (European Pharmacopoeia Commission, 1999), one dose (0.5mL) of Fluad paediatric contained 15 µg haemagglutinin (HA) for each of the strains: A/H1N1, A/H3N2, and B, as recommended annually by WHO (http://www.who.int/wer/en/) and CHMP.

The use of adjuvanted influenza vaccine has been promoted in response to the threat of pandemic and a vaccine using the same type and amount of adjuvant (Focetria) but different protein content has been authorised for use during the 2009 pandemic.

Currently the guidelines on influenza vaccine are under revision and no specific advice has been issued for adjuvanted vaccines intended for the paediatric population. During the review process, the CHMP asked to consult the VWP on the basis of the following rationale:

1. current guidelines do not apply to paediatric population
2. the Fluad paediatric application is related to an adjuvanted influenza vaccine to be used in children and no other similar products are currently approved in EU
3. the indication of use will be for yearly administration.

The VWP was asked to provide comments on the following questions:

1) Are the CHMP serologic criteria for estimating vaccine efficacy against influenza applicable to vaccine with primary paediatric indication?

VWP response: The CHMP serology criteria were derived from data obtained in healthy adults and using non-adjuvanted vaccines. These criteria are of unknown relevance for predicting the efficacy of Fluad in children and therefore are not applicable.

2) If serologic correlate for protection in adults are not applicable to children, is clinical efficacy mandatory for each of the strains included in the formulation?

VWP response: VWP is aware that it is not at all likely that a protective efficacy study, even if run over two seasons, could generate data on protective efficacy against all three influenza types (H1N1, H3N2 and B) since usually one of these types is very predominant in causing disease in any one year.

Subject to adequate justification (e.g. based on serological results and in vivo model data), a demonstration of efficacy against one influenza A strain in the vaccine could be considered relevant to other influenza A strains and B strains. Similarly, if an efficacy study were to be run during a year in which influenza B predominated then an extrapolation of efficacy against influenza A would have to be supported on similar grounds.

3) Is the effect of consecutive seasonal vaccinations in infancy to be investigated before licensure?

VWP response: Safety and immune responses to initial and at least one further vaccination in the second influenza season should be obtained from a subset before initial approval.

4) Are data collected in healthy children sufficient to predict efficacy in at-risk young children? (definition of at-risk population is needed)

VWP response: the assessment of protective efficacy by means of a placebo-controlled study is not possible in children for whom routine seasonal vaccination is recommended. Efficacy data in healthy children may be considered relevant to immunocompetent children with underlying chronic diseases but may not be relevant to immunocompromised children. Immunogenicity data in immunocompromised children should be obtained at least as post-approval.

5) Should the advantage of adjuvanted TIV also be shown for already primed subjects?

VWP response: Immunogenicity data may not necessarily demonstrate an advantage for an adjuvanted vs. non-adjuvanted vaccine in subjects with serological evidence of past exposure to influenza (whether natural or following prior vaccination). However, it is of interest to at least document both safety and immune responses to the adjuvanted vaccine vs. a non-adjuvanted vaccine in subjects who have previously received TIV.

6) What is the place of an adjuvant vaccine in paediatric patients as regards the Live Attenuated Influenza Vaccine (LAIV) recently licensed in EU (Fluenz) in children from 2 years of age. Is a direct comparison between LAIV and adjuvant vaccine needed and feasible? What are the risks of a decreased efficacy of the LAIV in children above 2 years that have been previously vaccinated with this adjuvanted TIV?

VWP response: The question on inter-changeability between different classes of vaccines (TIV vs. LAIV) should be addressed in a general sense (guidance) but not in the context of the ongoing procedure.

Previous vaccination with adjuvanted TIVs is expected to induce high levels of functional antibodies that are likely to inhibit replication of live attenuated viruses, which is a fundamental prerequisite for the functionality of live attenuated vaccines. In contrast the risk of impaired immune response might be less pronounced in case of using non-adjuvanted TIVs, due to the different mode of action of inactivated vaccines.

The opinion of VWP has been taken into account in the current evaluation.

Paediatric Investigation Plan (PIP)

A PIP was agreed with the Applicant as set out in the Agency's decision P/40/2009 of 23 March 2009. On 29 June 2010 the Applicant submitted to the EMA a request for modification of the agreed PIP since the Applicant encountered difficulties with its implementation. Following PDCO assessment, the original PIP was modified and the new paediatric investigation plan (PIP) (EMEA-C-000149-PIP01-07-M02) was approved, as set out in the EMA decision (Decision Number(s): P/208/2010) of 29 October 2010 (this modified PIP is provided in Module 1.10 of the dossier).

The most relevant aspects of the approved PIP plan are briefly described below:

- A waiver for the condition "Prevention of Influenza" was granted for "children from birth to less than 2 months of age" on the grounds that the specific medicinal product is likely to be ineffective.
- The indication targeted by the PIP was "Prevention of influenza"
- The date of completion of the paediatric investigation plan was July 2016

In total 1 Quality study on the development of suspension for injection, 0.25 ml pre-filled syringe and 5 clinical studies were included in the approved PIP.

The clinical studies are:

Completed study at the time of the PDCO review. Observer-blind, active-controlled (Vaxigrip) safety and immunogenicity study of revaccination with a third Fluad paediatric dose, administered approximately 1 year apart, in children from 16 months to less than 4 years of age. Date of completion June 2008.

Ongoing study at the time of the PDCO review. Observer-blind, active- and placebo-controlled (Agrippal SI/Influsplit SSW and Menjugate/Encepur Children) three-arm safety, immunogenicity and efficacy study of two doses of Fluad paediatric vaccine in children from 6 months to less than 6 years of age. Date of completion October 2010.

Completed study at the time of the PDCO review .Observer-blind, active-controlled (Fluzone) safety and immunogenicity study of two doses of Fluad paediatric vaccine in children from 6 months to less than 5 years of age. Date of completion October 2008.

Observer-blind, active-controlled (trivalent inactivated subunit vaccine) safety and immunogenicity study of a single dose of Fluad paediatric vaccine in children from 6 to less than 18 years of age, healthy and at increased risk. Date of initiation September 2012. Date of completion July 2013.

The Applicant submitted a request for Compliance check at PDCO on 8 November 2010. The procedure was an interim compliance check as some of the studies received a deferral and will be concluded in the coming years as granted in the PIP opinion. PDCO finalised the partial compliance check on 10 December 2010, and confirmed the compliance of all the studies contained in the agreed PIP (Decision P/208/2010) that were to be completed until this date (the extension study, the pivotal efficacy study, V70P6)

2.4. General comments on compliance with GMP, GLP, GCP

A GCP inspection was requested by the CHMP on the basis of the following considerations:

1. only one pivotal study was performed to assess efficacy;
2. efficacy and safety results formed the main basis for Fluad paediatric approvability;
3. several bias potentially affecting the correct interpretation of the results from the pivotal Phase III study have been identified;
4. the vaccine was indicated for a very vulnerable age group.

Three investigation sites (two clinical sites enrolling subjects: one in Germany and one in Finland (A, B) and one microbiological laboratory in Germany, defined in the dossier as the central laboratory for PCR influenza case confirmation (C), were inspected.

The GCP inspectors focused in particular on verifying:

A) At the investigator site:

- The existence of the patients;
- The availability of informed consent for each patient in the sample and the procedure to obtain this consent (obtained in this case by parents/legal guardians);
- The method used to demonstrate the safety, tolerability and protection of one or two doses of Fluad IM;
- The adherence to inclusion and exclusion criteria;
- Source data of baseline data and endpoints and in particular with focus on:
- Efficacy at timepoints as defined in the protocol;
- Safety at timepoints as defined in the protocol;
- Verification of the administration of study medication administration and accountability
- Collection, review, follow up and reporting of SAEs;
- Confirmation of the monitoring of the study by the sponsor.

B) At the laboratory site:

- Accreditation status of the laboratory (the methods) as fulfilment of national requirements of accreditation;
- Systems for QA and QC, including programmes for internal audits;
- SOP system (distribution, availability including holidays etc., audit-trail, clinical trials, archiving etc);
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV;
- Suitability and adequacy of premises;
- Apparatus available, in good working order and complies with relevant specifications;
- Definition of source data and source documents, retrieval and archiving. Data generated in automatic systems e.g. listings, graphs, record traces or computer printouts are archived;
- Samples obtained from subjects in the clinical laboratory, (date and time), identification, labelling, conditions, preparation, storage;
- Documentation of receipt (date and time), identification, condition, re-labelling and storage of samples by identifiable person;
- Procedures for acceptance or rejection of samples for analysis;
- Compliance with protocol and specified test methods;
- Traceability and identification of samples and controls;
- Recording of data and acceptance and release of results.

A total of 3 critical, 36 major and 52 minor findings have been observed in the sites inspected:

Sites inspected	Critical findings	Major findings	Minor Findings
Laboratory (C)	2	26	17
Investigation site –Finland Immunogenicity+efficacy/safety (A)	0	1	16
Investigation site - Germany – efficacy/safety (B)	1	9	19

The definitions of critical, major and minor findings are as follows:

- Critical: Conditions, practices or processes that adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.
- Major: Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.
- Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data. Observations classified as minor, indicate the need for improvement of conditions, practices and processes.

Critical findings

Three critical findings were recorded:

1. <u>Trial management</u>

In the Laboratory site in Germany (C) a QA system was not implemented at the laboratory site. QA responsible had insufficient resources to carry out QA activities and was not independent from processes. The laboratory was classified by the sponsor during a pre-qualification audit as a research laboratory with an adequate QA system in January 2008. Quote from Final Service Provider qualification audit report 20329: "The laboratory's Quality System can be considered adequate for a research laboratory in the context of evaluating exploratory clinical study parameters." Apparently, the study was upgraded later to become a pivotal trial.

This was a lack of overview by the sponsor but also by the laboratory head. The sponsor selected a central facility with an insufficient QA system. No follow up after the initial qualification audit regarding major observations was performed by the sponsor. No quality assurance audits were performed by the sponsor during the conduct of the study. QA and QC systems of the sponsor regarding the laboratory site failed.

The laboratory methods described in the dossier were different from used in practice.

2. <u>Quality of data</u>

At the German investigation site (B), there are indications and reasonable doubts that memory aids for visit 4 and 5 were not handed out to parents by the PI. This relates directly to the quality of data of the safety follow up of the study. Monitor reported to the sponsor that all memory aids for visit 4 and 5 were present at the site, seemed to be completed in the same way, and had no signs of usage. There is no evidence of an adequate follow-up by the sponsor regarding this issue. The reliability of data collected at this site is questioned.

Moreover, there are other **major issues** related to the quality of data:

2a) The pre-screening list included information regarding number of (pre)screened subjects and (pre)screen failures. This list was not kept at the site.

2b) Inspectors cannot be sure that all patient source data were be made available to the inspection team for reviewing e.g. medical history, prior medication, concomitant medication. Inspectors were probably not able to review all the necessary information to assess the protocol and GCP compliance at this site. Patient's charts were partly incomplete and some charts were possibly not available for inspectors review.

2c) No documentation by the PI of physical examination regarding blood pressure, heart rate, or respiratory rate in the source documents of study subjects.

2d) No source data were available for reviewing the administration time of the vaccines.

The Applicant performed a "robustness" analysis with and without data from this site, showing no effect on the final estimates.

CHMP considered that the GCP problems found at the inspected clinical site cannot be considered solved by just excluding the safety and efficacy data from this inspected site. It is considered that a similar lack of appropriate supervision could have occurred in other clinical sites not subjected to GCP inspection, and therefore the whole safety data of the trial is questioned.

Moreover, from the efficacy point of view, the finding that none of the 152 children vaccinated at the site was reported to have ILI during the study period (several months) also questions the validity of overall efficacy data obtained in the trial. It is in fact noted that in total 4702 children were recruited in the pivotal trial, and 1114 of them had ILI (i.e., a 23.6% of all vaccinated children) during the trial period. Thus, the probability of not having any child with ILI out of the 152 vaccinated children in the site was: 0.000000000000000002 (= 2x10-18). The fact that the Applicant did include in the efficacy analyses data from this site, which are extremely unlikely to have occurred in reality, suggests that there was no appropriate supervision of the efficacy data by the Applicant. Therefore, the problem detected in the site could have also happened in other sites, and as consequence the reliability of overall efficacy data from the Pivotal Study is questioned.

3. <u>Data handling</u>

In the Laboratory site in Germany (C) there were no 100% data check (reconciliation) of data included in the Standardized Excel Sheet, the MS Access database, the MS Excel worksheets and ELISA reader values before the transfer of data to the sponsor was performed. No information could be provided how many per cent of data cross-checks were performed.

- The MS Access database was not validated. The protection of MS Excel files and the MS Access database was insufficient. The MS Access database is a live database and had not been locked to freeze the results of the study before the transfer of results to the sponsor.

- An audit trail was implemented and enabled but it was not trained, used, reviewed, or accessible by the QA responsible.

- According to the site the former head of laboratory (C) used and reviewed the audit trail, but no documentation was available. As a consequence, it has to be stated that no QA regarding the audit trail was performed during the conduct of the study.

Major findings

Among the 36 major findings, the following two general issues are highlighted:

1. Major finding. Quality of the samples and the analytical methods used for PCR and sequencing (Laboratory site (C))
The main tool used for the determination of the efficacy endpoint was not validated before the study started. Also, there were inconsistent source data regarding the analysis performed, since there was not a procedure in place for printing and filing of the runs of the analysis performed.

The kit for the extraction of viral nucleic acid in swab samples (as in the study) was not validated.

In total of 1215 samples were analyzed by PCR at the laboratory site. Samples were routinely analyzed in runs that included 4, 9 and 18 samples. In total, 176 runs were performed with the 1215 samples. The influenza positive controls A and B used were not adequate since only 10 out of 176 runs included either an Influenza A or B positive control. Moreover, the technique did not incorporate an internal control to check for the adequate functionality of the technique in each of the samples analyzed. Due to the lack of an internal control the performance did not allow a clear interpretation of the received results.

Concerning the samples from Germany, these were not fully controlled. No temperature control for these shipments was recorded. In fact, the clinical samples from the German investigator sites were sent by post mail at room temperature without any record of the temperatures reached during shipment. Some of the samples may have reached temperatures that could have resulted in degradation of the pathogen present in the sample and as a consequence this will mean a loss of sensitivity for that particular sample.

The Applicant retest samples from ILI cases (nasal specimens from subjects with ILI symptoms were stored at minus 80°C at laboratory (C) in a fully qualified laboratory using validated methods and performed a reanalysis of the efficacy endpoints).

Among 1,216 samples of seasons 2007/08 and 2008/09, re-testing was performed on 1208 samples in another laboratory (D); 8 samples were not re-tested as the material left was insufficient for the re-testing to be performed.

Analyses of the re-test results were remarkably similar to the original analyses, confirming the original overall study conclusions regarding the high absolute and relative efficacy of Fluad as compared with non- adjuvanted influenza vaccines.

A) Sample re-testing

The GCP inspection found that the laboratory, (C) where all 1216 nasal samples from the pivotal clinical efficacy study were analyzed by PCR to indentify those containing influenza virus, besides having no Quality system in place did not implement any control on the quality and validity of the PCR test used. The PCR test used was not validated before analyzing the samples and, in addition, the test had many deficiencies that question the reliability of the influenza cases detected in this laboratory. A similar situation is observed in the second laboratory,(E) where some nasal swabs were analysed. As a consequence of the deficiencies in the PCR analysis highlighted by the inspectors, the Applicant has decided to retest, using a third different PCR method, the nasal samples in a new laboratory (D).

As it had also already claimed for the two other PCR methods used, the Applicant claims that this third PCR method is fully validated. This conclusion is not supported by the CHMP. In fact, the validation

reports provided from the three PCR tests on nasal/swab samples performed at the three sites (C, D and E), are not considered adequate to unambiguously identify influenza cases. The following deficiencies are noted:

- The validation report of the PCR technique used in the laboratory (C) was performed in 2011, thus several years after the final analysis of all nasal samples from subjects with ILI from the pivotal efficacy study was completed. The validation report should have been done before starting the analyses of the samples.
- It is not known whether the laboratories (D and E) were actually running under a quality system.
- None of the validation reports has demonstrated that the extraction kits used to extract nucleic acids from nasal aspirates/swabs were actually validated for this purpose.
- Most of the validation studies were performed using highly purified influenza virus (grown in cell culture) dissolved in saline and not real samples (i.e.: nasal aspirates/swabs, that will contain cell debris, proteases, RNAses, in some samples other viral/bacterial pathogen, etc). The different composition of the samples used in the validated reports may have an impact on the sensitivity, specificity and limit of detection of the assay, and thus all data obtained with highly purified virus are not considered demonstrative of the validation of the PCR tests.
- The retrospective validation strategy has been performed taking into account only two parameters: specificity and robustness, as the PCR assays have been regarded by the Applicant simply as "identification tests". However, these are primarily detection and identification assays, therefore a re-assessment of the sensitivity parameter is critical. Apparently, the sensitivity parameter has not been re-assessed during the retrospective re-validation. According to the Applicant, the sensitivity of each method (on virus culture supernatants or allantoic fluid, but not on nasal swabs) was assessed in the initial validation studies. For each method, however, sensitivity is expressed differently. The lack of these data does not allow the comparison of sensitivities among the different PCR assays used, and does not help in understanding the reasons for the discrepant results obtained with the different assays.
- The validation report "influenza A and B RNA, qualitative real-time PCR, states, in page 17 of 24, "it is recommended that the stability data for RSV be extrapolated to influenza virus, with stability of 2 days at room temperature". Thus considering that the nasal swabs/aspirates collected in the German sites were sent at room temperature to the central lab, many of the samples analyzed by PCR have been for more than two days at room temperature and therefore according to the validation report submitted by the Applicant were not valid since the influenza virus nucleic acid could have been degraded before reaching the Central lab (C).
- The Applicant claims that the three PCR assays were well validated as far as sensitivity and specificity are concerned. If this were true, the three assays should have identified the same number of positive and negative influenza cases following analyses of the nasal samples. However as stated in the Addendum 3 to the CSR of the pivotal efficacy study, dated 09 November 11 (pages 15 and 20 of 35), there were 110 influenza PCR–confirmed cases at the laboratory but there were 125 positive cases at (D) and (E) . Moreover, there were 51 samples that were positive at laboratory site but negative at another site; and 14 cases that were positive in the laboratory site (C), negative in another site (E) and positive at another site (D). Inconsistencies are evident, but the cause has not been identified. It is not possible to exclude problems in the labelling of the samples when there was no quality system in place in the central laboratory (C). Similarly, it is not possible to exclude that some of the sample shipment/storage deficiencies, previously evidenced, may have been responsible for the differences observed in the various laboratories. Moreover, only some of the PCR positive cases were included in the new efficacy analyses, with no explanation for not considering the others, being provided. For example, the Applicant did not use the 37 samples that were only positive at laboratory site. Indeed, these samples could be true positive samples that converted into negative ones upon storage, due to degradation of the viral nucleic acid.
- In the multiplex PCR ELISA procedure use there is no mention of the use of an internal positive control (IPC), which should have been added to each sample to ensure that no Taq polymerase inhibitors were present in the clinical specimens. The lack of an IPC designed to work with the same primers used for the clinical samples increases the risk of false negative results, which in turn would artificially increase vaccine efficacy. In this regard, it is noted that in the 2007-08 season and up to January 2009, all samples found to be negative at the central laboratory (C) were not retested by any other laboratory using an IPC.

In conclusion, the validation of the PCR tests cannot be regarded as adequately performed; consequently, the reliability of the PCR test is not demonstrated. It is thus not possible to use any of the three sets of PCR data for the identification of influenza positive samples.

B) Sample shipment

All nasal samples from children vaccinated in Germany (but not those from Finland) were sent by ordinary mail at room temperature from the study sites to the two German labs (C and E). This fact could have resulted in partial/total degradation of the virus that could be present in the sample, a situation that will have a major impact in samples containing low amounts of viral particles.

According to the inspectors' findings, before shipment the samples were kept at either RT, +4°C or -20°C, without a common protocol. Moreover, at the time of receipt at the laboratory (C) "the shipped sample tubes were immediately stored at 4°C or at <-20°C". As indicated in the Manuals for the laboratory diagnosis and Influenza surveillance of WHO (1, 2), storage at -20°C is to be avoided at all times because influenza viruses are extremely unstable at -20°C. This is underlined also in the Realtime PCR validation report of laboratories (D). Influenza-containing specimens should be kept at +4°C for short periods of times or frozen at -80°C. This specimen handling system may have further reduced the chance of detecting positive samples.

The Applicant has provided a validation of the stability of influenza viruses spiked in saline solution kept at room temperature over a 7 days period, performed at other laboratories (D). Three points should be highlighted: 1) the viruses used to perform stability studies of the RNA in clinical samples are A/Perth/16/09 and B/Brisbane/60/08, included in the vaccine composition for the 2010-11 campaign, therefore they are not the same as those circulating in the two seasons considered for the efficacy studies (2007-08 and 2008-09), whereas influenza virus stability is strain-dependent. There is also no rationale for not performing the same type of study on an H1N1 virus; 2) even with the above strains a reduction in sensitivity from day 0 to day 7 is evident and could make the difference between a positive and a negative result particularly in samples with an initially low viral load; 3) last but most important, the validation has been performed, while the clinical specimens are represented by nasal swabs or aspirates, often containing RNAses which degrade very rapidly the viral RNA, and particularly at temperatures above -80°C, unless RNA stabilizing buffers are added before storage and/or they are lysed and RNA is immediately extracted and kept at -80°C until use. See in this regard the review from Holland et al. (3). A proper validation of the handling and storage conditions of influenza RNA-containing fresh respiratory specimens should have been performed before starting the trial, for example by spiking a pool of influenza negative nasal swabs or aspirates from children with infections caused by other respiratory viruses, kept at +4°C or RT, and tested at different time intervals for RNA recovery to identify the best conditions to guarantee RNA stability in clinical specimens before extraction and analysis. The importance of this step to avoid the risk of RNA degradation in positive respiratory or other biological samples has been clearly highlighted by several authors (4,5). In particular, this type of study has been performed by Loens (4) showing that rhinovirus RNA from specimens kept at +4°C and RT started degrading already after 2 hours and several logs were lost after 2 days. Therefore, the validation of the stability of specimens shipped at room temperature in (D) is not relevant to the actual specimens collected in Germany and does not rule out the (very likely) possibility that a number of initially positive samples had become negative by the time they reached the diagnostic laboratory. The applicant has also stated that in Germany the standard approach for handling of diagnostic respiratory (swab) specimens from clinics to diagnostic laboratories (C) for PCR-based diagnosis is to send such specimens unfrozen at ambient temperature by ordinary post. This can

be true and appropriate for specimens containing DNA, which is stable even at 37°C (3), but not for RNA, particularly when sensitivity of RNA recovery should be as high as possible as in this case. In addition, if the vaccine actually reduces viral replication, samples from children vaccinated with Fluad will most likely have lower number of viral particles in nasal swabs and/or viral shedding will last fewer days than the children vaccinated with placebo. Thus, partial degradation of viral particles by sending the samples at room temperature could artificially increase the estimated efficacy of Fluad vs. the placebo vaccine.

In conclusion, by sending nasal swabs at room temperature from German study sites to the laboratory testing sites (C and E), a bias could have been introduced that may have artificially increased the clinical efficacy of Fluad. Thus the results from PCR tests from German samples shall not be considered for the efficacy analysis.

References:

WHO. Manual for the laboratory diagnosis and Influenza surveillance. 2011

WHO. Manual on animal influenza diagnosis and surveillance.rev.1 2002

Holland NT, Smith MT, Eskenazi B, Bastaki M.(2003) Biological sample collection and processing for molecular epidemiological studies. Mutat Res. 543(3):217-34.

Loens K, Ieven M, Pattyn S, Sillekens P, Goossens H. Sensitivity of detection of rhinoviruses in spiked clinical samples by nucleic acid sequence-based amplification in the presence of an internal control. J Microbiol Methods. 2006 Jul;66(1):73-8

Ginocchio CC, Wang XP, Kaplan MH, Mulligan G, Witt D, Romano JW, Cronin M,Carroll R. Effects of specimen collection, processing, and storage conditions on stability of human immunodeficiency virus type 1 RNA levels in plasma. J Clin Microbiol. 1997 Nov;35(11):2886-93

C) Samples storage

Samples from the pivotal clinical study were received at the laboratory site (C) from January 3, 2008 to July 3, 2009 and stored at -80ºC in a REVCO freezer until two years later (September 2011), when samples were sent to a laboratory site (D) for PCR retesting. The Applicant states that samples were still valid for analyses since no dysfunction of the freezer took place between January 3, 2008 and September, 2011.

This conclusion is not supported by the CHMP since there was no continuous monitoring of the temperature of the freezer during the three years elapsed from the moment the first sample was received. The Applicant claims that the alarm of the freezer was working in a test that they performed in September 6, 2011, and that if the freezer had been out of the range of temperature, personnel from the technical support unit of the University would have contacted people from the lab to solve the problem. However, since the laboratory (C) was running without any Quality System in place there are no written documents to state that the freezer was actually working as expected for the three years between 2008 and 2011. In addition, and importantly, the samples from the pivotal clinical trial were stored together with other clinical nasal specimens from children hospitalized with a respiratory disease not enrolled in the pivotal efficacy study. Since the laboratory lacked a Quality System, these samples were manipulated and tested (and stored) at the same time as those from the clinical trial, so it cannot be ruled out that these manipulations resulted in cross-contamination or mislabeling of the samples

from the pivotal efficacy trial. Indeed, the different PCR results described above showing that samples originally tested as positive by laboratory testing site (C) were not positive later in the other two laboratory testing sites (C) could be explained by degradation upon storage of the samples and/or cross-contamination or mislabeling of the samples.

2. Major finding. Appropriateness of Prevenar administration to a significant number of subjects in Finland

Prevenar 7 pneumococcal vaccine was given to the majority of the subjects in the investigator study site (A) outside study protocol. This was agreed between the coordinating investigator and the sponsor, but no sponsor assessment of the effects of the additional vaccine on study outcomes has been presented. The sponsor did not mention it in any of the study protocol versions or in the clinical study report body text. The clinical study report understates the proportion of subjects who received this concomitant vaccination.

Data on which subjects received Prevenar, when and how many doses, were not always documented. Pneumococcal vaccine prevents respiratory infections and thus may impact the incidence of ILI and both safety and efficacy results, but this has not been analysed and reported in the clinical study report in detail. Since Prevenar was not considered as an investigational medicinal product the cold chain was not monitored, no vaccine accountability was recorded and no adverse events were captured. Many of the families were given Prevenar to take to the well baby clinic and ask the staff to vaccinate the child there. One subject received too many doses. Other Finnish sites have vaccinated subjects with Prevenar as well.

SPONSOR RESPONSE

PCV7 in this trial was administered as a non-study vaccination - it was given just as other routine childhood vaccines are given according to medical need and judgment as part of routine care.

PCV7 was administered to children in Finland as the PI deemed it medically necessary. The concurrence of local and national ethical bodies for its administration in the trial is indicated by their acceptance of the letter from the PI. Further, approval of the protocol by the national competent authorities and ethical committees, as well as PDCO underlines their acceptance of routine administration of other childhood vaccines during the study.

Importantly, there was no imbalance in the distribution of children receiving PCV7 across study groups. Thus, any bias in the results of the study caused by Prevenar is highly unlikely.

Table 3 Distribution of Prevenar* administration (percentage of subjects) by study vaccine group and age cohort

		06-<36 Months of Age			36-<72 Months of Age		
		Fluad	**Flu control**	**Non-flu control**	**Fluad**	**Flu control**	**Non flu control**
Finland	Total N	485	481	249	347	344	174
	% received PCV7	56%	55%	56%	37%	38%	39%
Gemany	Total N	669	565	346	490	433	248
	% received PCV7	21%	23%	21%	1%	1%	1%
All	Total N	1154	1046	595	837	777	422
	% received PCV7	36%	37%	35%	16%	18%	16%

*Note: A very small minority of subjects (<10) received a pneumococcal conjugate vaccine other than Prevenar (either unspecified, Pneumovax, or Synflorix).

Finally, the analyses done on subgroups with and without Prevenar shows that Prevenar administration had no impact on the frequency of ILI.

Evaluation of the finding and corrective measures implemented by the Applicant:
It is indeed unlikely that the administration of Prevenar to some of the children from the pivotal efficacy study in Finland would have significantly biased the results of this study. Nonetheless, it is not up to the standard of a trial performed according to GCP rules, not to have included and discussed this information in the CSR submitted by the Applicant. In this specific situation as the immunogenicity study was only conducted in Finland any intercurrent vaccination as well as of any other event potentially affecting observed immune response to the study vaccine should have been properly and systematically recorded.

In conclusion, the finding that the Prevenar vaccine was administered to most of the children enrolled in Finland, but no information on the modalities and consequences of the Prevenar administration.

Final conclusions from inspectors as reported in the Integrated Inspection Report
Recommendation of use for inspected data
The inspection team concludes from the observed critical and major findings at the investigator site (B) and the clinical laboratory (C) that the conduct of the pivotal study was not fully compliant with GCP. Findings on trial documentation, trial management, sites management, quality of data/source data verification, including specimen handling and procedures (PCR) data handling, and reporting of data, contribute to this conclusion.

The investigator site in Finland revealed only one major finding: However, the inconsistent and incomplete information regarding the use of Prevenar at this site, and the fact that its administration in a systematic way during the study without any discussion, led the inspectors to conclude that the site has breached the GCP principle of not recording all concomitant medications, and therefore the data obtained at this site in this respect are incomplete, and thus, cannot be used for the authorisation

application at this point. It also must be mentioned that this same conclusion might apply to other or even all 15 Finnish sites that have used Prevenar but have not been inspected.

Assessment of the relevance of the findings for the full study
Several of the findings indicate a need for improvement of the QMS of sponsor, the central laboratory and the investigation site (B).

Given the findings observed at the aforementioned sites, the processes/procedures used by the sponsor for their management and since these problems could have been repeated in other investigational sites, a negative impact on the full study cannot be excluded.

The sponsor failed in an adequate oversight of the sites, the delegated activities from the investigator/head of laboratory and the systems and procedures used. The quality assurance and quality control implemented were not sufficient and not applied properly.

The combination of the not fully adequate quality assurance/control at the sites and the inadequate oversight of the sponsor have been crucial in the opinion of the inspectors for causing many of the findings identified.

Recommendation for the use of the inspected data and procedures as a basis for acceptance/non-acceptance of the submitted trial

Following the inspections at the three sites, and given the critical and major findings observed that reflect a need for improvement of the procedures and processes performed when the trial was conducted, the inadequacy of the oversight of the sponsor, and in consequence, the impossibility to exclude the issues identified that could have been repeated in other investigational sites, the inspectors conclude that it is not recommended to accept the data submitted for the decision about marketing authorisation at this stage.

Discussion

It is relevant to underline that the safety and efficacy of any influenza vaccine intended for paediatric use has to be proven within clinical studies, as the serologic correlates for protection, set up for the adult population, are of unknown relevance in children.

The current MA application, although related to a product developed more than 15 years ago and authorized for use in elderly, includes only one study addressing clinical vaccine efficacy.

The quality of this only study is therefore crucial to the entire product evaluation and on these grounds a GCP inspection was requested.

The GCP Inspection found not only lack of GCP compliance in the three inspected sites but also identified a number of issues, regarding the clinical efficacy data from the pivotal trial, that were incorrectly stated in the first dossier submitted by the Applicant (see list of issues below).

The PCR test that was performed on nasal swabs from children with ILI was the critical assay for determining the clinical efficacy of the vaccine in the pivotal efficacy study. In relation to this PCR test and its results, the GCP inspection detected inaccurate information reported in the first submitted clinical dossier, which are briefly summarized in the following paragraphs:

1. The Applicant provided in the original MA dossier two references from peer-reviewed journals (one including a partial validation of the assay) describing the PCR test used in the central testing laboratory (C). However, the inspection visit found out that the actual PCR test performed in was not the one stated in the submitted dossier but a different PCR test, which was not yet published in any peer-reviewed journal and was not validated at all before starting the analysis of the samples.

2. The original MA dossier indicated that another laboratory (E) in Germany had also analyzed some nasal swabs using the same PCR test as that used in laboratory site (C).
3. However, the Inspection team found that a different PCR test was used in laboratory site (C) and this PCR test was not mentioned in the first dossier.
4. Despite stating in the submitted dossier that "If the PCR assays test positive for influenza A or B, viral culture confirmation had to follow"; it was found at the inspection visit that viral cell culture was not performed as part of the study. In other words, the original MA dossier gave the impression that influenza PCR-positive cases were further confirmed by another test (cell culture), a fact that did not give sufficient reassurance of influenza case identification.
5. During the inspection visit it was found that laboratory site (C) received all 1216 nasal swabs, but that the lab received: i) in 2007-08 and up to 20th January 2009, nucleic acid extracted in laboratory site (C) only from nasal samples which had tested PCR-positive in laboratory site (C) and, ii) from 20th January 2009, nucleic acid extracted in laboratory site (C) as before, as well as nasal samples from selected ILI cases, but in this case the sample was different from the one sent to laboratory site (C) (i.e., from the same child, two nasal swabs were taken, and each of them was sent to a different lab). This flow and different type of samples was not mentioned in the first dossier.

Although the Applicant in its first submitted dossier repeatedly stated that there were only 110 PCR-confirmed influenza cases in the pivotal Phase III study, it was found that in a total of 195 children had PCR-confirmed influenza and when using the PCR test from the other German laboratory (E) this number was 136. These results were not mentioned by the Applicant. In the newly submitted data it was revealed that there were 26 children that had PCR-confirmed influenza in samples obtained less that 3 weeks after the last vaccination and that these cases were not mentioned in the first submitted data. The implications on these data in the efficacy analyses have not been discussed by the Applicant.

Conclusion

Based on the above considerations the conclusion from the Integrated Inspection Report that recommends not to accept data from the pivotal Phase III study for the decision about marketing authorization of Fluad are fully agreed by the CHMP.

2.5. Type of application and other comments on the submitted dossier

The legal basis is:

1. Article 31 of Regulation (EC) No 1901/2006. Date of acceptance/confirmation by CHMP: 2010-03-23.
2. Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application, (i.e. complete dossier with administrative, quality, non-clinical and clinical data) - Known active substance.

Fluad was first registered in Italy in 1997 for the prophylaxis of influenza in elderly people (65 years of age and over) especially for those with an increased risk of associated complications.

Since 1997, it has been approved in 12 European countries through a Mutual Recognition (MR) Procedure that concluded on April 23rd 2000. Since its first registration, the vaccine has obtained approval in 30 countries worldwide for use in the elderly population. Fluad is also licensed for use in the paediatric population (6 to 36 months of age) in Mexico. The product complies with influenza vaccines, surface antigen, inactivated and includes MF59C.1 as adjuvant Ph.Eur. monograph.

The main difference between Fluad MRP and the product submitted with the current application consists in the addition of a 0.25 mL presentation: currently the 0.5 mL/dose presentation is registered for use in the elderly; an additional 0.25 mL/dose presentation is included in this MAA for paediatric use.

THIS APPLICATION DOES NOT FALL WITHIN THE SCOPE OF ARTICLE 8 OF THE PAEDIATRIC REGULATION

ARTICLE 30 (PUMA) OF THE PAEDIATRIC REGULATION APPLIES TO THIS APPLICATION since:

- the application relates to a medicinal product, which is not protected by either a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate.

- PIP Decision Number(s): P/208/2010.

THIS APPLICATION WAS SUBJECTED TO PIP COMPLIANCE VERIFICATION n. EMEA-C-000149-PIP01-07-M02

EMA confirmation for eligibility for submission of an application for Community Marketing Authorisation under Article 3(2)b – Interest of patients of Regulation (EC) No. 726/2004 was received on March 23rd, 2010.

- Conditional approval
  Not requested by the Applicant.
- Approval under exceptional circumstances
  Not requested by the Applicant.
- Accelerated procedure
  Not requested by the Applicant.
- Biosimilarity
  Not applicable.
- 1 year data exclusivity
  Not applicable.
- Significance of paediatric studies

This application concerns the PUMA for Fluad paediatric vaccine intended for the active immunisation against seasonal influenza in infants and children from 6 months to less than 9 years of age. All the studies supporting this applicant were performed in children.

The peculiar characteristic of this product is that it is the first trivalent adjuvanted Influenza-virus Vaccine for paediatric population. Two strengths are presented: 0.25 ml and 0.5 ml. The posology proposed is:

Infants and children from 6 to less than 36 months:

- who are receiving their first seasonal influenza vaccination: Two 0.25 ml doses, 4 weeks apart.
- who have previously received seasonal influenza vaccination: A single 0.25 ml dose.

Children from 3 years to less than 9 years:

- who are receiving their first seasonal influenza vaccination: Two 0.5 ml doses, 4 weeks apart.
- who have previously received seasonal influenza vaccination: A single 0.5 ml dose.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Quality aspects

Drug substance

The Drug Substance is a sterile suspension containing predominantly the purified outer membrane proteins, haemagglutinin (HA) and neuraminidase (NA), of influenza virus strains Type A and Type B from the influenza virus strain recommended every year by the WHO/CHMP/CBER/CDC. The viral envelope parts may be present in traces.

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 strain designation for influenza virus types A, B, and C contains, a description of the antigenic specificity of the nucleoprotein antigen (types A, B, or C), the location of isolation, the isolate number, and the year of isolation.

For type A viruses the antigenic description follows (in parenthesis) including the antigenic character of the haemagglutinin (H) and the antigenic character of the neuraminidase (N).

Virus type	Location of isolation	Isolate number	Year of isolation	H and N subtype
A /	Taiwan /	1 /	86	(H1N1)
A /	Beijing /	353 /	89	(H3N2)
B /	Panama /	45 /	90	

Influenza A viruses are divided into subtypes based on the HA and NA proteins on the surface of the virus.

Influenza B is not classified according to subtype. Both the influenza A subtypes and influenza B viruses can be further broken down into different strains that change as the influenza viruses evolve. Each year, the three strains used in the seasonal influenza vaccine consist of one influenza A (H1N1) virus, one influenza A (H3N2) virus, and one influenza B virus.

HA is a cylindrically shaped trimer ~135Å long, varying between 35 and 70 Å along the radial direction. It is composed of three identical monomers assembled into a central α–helical coiled coil that forms the stem-like domain, and three globular heads containing the sialic acid-binding sites. The monomers Originate upon cleavage of the individual chins of the fusion-inactive precursor (HA0) into two polypeptides, HA1 and HA2. The polypeptides HA1 and HA2 are linked by two intramonomer disulfide bridges that are presumably formed during the folding of HA0 in the endoplasmic reticulum.

NA cleaves terminal sialic acids from carbohydrates. It is critical for viral release from infected cells and facilitates viral spread in the respiratory tract.

NA has a head consisting of four co-planar and roughly spherical subunits, and a hydrophobic region that is embedded within the interior of the virus' membrane. It is comprised of a single polypeptide chain that is oriented in the opposite direction to the hemagglutinin antigen. The composition of the polypeptide is a single chain of six conserved polar amino acids, followed by hydrophilic, variable amino acids.

HA is a glycoprotein integral to the influenza virus envelope. HA is involved in two major functions: recognition of target cells by binding to their sialic acid-containing receptors, and fusion of the viral and the endosomal membranes succeeding endocytosis.

The function of NA is mainly at the end of the life-cycle of the virus. A sialidase enzyme removes the sialic acid from glycoconjugates and facilitates the release of the virus particles from the infected cell surfaces during the budding processes and this prevents self-aggregation of virions by removing sialic acid residues from viral glycoproteins. It has also been suggested that NA helps the virus to wade through the mucin layer in the respiratory tract to reach the epithelial cells, which are the target cells for the virus.

The notation MF59™ is used to describe the family of Novartis squalene-in-water emulsions. In the past, a number of terms (laboratory codes) have been used to describe these emulsions at Novartis.

The term MF59C.1 refers to the MF59™ emulsion with a sodium citrate - citric acid buffer aqueous phase.

Within the dossier and supporting documentation, MF59C.1 is also generally referred to as the following:

- MF59
- Adjuvant
- MF59C.1 (or MF59) Adjuvant
- MF59C.1 (or MF59) Bulk
- MF59C.1 (or MF59) Bulk Adjuvant
- MF59C.1 (or MF59) Adjuvant Bulk

Squalene (the primary component in MF59C.1) is an unsaturated trans isopreneoid hydrocarbon containing six isoprene units. It has a molecular weight of 410.70 and the following chemical formula:

2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene

MF59C.1 adjuvant is an oil-in-water emulsion containing squalene as the oil phase together with the emulsifying agents polysorbate 80 and sorbitan trioleate, formulated in a citrate buffer as the aqueous phase.

The primary ingredient of the MF59C.1 adjuvant is squalene, which is a highly unsaturated hydrocarbon biosynthesized in the liver. Squalene is an intermediate in the human steroid hormone biosynthetic pathway and is a direct precursor to cholesterol. Squalene is also the principal hydrocarbon of human surface lipids. Squalene used in the production of MF59C.1 is derived from shark liver.

Polysorbate 80 and sorbitan trioleate are two nonionic surfactants used for stabilize the emulsion in the formulation.

Squalene

The MF59 adjuvant has been used in pre-clinical and clinical studies for a range of different vaccines. Squalene is used as the oil phase in MF59C.1 Adjuvant Bulk, which is an oil-in-water emulsion. The squalene component of the adjuvant is known to act as an oxygen carrier. From the 1999 Fluad has been formulated using adjuvant containing citrate buffer, designated as MF59C.1.

The redistillation of squalene is performed under known, controlled conditions, following cGMP guidelines, in order to ensure high quality regardless of the initial squalene source. The introduction of this redistillation step into the current squalene purification process is further expected to inactivate and remove any potential viral contaminants from the final product.

Since squalene is a small molecule, it can be extensively characterised. Based on characterisation data, equivalency of the redistilled squalene derived from the different vendors was demonstrated. Pre-distilled squalene obtained from qualified suppliers is redistilled using falling film distillation equipment under cGMP conditions.

A Monovalent Pooled Harvest is a buffered suspension containing predominantly the purified surface membrane proteins, HA and NA, of a single influenza virus vaccine strain.

The Influenza Virus Strain is propagated using chicken embryonated eggs.

Thiomersal removal
Thiomersal has been completely eliminated from the production process.

With the exception of squalene, that is the main component of MF59C.1 and derived from the shark liver, all the other ingredients of MF59C.1 Adjuvant Bulk meet with Ph.Eur. and/or USP/NF specifications. These materials do not contain any human or animal-derived components, sera, or dyes (Section 3.2.A.2). Squalene is tested according to an in-house specification.

Drug product

The vaccine is presented as a 0.5 ml or 0.25 ml single dose sterile suspension for injection in a milky-white emulsion, contained in a glass pre-filled syringe.

The potency of the vaccine is expressed as the concentration of the HA protein.

A number of substances are used during manufacture of the vaccine.

The concentrations of these substances are controlled in the Monovalent Pooled Harvests, and hence the final vaccine:

- cetyltrimethylammonium bromide
- barium sulphate
- sodium citrate
- formaldehyde

Fluad final formulation is a combination of Monovalent Pooled Harvests, buffer solutions and MF59C.1 adjuvant bulk, which has been demonstrated in clinical studies to improve the immunogenicity of the final product.

The Monovalent Pooled Harvests used to manufacture Fluad are the same as those in Agrippal, an inactivated influenza virus subunit vaccine also manufactured by Novartis Vaccines and Diagnostics. Agrippal has been licensed in Italy since October 1986 and since December 1998 has been registered in 12 EU countries through a Mutual Recognition Procedure. The Monovalent Pooled Harvests (and the Agrippal finished product) comply with the Ph Eur monograph on Influenza Vaccine, Inactivated (Surface Antigen).

With respect to the transmission of Transmissible Spongiform Encephalopathies (TSE), the only animal derived starting materials are eggs (used in production of the Drug Substance) and squalene (used in the MF59C.1 adjuvant). There is no scientific evidence to suggest that eggs are likely to present any risk of contamination from TSE-agents.

Regarding squalene, derived from shark liver, it does not present any risk of potential contamination from TSE agents as well.

Discussion on chemical, pharmaceutical and biological aspects

The manufacturing process is well documented. The flow diagrams include the operating parameters and in-process controls as recommended. Particular care is dedicated to the control of Bioburden during all the process. The in-process controls through the production and the purification process are

extensive and assure compliance with the Ph.Eur. where required. Purification procedure and reaction conditions are well described with a rational for each step being explained. The description of the process, consistency and controls are adequate and based on the large experience gained on the Drug Substance for Fluad. As soon as the clarified allantoic fluid is concentrated it is immediately inactivated.

Details of the ultrafiltration system (e.g., type of filters) used to concentrate the allantoic fluid have been clearly indicated.

Reuse and cleaning procedures are put in place, when applicable, according to validated cycled described in SOPs. As clarified by the Applicant, the peak fraction, collected after sucrose density purification, is never treated with Barium sulphate since historical and current data on seasonal influenza vaccines show. For this reason, the Company has decided to amend the internal SOP as well as the dossier, to remove the option for the peak fraction to undergo barium treatment. This means that no lots exceeding the proposed endotoxin limit will be used. The Applicant has also introduced an alert limit for the endotoxin content at this and at other steps in the purification process to monitor the process and any anomalous trends, and if the endotoxin exceeds the alert limit an Investigation Report is initiated However, the Applicant states also that "The procedure foresees to open a deviation report to manage all the corrective activities (i.e. an additional treatment with barium) and a new test for endotoxin after the barium treatment." Thus, the possibility of an additional treatment with barium of the peak fraction seems in contrast with the intention to remove this optional step from the internal SOP. The Applicant should better clarify this point.

Virus inactivation is performed using validated cycles with formaldehyde. A study for the kinetic of inactivation and a viral inactivation test are performed at that level, to verify the efficacy of the inactivation. Several tests are performed exclusively on lots manufactured after the validation of the viral inactivation and on the sample when the virus inactivation has been confirmed. This precaution does not seem to have any impact on the quality of the process. Some intermediates are not processed within hours, but are held for longer.

The Whole Virus Concentrate (WVC) can be held up to days to allow the Quality Control laboratory to perform the Split Test. Data supporting this holding time, which is strain specific, have been provided only on one lot of WVC. The Applicant should provide the validation data for two additional lots, unless otherwise justified.

The process validation could be considered as adequate. Certificates attesting the removal of adventitious agents and viral safety linked to the use of production eggs as starting material are provided. Residual of production and impurities coming from the use of the eggs are controlled in the Drug Substance, in accordance with the Ph.Eur. requirements.

The manufacturing process development presented by the applicant gives an acceptable overview of the process history, focusing on its key aspects. The removal of the Thiomersal from the formulation was started in 2002, with the reduction to trace amounts at the level of antigen production, and then completely eliminated from the production process (starting from 2003/2004 NH campaign). Precautions were taken to ensure the control of bioburden during the process and reduce the risk of contamination.

Furthermore, the applicant summarized all the post-approval changes to the process, justifying them and commenting their impact on the quality.

The Applicant has clarified that alert limits and action limits have been established on the historical data and on statistical evaluation according to internal procedures for most intermediate products. As an example, the alert and action limits of bioburden and endotoxin levels, are provided. However,

there is a clear mistake in the endotoxin table. The alert limit seems inconsistent with both the alert limits of the previous phases as well as the specification limit. The Applicant should clarify this point.

Drug substance - Monovalent Pooled Harvest – Characterisation

The Drug Substance is typical of a conventional surface antigen inactivated influenza vaccine. Its general characteristics and structure are known and comply with the description given by the applicant. During the manufacturing process development, the applicant performed a specific structure characterization study by electron microscopy on the B and H1N1 components, showing the structure of the product before and after splitting. However, being the structure of the flu proteins well known, this study has not been repeated since it is not mandatory. Concerning the process-related impurities, they are controlled during the process or in the Monovalent Pooled Harvest. Limits applied comply with the requirements of the Ph.Eur. monograph, where relevant. Where no limits are indicated in Ph.Eur. the applicant applied limits based on its experience. The approach is acceptable and the level of the impurities claimed for the product is appropriate to define the product as safe. No product-related impurities have been qualified for the Drug Substance. Impurities resulting from the degradation of the proteins including eventual virus residuals like nucleoprotein and matrix are controlled at release and during stability, using an SDS-PAGE method. This test ensures consistency in the purity profile of the produced lots as well as the absence of product degradation during stability.

Drug substance - Monovalent Pooled Harvest - Control of Drug Substance

Specifications and limits fulfil the requirements of Ph.Eur. for the Monovalent Bulk of a surface antigen influenza vaccine. Most of test methods are standard and well described. They are currently applied and approved for the Monovalent Pooled Harvests for Novartis non-adjuvanted and adjuvanted influenza vaccines. Method validations provided by the applicant are adequate for the Drug Substance. validation reports for mycoplasma detection, split test, spot HA and sucrose content have been provided. For the infectivity test, all the validation activities will be completed by the end of this year. The Applicant committed to provide the report as soon as available.

For sterility testing on the MPH batches, two alternative methods are presented, the compendial method (membrane filtration) and a rapid test. The routine test will be the rapid test, whereas the compendial method will be used in all those circumstances in which the rapid test cannot be used (e.g. the reader is out of service, the isolator is out of service, or the reagents and /or the plates used for the Rapid sterility testing are run out).

Batch analysis supplied for three lots of Monovalent Pooled Harvest for each of the three strains, H1N1, H3N2 and B, respectively, complies with specifications and supports batch-to-batch consistency. The set of test methods to be routinely applied to Drug Substance specifications is acceptable and provides compliance with the Ph.Eur. Some limits for impurities and endotoxins have been set up on the Drug Substance to ensure that the Ph.Eur. specification for the Final Lot is met as well.

Drug substance - Monovalent Pooled Harvest – Container closure system

Supplier(s) of the container closure system have been properly identified.

Based on the information provided by the Applicant, the stainless steel containers are suitable for storage of the monovalent bulk harvest.

Drug substance - Monovalent Pooled Harvest – Stability

The presented stability data are consistent with the stability claim for the Monovalent Pooled Harvest of a re-testing time of 1 year for the Drug Substance when stored at 2-8 °C. The post-approval stability protocol is acceptable. The commitment by the Applicant to report stability data if outside specifications is acknowledged.

Drug substance - MF59C.1 – Manufacture

The manufacturing process of the adjuvant is well documented. The flow diagrams include the operating parameters and in-process controls as recommended. The adjuvant MF59C.1 is an oil-in-water emulsion composed of squalene that is an intermediate metabolite in the synthesis of cholesterol. The other ingredients specified in the Composition are well established for use in injectable medicinal products.

Drug substance - MF59C.1 – Characterisation

The general characteristics and structure of the adjuvant MF59C.1, whose main component is squalene, are described by the applicant. Concerning the process-related impurities, those arising from the manufacturing process of the MF59C.1 adjuvant are controlled in the adjuvant bulk, as they are not expected to increase in the formulated product.

Drug substance - MF59C.1 – Control of Drug Substance of MF59C.1

Analytical procedures are in accordance with the Ph. Eur. where a monograph exists. Otherwise, specifications are adequate. The procedures are, in general, properly validated. As regards Mean particle size, accuracy is a critical parameter regarding instrument performance and therefore not part of the analytical method validation. This parameter was successfully checked during the instrument qualification process.

Data supplied for the lots of MF59 produced in Marburg with 3 different lines support batch-to-batch consistency.

Drug substance - MF59C.1 – Reference standards

There is an in house reference standard in place for MF59C.1. This standard is taken from the Company in-house manufacturing process, aliquoted by the Quality Control department and stored between 2°-8°C protected from light. The material is light and oxygen-sensitive and has a shelf-life of according to our stability studies. After opening each aliquot can be used for

Drug substance - MF59C.1 – Container Closure System

Results and the evaluation and conclusions of the toxicological assessment, are provided. Data demonstrate that there is no negative impact of bags on the quality of MF59C.1 when stored.

Drug substance - MF59C.1 – Stability

The presented stability data are consistent with the stability claim for MF59C.1 Adjuvant Bulk when filled in either glass bottles or in bags.

Drug product - Description and Composition

The main difference between the product currently licensed (Fluad MR for the elderly) and the product submitted with the current application, consists in the addition of a 0.25ml presentation: currently the 0.5ml/dose presentation is registered for use in the elderly. The primary container proposed for 0.25ml presentation is the same as that currently used for Fluad 0.5ml

Drug product - Pharmaceutical Development

Drug product - Manufacture

An example of batch formula for the Final Bulk vaccine is provided by the applicant, showing the sequence of the addition of the components and their quantity. The information provided is adequate. The manufacturing process is well documented. The flow diagrams include the operating parameters and in-process controls. In-process controls proposed by the applicant are suitable for such a process and for the following fill and finish operations. The final container for the 0.25 ml presentation is the same as the 0.5 ml presentation.

Drug product - Control of Excipients

Squalene is a commercially available natural product. Novartis has qualified different suppliers.

Drug product - Control of Drug Product

The release specifications of the final bulk and final product for the 0.5 ml presentation are the same as those approved for Fluad MR product. The release specification parameters for the 0.25 ml product are identical to those of the 0.5 ml presentation. As regards the 0.25 ml product specification limits, they are halved compared to the 0. 5 ml presentation.

Most analytical test methods are standard and well described. They are currently applied and approved for the Drug Product of Novartis adjuvanted influenza vaccines.

In general, all the validation reports provided are adequate and indicate that the assays are suitable for the purpose. The results of the Batch Analysis comply with the specifications for both 0.5 ml and 0.25 ml presentations. However, consider the above comment on the endotoxin specification limit for the 0.25 ml presentation. Tests for impurities arising from the manufacturing process of the MF59C.1 adjuvant

The specifications are justified.

Drug product - Container Closure System

The applicant has determined the leachable profile of the plunger stopper and of the tip cap material.

Drug product – stability

The stability reports for the pre-filled syringes of Fluad 0.5ml presentation of the last seasons are provided.

Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality aspect of the Fluad paediatric vaccine is considered acceptable provided that the Applicant satisfactory answers the remaining non solved issues.

Among the 6 quality other concerns, 4 are on the drug substance, and 2 on the drug product manufacturing. Unsolved issues pertain to the:

- clarification needed on the endotoxin limit in the peak fraction, in particular on an additional treatment of lots that seems in contrast with the intention to remove this optional step from the internal procedures;
- request of holding time validation data of 3 lots;
- clarification needed on the indication for INF 140 phase (Monovalent Pooled Harvest) that has a strict specification limit ; the alert limit seems inconsistent with both the alert limits of the previous phases as well as the specification limit;
- request of stability data up to 12 months;
- clarification needed on measures that will be taken when formulating the batches to prevent decrease of HA content below the acceptance limit before the end of the proposed shelf-life.
- Moreover, the Applicant is requested to present the report of the validation of the infectivity test as soon as available.

3.2. Non clinical aspects

Pharmacology

Traditional pharmacology studies are not considered relevant for a vaccine. The non-clinical data supporting Fluad is based on studies performed with Fluad or early formulations that are equivalent to Fluad (Agrippal+MF59W.1). Data from another Novartis vaccine, Aflunov (H5N1), is supportive because this vaccine contains the same amount of adjuvant. The relevant formulations are described in the table below:

Table 2.6.2.1-1 Product composition overview

Product	Composition
Fluad	Agriflu + MF59C.1
Aflunov	Monovalent H5N1 influenza vaccine, surface antigen, inactivated, adjuvanted with MF59C.1
Agrippal	Trivalent seasonal influenza vaccine, surface antigen, inactivated, non-adjuvanted, also called Agrippal S1 or Agriflu
MF59C.1	Squalene, polysorbate 80, sorbitan trioleate, citric acid, sodium citrate monohydrate, in water
MF59W.1 MF59 (water) MF59-0	Squalene, polysorbate 80, sorbitan trioleate, in water

Note: for detailed information on the composition of MF59 refer to the Quality section.

The non-clinical studies performed with Fluad to assess immunogenicity (mice, rabbits) and efficacy (mice) are the following:

Table 2.6.2.2-1 Immunogenicity and/or challenge studies with Fluad

Study number	Study type	Species	Vaccine
94-0184 93-847	Antibody response and lymphoproliferative response in young and old mice	Mouse	Fluad equivalent: Agrippal+MF59 (water)
94-0307 94-0214 94-0215	Antigen dose versus antibody response, Post-challenge lung viral load, Protective efficacy against challenge	Mouse	Fluad equivalent: Agrippal+MF59 (water)
MF-1/MF-2 2003/04	Potency study of MF59 for influenza trivalent subunit vaccine in Balb/c mice of 8 weeks and 18 months of age	Mouse	Fluad
486688	Repeat dose toxicity study with immunogenicity evaluation of Fluad and Fluad-based formulations	Rabbit	Fluad
6560-106	Repeat dose toxicity study with immunogenicity evaluation of Fluad and Fluad-based formulations	Rabbit	Fluad
488182	Repeat dose toxicity study with immunogenicity evaluation of Fluad and Fluad-based formulations	Rabbit	Fluad

Antibody Responses and lymphoproliferative response with Influenza Vaccines in Young and Old Mice - Study No. 94-0184

Groups of 9 young (3 months old) and old (18 months old) mice were immunised twice with vaccine (containing 9 µg total HA from 3 influenza virus strains, A/Beijing (X-117)/32/92, A/Texas (X-113)/36/91 and B/Panama 45/90, in a volume of 200 µL).

The vaccine was administered subcutaneously, either alone or in combination with MF59 adjuvant (water formulation). Control animals were treated with PBS. Antigen specific antibody titres were measured after the second immunisation. Two weeks after the second subcutaneous immunisation, all animals were euthanized, the spleens removed, and single cell suspensions prepared and cultured in vitro. Cells from all groups were stimulated with influenza virus for 6 days. Control cell samples from all groups were also treated with ovalbumin for 6 days or PHA for 3 days.

Study No. 94-0184 Study period: 09/1994 – 10/1994 Test material: A/Beijing 32/32 (X117) A/Texas 36/91 (X113) B/Panama 45/90 MF59 (water)	Antibody Responses with Influenza Vaccines in Young and Old Mice (94-0184)	**Findings:** A dose-related antigen-specific antibody response were elicited to all three HA antigens present in Agrippal® vaccine either alone or combined with adjuvant. The antibody response to Agrippal® in young mice was 21-to 72-fold higher that that in old mice. The addition of MF59 adjuvant to the vaccine boosted the response both in young mice (by 12- to 31-fold) and in old mice (by 19-to 253-fold), depending on the antigen
	Lymphoproliferative Response with Influenza Vaccines in Young and Old Mice (94-0184)	**Findings:** Lymphoproliferative response to non-adjuvanted influenza antigen resulted 3-fold lower in elderly mice than in young mice and MF59 can significantly increase the lymphoproliferative response in elderly mice (3-fold on average). The presence of the adjuvant increased response in young mice by 1.85-fold on average.

Antibody Response in Seropositive Young and Old Mice - Study No. 93-847

Groups of 10 young and old mice (of unspecified strain and age) were infected intranasally with a mouse-adapted influenza virus strain (A/Taiwan/1/86) and allowed to recover for 10 weeks. They were then immunised once with Agriflu vaccine (containing 9 µg total HA from 3 influenza virus strains A/Beijing 353/89, A/Taiwan 1/86 and B/Panama 45/90, in a volume of 200 µL). The vaccine was administered subcutaneously, either alone or in combination with MF59 (water) adjuvant. A control group was treated with PBS. Blood samples were taken on the day before immunisation and 2 weeks after, and sera were assayed by ELISA for antibodies to the 3 influenza antigens.

Study No. 93-847	**Method of Administration**	**Findings**
-Antibody Response in Seropositive Young and Old Mice	Subcutaneous	An antigen-specific antibody response was elicited by the vaccine in seropositive mice which had previously been infected with influenza virus. This response is more pronounced in young animals compared to that seen in elderly animals after administration of Agrippal®. The addition of MF59 (water) to the vaccine had no effect on the responses to all three antigens in young mice, but significantly (P=0.0287) increased the response in old mice by 2.5- to 7-fold, depending on the antigen.

Antibody Responses to Various Doses of Influenza Vaccine in Mice

In this studies (Nos. 94-0307, 94-0214 and 94-0215) groups of 15 eight week old Balb/C mice were immunised on day 0 and day 28 with various doses of Agrippal ('Biocine Influenza Vaccine' in the study report) containing HA antigen from each of the following influenza virus strains: A/Texas 36/91 (X-113), A/Beijing 32/32 (X-117) and B/Panama 18-19/93A). All antigen doses were administered intramuscularly in a volume of 0.025 mL mixed with 0.025 mL of either PBS or MF59 (water) adjuvant. Antigen doses ranged from 0.4-0.002 µg HA when administered with PBS, and from 0.04-0.0002 µg HA when administered with MF59 (water). On days 42, 98 and 182, blood samples were collected and sera analyzed by ELISA for antibodies to each antigen. No control group was included in this study.

Study Number		Findings
Study No. 94-0307 - Antibody Responses to Various Doses of Influenza Vaccine in Mice Study period: 12/1994-08/1995 Method of Administration: Intramuscular	**Test material** A/Texas 36/91 (X113) A/Beijing 32/32 (X117) B/Panama MF59 (water)	Immunisation of mice with Agrippal® containing various antigen doses promotes a dose-dependent increase in immune response which is maintained for 182 days. For all three antigens a cut off was evident at 0.0006µg HA. The presence of MF59 adjuvant increases the antibody response by 20- to 300-fold depending on the antigen. The enhancement of the antibody response is more evident in old mice, however a strong adjuvant effect of MF59 is also evident in young animals. Other effects: -a dose-dependent reduction in lung viral load following challenge with influenza virus. The presence of MF59 adjuvant significantly decreased the antigen dose required to give similar levels of viral titres in the lung (Study 94-0214). -a dose-dependent protection against challenge with a lethal dose of influenza virus. Immunisation with vaccine plus MF59 adjuvant improved survival, allowing 100% protection at doses 65- to 80-fold lower than those obtained with the vaccine alone (Study 94-0215).
Study No. 94-0214 -Post-Challenge Relative Viral-Load in Lungs of Immunised Mice Study period: 09/1994-07/1995 Method of Administration: Intramuscular		
Study No. 94-0215 - Protective Efficacy of Influenza Vaccines Study period: 09/1994-08/1995 Method of Administration: Intramuscular		

The study No. MF-1/MF-2 2003/04 evaluated the dose-response when various amounts of influenza trivalent subunit vaccine were combined with fixed amounts of MF59C.1 (1:1 volume-to-volume ratio), keeping the volume of injection constant. The study also evaluated the ability of MF59 to enhance the antibody response, measured using ELISA and haemagglutination inhibition (HI) assays, in young adult (8 weeks-old) and in old BALB/c mice (18 months-old).

Study No. MF-1/MF-2 2003/04 Potency study of the MF59 adjuvant for influenza trivalent subunit vaccine in Balb/c mice of 8 weeks and 18 months of age **Study Period:** 2003-2004 **Method of Administration**: Subcutaneous	**Test Material** A/New Caledonia/20/99 (H1N1) A/Panama/2007/99 (H3N2) B/Shandong/7/97 MF59C.1	**Findings:** MF59 significantly enhances the HA-specific antibody response in ELISA and HI assays for all antigens in both young and old mice allowing the reduction of the amount of HA by 100 folds or more to get antibody response induced by the non-adjuvanted vaccine. (HI against H1N1 was not performed due to limitation in the availability of sera).

Immunogenicity in Rabbits

In Studies Nos. 486688 and 6560-106, groups of 8/sex/group received 2 intramuscular administrations of Fluad 2 weeks apart (days 1 and 15). In Study No. 488182, 8/sex/group received 3 intramuscular administrations of Fluad 2 weeks apart (days 1, 15, and 29). Samples were collected for analysis prior to initiation of dosing, during in-life, and at necropsy. Samples were analyzed non-GLP using a standard HI assay. In each study, samples were tested for antibodies to at least one of the three strains contained in the trivalent Fluad vaccine to confirm immunogenicity. **Data are discussed only for animals receiving Fluad, because the other vaccine formulations tested in the toxicology studies are not relevant to this submission.** Data for individual animals from all groups are located in the toxicology reports (see below).

Title	Study period and Method of administration	Test material	Findings
Study No. 486688 (performed under GLP). Immunogenicity and local and systemic toxicity of two intramuscular doses with Fluad + adjuvant	2007-2009 intramuscular	A/Solomon Islands/3/2006 IVR-145 (H1N1) A/Wisconsin/67/2005 NYMCX-161-B (H3N2) B/Malaysia/2506/2004 MF59C.1	In both males and females treated with Fluad (Group 1) an immunogenic response (titer 80-320) was first seen 14 days after the first dose (Day 15) and two days after the second dose (Day 17). A titer of 320-1280 was observed in all Group 1 animals 14 days after the second dose (Day 29).
Study No. 6560-106 (performed under GLP).Local and systemic toxicity and immunogenicity of two intramuscular doses of MF59-adjuvanted influenza vaccine (Fluad) with or without adjuvant	2006-2007 intramuscular	A/New Caledonia/20/99 (H1N1) A/NY/55/04 (H3N2) B/Jiangsu/10/03 MF59	On Day 15, in response to the first dose administration for each test article, positive titers were detected for all three antigens, so both vaccine formulations were considered immunogenic. This was further substantiated by an increase in the titers in the Day 29 samples collected after the second administration.

Study No. 488182 (performed under GLP). Immunogenicity and local and systemic toxicity of three intramuscular doses of Fluad, Fluad formulations torabbits.	2008 intramuscular	A/Solomon Islands/3/2006 IVR-145 (H1N1) A/Wisconsin/67/2005 NYMCX-161-B (H3N2) B/Malasia/2506/2004) MF59C.1	Analysis of serum samples for neutralizing antibodies to the influenza A (H3N2) strain and Influenza B strain revealed an immunogenic response in all males and females treated with Fluad and Fluad formulations on Days 15 and 29 (14 days after the first and second dose, respectively) and after a Recovery period (Day 43).

Supportive studies with Aflunov (H5N1)

Non-clinical studies performed to assess immunogenicity and efficacy of Aflunov provide additional support for Fluad. The antigen manufacturing process is the same for Aflunov and Fluad, and both vaccines contain the same amount of MF59 adjuvant. Aflunov is monovalent (H5N1) and the doses tested non-clinically range from 0.2 to 15 µg HA per dose. The Aflunov program is summarised below.

Study number	Study type	Species	Vaccine
NIH Mouse Study	Challenge with homologous and heterologous wild-type virus	Mouse	Aflunov (Vietnam)
UBA00021	Immunogenicity data from GLP reproductive and developmental toxicity	Rabbit	Aflunov (Vietnam)
780-N007104	Challenge ~4 months post-vaccination with wild-type virus homologous and heterologous to the vaccine strain	Ferret	Aflunov (Vietnam) Aflunov (Turkey)
765-N106857	Challenge with wild-type virus homologous and heterologous to the vaccine strain	Ferret	Aflunov (Vietnam) Aflunov (Turkey)
673-N106850	Challenge with homologous wild-type virus	Ferret	Aflunov (Vietnam)
CBI-PCS-008 & VIV-PCS-001	Challenge with homologous reverse genetics virus (GLP)	Ferret	Aflunov (Vietnam)

Studies with Aflunov formulations have shown that monovalent MF59-adjuvanted influenza vaccine formulations containing antigen manufactured using the Fluad process are immunogenic (mice, rabbits, and ferrets) and protective (mice and ferret) against challenge with virus homologous or heterologous to the vaccine strain. Aflunov protected mice and ferrets against a lethal challenge with highly pathogenic virus homologous and heterologous to the vaccine strain. The immunogenicity of Aflunov has been demonstrated in mice, nulliparous then pregnant rabbits, and ferrets. Serological cross-reactivity has been demonstrated by HI and microneutralization assays.

Safety pharmacology

No dedicated safety pharmacology studies have not been performed with Fluad. An overview of the study designs and results is provided below.

Safety pharmacology evaluations – MF59 in dogs

Study No.	Test materials and intramuscular dosing schedule	Number of animals (M/F)	Cardiovascular and neurological evaluations*
Study 89-6193	0.5 mL saline (control) or 1:1 saline:MF59, 3 injections on days 1, 16 and 29	2/2	Cardiovascular: no relevant changes noted Neurology: all dogs showed normal reactions
Study 90-6231	0.5 mL buffer (control) or 1:1 buffer:MF59 3 injections on days 1, 15 and 29	2/2	Cardiovascular: no treatment-related abnormalities Neurology: no abnormalities detected

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

In Study No. 89-6193, groups of 2 dogs/sex/group received three 0.5 mL intramuscular injections of MF59 on study days 1, 16 and 29. The control group received saline. Cardiovascular and neurological evaluations were performed pre-study and prior to necropsy in week 5. Cardiovascular parameters (electrocardiograms and phonocardiograms) were recorded in untrained animals without anaesthetic. Neurological examinations for function included:

- landing or support responses
- extensor strength; tonic neck reflexes
- hopping response
- flexor reflex
- head position in lateral recumbent position
- head position in righting from lateral recumbent position
- acoustic startle response
- tactile and visual placing reactions
- standing on a straight line and pupil reaction to light

Gait observations were also performed, and included activity, muscle coordination, and wide stance of hind legs. Under the conditions of the study, three intramuscular doses of MF59 at two-week intervals did not cause any treatment-related effects on either cardiovascular or neurological parameters in dogs

In Study No. 90-6231, groups of 2 dogs/sex/group received three 0.5 mL intramuscular administrations of MF59 on study days 1, 15 and 29. The control group received buffer. Cardiovascular and neurological evaluations were performed pre-study and prior to necropsy in week 5. Electrocardiograms were recorded and examined visually for electrical complex abnormalities and numerical data consisting of the R-R interval (from which the heart rate was derived) P-R, QRS and QT intervals were extracted. Neurological examinations were performed by a veterinarian, and included proprioception (hind and forelimb), righting reflex, posture and gait, hind limb pinch reflex, and anal sphincter tone. Under the conditions of the study, three intramuscular doses of MF59 given at two-week intervals did not cause any treatment-related effects on either cardiovascular or neurological parameters in dogs.

Pharmacokinetics

In accordance with current guidelines, pharmacokinetic or classic absorption, distribution, metabolism and excretion (ADME) studies with Fluad were not conducted because such studies are not considered relevant for a vaccine. Since the squalene component of MF59 is involved in normal metabolic pathways, distribution and clearance of squalene has been evaluated.

Squalene is an intermediate in the biosynthesis of cholesterol and is a natural constituent in dietary products, which include vegetable and fish oils. The small volume of squalene administered with each vaccination is unlikely to have measurable metabolic implications.

The distribution of MF59 after intramuscular injection in mice was evaluated. The goal of the study was to determine the distribution of MF59 injected with soluble antigen gD2 from type 2 herpes simplex virus (HSV) and to compare the distribution of gD2 injected with or without MF59. At 4 hours, 36% of the injected dose of labelled MF59 was in the quadriceps muscle and about 50% was in the inguinal fat surrounding the muscle. Half of the initial amount of labelled MF59 in muscle was detected 42 hours after injection. The amount of labelled MF59 in the draining lymph nodes was maximal 2 days after injection, which represented 0.1±0.3% of the injected dose. At 4 hours, 12% of the injected dose of labelled gD2 was found in the muscle. The presence of MF59 did not significantly modify the distribution of gD2. The results indicate that MF59 and gD2 distribute and are cleared independently after intramuscular injection.

Clearance studies in rabbits injected intramuscularly with 125I-squalene labelled MF59 demonstrated that the adjuvant is rapidly cleared. Only 10% of the administered squalene remained at the injection site at 6 hours post-injection and decreased to 5% at 120 hours after injection.

Toxicology

Ecotoxicity/environmental risk assessment

Ecotoxicity/environmental risk assessment studies have not been conducted. This is acceptable according to the guideline Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00).

Discussion on non-clinical aspects

Because this application is based on Fluad for the elderly and Agrippal, the non-clinical studies with these vaccines and the supportive studies with MF59 adjuvant form the basis of non-clinical sections of this dossier. This is justifiable because the manufacturing processes for all these products are the same and, in some case, also the formulation is the same.

Primary pharmacodynamic

The data submitted by the Applicant evidenced immunogenicity results in old and young mice and in rabbits and clearly demonstrated that MF59 enhances the HA-specific antibody titres to H1N1, H3N2 and B in both young and old mice. Moreover, these studies have been extensively evaluated during previous Novartis' vaccine registration procedures.

No studies in the ferret model have been performed with Fluad. The Applicant has mentioned some supportive studies based on Aflunov: protective activity using the ferret model, immunogenicity using the mouse model and reproductive/developmental toxicity study in rabbits. These studies were not included in the dossier but they have been extensively evaluated during the Aflunov registration procedure.

These experiments demonstrated that Aflunov is more immunogenic than non-adjuvanted H5N1 antigens. The antibodies induced by Aflunov cross-reacted with at least one heterologous strain of

H5N1 virus. Furthermore, Aflunov induced protection from homologous and heterologous viral challenge in mice. The vaccine was effective in preventing clinical signs of illness/death and viral replication in brain, lung and spleen, in mice challenged with homologous or heterologous H5N1 virus.

Aflunov was immunogenic in maternal rabbits, developing foetuses and in F1 pups. In particular HI titres were measurable beginning on day 15 of the study in all treated animals. HI titres increased or remained sufficiently elevated to demonstrate continued immune response to the vaccine. Interestingly, anti-influenza antibodies were detected in all foetal pooled samples at the time of C-sectioning at levels comparable to those of respective maternal sample. The antibodies persisted through the first 4 weeks of life in F1 offspring.

Efficacy data from ferret studies indicated the protective and cross-protective efficacy of Aflunov vaccine formulations in ferrets given a lethal challenge of highly pathogenic avian influenza (HPAI).

Secondary pharmacology (safety)

No dedicated safety pharmacology studies have been performed with Fluad. However there are sufficient clinical tolerability data available in humans with Fluad, Aflunov and Agrippal to override these concerns. Moreover, there is pertinent information on MF59 adjuvant that provides supportive data. These data have already been assessed during the Fluad first registration application. Two repeat-dose dog studies were conducted to evaluate the toxicity of vaccine formulations with antigens that are unrelated to this dossier.

No treatment-related effects on either cardiovascular or neurological parameters in dogs have been observed after treatment with three doses of 0.5ml of MF59 given intramuscularly. Based on these data, and also considering the known safety of influenza antigens and Fluad in animals and humans, the risk of unanticipated secondary or safety pharmacological effects in subject receiving Fluad is considered extremely unlikely.

Lachrymal glands model was not included in the standard package of tissues in repeated dose toxicity studies performed by the Applicant for MF59 adjuvant. Recent data on other adjuvants (Van der Laan et al, 2008) have highlighted a slight increase in the apoptosis/necrosis of acinar cells in lachrymal tissues. These minimal histological findings were not associated with any microscopical structure changes in the eyes and with any ophthalmologic dysfunction.

Pharmacokinetics

Owing to the nature of vaccine, the guideline for non-clinical testing of vaccines (CPMP/SWP/465/95) and the guideline on adjuvants (EMEA/CHMP/VEG/134716/2004) state that pharmacokinetic studies are not needed. This concept can be extended also for drug-drug pharmacokinetic or pharmacodynamic interaction studies. Such non-clinical studies would not provide clinically-relevant information. Then, according to its status as a vaccine, it is acceptable that no formal studies on pharmacodynamic drug interactions have been conducted.

The MF59 adjuvant is rapidly cleared in rabbit suggesting a low toxicity of the adjuvant when administered intramuscularly. Only 10% of the administered squalene remained at the injection site at 6 hour post-injection and decreased to 5% at 120 hours after injection.

Toxicology

The toxicology program was designed based on Doc. Ref. EMEA/CHMP/VWP/263499/2006, CPMP/VEG/4717/03, and appropriate global regulatory requirements for the non-clinical testing of vaccines and adjuvants. The toxicology aspects of Fluad, consists of GLP studies in Guinea pigs and

rabbits, are derived from data generated of non-clinical Fluad and Agrippal licensed formulations and a "Reproductive toxicity study in rabbits" performed with Aflunov. This latter study provided additional information on the candidate vaccine itself because it demonstrated that the vaccine was immunogenic in maternal rabbits and developing foetuses and antibodies persisted through the first 4 weeks of life in F1.

No single dose toxicity study was performed with Fluad consistently with the WHO Guideline on Non-clinical Evaluation of Vaccines (WHO Technical Report No. 927, 2005) and the Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95).

In the Fluad program, toxicity after a single dose of vaccine was assessed during all repeat dose studies. No necropsies were performed after a single dose of vaccine, however all in-life parameters were evaluated, and no evidence of toxicity was observed.

In all repeat dose toxicity studies, comprehensive evaluations of local and systemic toxicity were performed, and a recovery period was included to assess delayed effects and reversibility. The vaccine formulations used (Fluad, Agrippal, Aflunov and different MF59 formulations) were well tolerated locally and systemically.

Because Novartis is now applying to extend the Fluad age indication to children aged from 6 months to less than 9 years of age, the need for toxicity studies in juvenile animals was evaluated. Because there is no vaccine-specific guidance, the evaluation was based on EMEA/CHMP/SWP/169215/2005 (Guideline on the need for nonclinical testing in juvenile animals of pharmaceuticals for paediatric indications). In the case of Fluad, no additional non-clinical study was warranted because no target organ or systemic toxicity was identified and no adverse or irreversible reactions were observed in any non-clinical study. The safety of Fluad has been assessed clinically in children, and administration of the vaccine resulted in the same pharmacological effect (elicitation of antibodies) in children and adults. Because the nonclinical and clinical programs did not identify any finding that requires additional investigation, it was concluded that studies in juvenile animals are not necessary. The delayed contact hypersensitivity potential of Fluad was investigated using the Magnusson-Kligman Maximization Test (Study No. 564110). Female Dunkin-Hartley Guinea pigs (10/group) were used in this study. Based on range finding, Fluad was used without dilution. Fluad was not a skin sensitizer in Guinea pigs in this study.

MF59 adjuvant

A stand-alone toxicology program was conducted for MF59 adjuvant. In general, MF59 is not associated with any potential for systemic toxicity and it has a low order of local reactogenicity.

Conclusion on non-clinical aspects

The pre-clinical program of Fluad has been performed over a long period of time (more than 15 years) and includes testing seasonal HA antigens from different viral strains.

Moreover, a summary of studies performed with the monovalent H5N1 MF59-adjuvanted influenza vaccine Aflunov has been provided. Aflunov and Fluad contain the same amount of MF59, and the antigens in both vaccines are manufactured using the same process; the content of antigen is different being in Aflunov half than in Fluad paediatric (7.5 ug vs 15 ug per 05 ml), moreover the intrinsic characteristic of the antigens included are different as Aflunov is based on antigens of a virus from avian origin and Fluad on human adapted viruses. However, data obtained with Aflunov are considered supportive of the adjuvant role of MF59.

Pharmacology studies are in line with the requirements of the current CHMP and WHO guidelines. Nonetheless, it would have been desirable to have a more complete set of data, i.e. data obtained with the final MF59 formulation, all studies (and not only some of them) being performed under GLPs, more combinations of antigen—adjuvant tested; more comprehensive data on the immunogenicity and protection conferred by the seasonal vaccine in rabbits and ferrets. Regarding study in the ferret model (the animal model preferred for non clinical testing of seasonal vaccines), the Applicant has mentioned some supportive studies based on Aflunov: protective activity using the ferret model, immunogenicity using the mouse model, and reproductive/developmental toxicity study in rabbit. These studies were evaluated during the Aflunov registration procedure but not included in the dossier.

Despite these deficiencies, it is considered that the pharmacology documentation submitted by the MAA is sufficient, taking into account that the vaccine was authorized firstly in Italy in 1997, and it is now registered in more than 30 countries and that its immunogenicity and safety have been tested in many clinical trials in different age populations.

The Applicant justification for not conducting studies on juvenile animals could be accepted only if clinical data in children would show, besides safety that clinical protection was obtained with all the three strains. Although clinical data on efficacy and safety in the paediatric population are available VE only against the A strain was successfully estimated. Clinical data provided by the Applicant are therefore not considered sufficient alone to justify the extrapolation of VE from A to B strains, also taking into consideration the opinion of VWP which recommended the use of additional methods (e.g. serological results and in vivo model data). The Applicant should address this issue in its response to the clinical major objection Q2. Moreover, pre-clinical data on multiple administration (in different seasons) of Fluad paediatric are still lacking, and insufficient information on this issue is provided by clinical trials. In this context, it is considered that pre-clinical data cannot vicariate for the lack of clinical data. Thus, in the absence of clinical data, additional data in animals are not considered useful to solve this issue. The Applicant is requested to submit clinical data on annual re-administration (see the clinical major objection Q3).

3.3. Clinical aspects

Tabular overview of clinical studies

Pharmacokinetics/Pharmacodynamics

According to the EMA Note for Guidance on Clinical Evaluation of New Vaccines, PK studies are generally not required for injectable vaccines, and kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations, thus pharmacokinetic studies are generally not required and therefore were not performed for Fluad development.

No pharmacodynamic studies were conducted and information on characteristics of the immune response according to the known or presumed activities of the vaccine was based on previous experience in the development of influenza vaccines. Therefore no reports are provided in this application.

According to the CHMP Note for Guidance on the Harmonization of Requirements for Influenza Vaccines, CPMP/BWP/214/96 and in compliance with the European Pharmacopoeia requirement (European Pharmacopoeia Commission, 1999), one dose (0.5mL) of Fluad MRP contained 15 µg hemagglutinin (HA) for each of the strains: A/H1N1, A/H3N2, and B, as recommended annually by

WHO (http://www.who.int/wer/en/) and CHMP. In the Fluad paediatric clinical studies, the vaccine is administered with a similar dosing regimen to other vaccines that are licensed for administration in the paediatric population.

Methods for Immunogenicity Assessment

Limited knowledge has been gathered on the efficacy of influenza vaccines in infants and toddlers. Protection against influenza is mainly conferred by serum antibodies, although mucosal IgA antibodies and cell mediated immune responses also may contribute (Weekly Epidemiological Record, 2002). Therefore the efficacy of influenza vaccines is generally assessed using a serological surrogate of protection, HA antibody. A serological correlate of protection in the childhood population has not yet been identified. As a reference for evaluation of seasonal influenza vaccines for use in children, the CHMP criteria for assessment of vaccine immunogenicity in adults aged 18 to 60 years are commonly used (shown in the table below).

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

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

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

As Guideline on scientific documentation to be submitted for approval of influenza vaccines are under revision on the specific issue the VWP has been consulted:

Question: Are the CHMP serologic criteria for estimating vaccine efficacy against influenza applicable to vaccine with primary paediatric indication?

VWP response: The CHMP serology criteria were derived from data obtained in healthy adults and using unadjuvanted vaccines. These criteria are of unknown relevance for predicting the efficacy of Fluad in children and therefore are not applicable.

Therefore, results from immunogenicity cannot be assessed using the CHMP criteria as a reference for efficacy. CHMP criteria should be considered as the minimal criteria to be fulfilled and have been presented for many analyses.

The Applicant has attempted to establish the correlation between antibody titers and observed clinical efficacy in the pivotal study. Results suggest that a much higher antibody titer (HI >320 compared to HI>1:40) is associated for H3N2 to VE of 80%.

The immune response was evaluated by haemagglutination inhibition (HI) and single radial haemolysis (SRH) assays, and Microneutralization (MN). In the largest study SRH and MN assays were performed on a sub-set samples

Microneutralization

In the present application, MN assay results are presented using the following arbitrary (as no defined criteria have been set) values:

- percentages of subjects achieving an antibody titer of at least 1:80,
- percentages of subjects achieving 4-fold increases in MN titers from pre- to post-vaccination,
- GMTs and mean geometric increases in MN titers from pre- to post-vaccination.

No data on CMI have been provided.

Discussion on clinical pharmacology

It should be mentioned that the current guideline on clinical evaluation of new vaccines is the guideline EMEA/CHMP/VWP/164653/2005 that replaced the old one (CPMP/EWP/463/97), which is the one mentioned by the Applicant. Nonetheless, the new guideline states that "Pharmacokinetic studies are usually not required for vaccines" but it also mentions that "However, such studies might be applicable when new delivery systems are employed or when the vaccine contains novel adjuvants or excipients. The need for pharmacokinetic studies and their design should be considered on a case by case basis and it is recommended that applicants should obtain scientific advice from EU Competent Authorities".

The presence of adjuvant MF-59 in Fluad may be interpreted so as to ask for Pharmacokinetics studies. However, taking into account that the adjuvant MF-59 has been used as a component of the seasonal vaccine authorized by MR in 1997 and also as a component of the pandemic H1N1 vaccine Focetria, it is considered that MF-59 is not a novel adjuvant and thus it is agreed with the company that pharmacokinetics studies are not needed.

Conclusions on clinical pharmacology

In the guideline EMEA /CHMP/VWP/164653/2005 it is stated: "In relation to vaccines, pharmacodynamic studies are essentially comprised of the immunogenicity studies that characterise the immune response to the vaccine". The Applicant has provided immunogenicity data obtained in several clinical trials and these data are discussed later in this Assessment Report in the context of the individual clinical studies.

The guideline also indicates that a comprehensive analysis of the immune response induced by the vaccine should be performed. In this regard, we are making here some general comments that will be discussed later in further detail:

- The guideline indicates that all the immunological tests used should be validated. We have found no validation report of the Microneutralization (MN) test.

- The guideline mentions that both the humoral and cellular immune response should be studied, but the dossier submitted includes no analysis of cell-mediated immune response.

The Applicant is currently performing a randomized, controlled, observer-blind, phase II study (V70_34) that investigates the CMI response to Fluad to evaluate how the adjuvanted vaccine activates cell-mediated immunity and the antibody response, and to evaluate if there is any correlation between the two, in previously unvaccinated healthy subjects aged 6 to <36 months.

Clinical efficacy

Fluad Paediatric is a trivalent influenza virus vaccine, containing purified haemagglutinin (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 WHO and CPMP for the Northern Hemisphere,

adjuvanted with MF59C. The current application is based on 4 clinical studies, among which an efficacy trial aimed to show the degree of protection conferred to children aged between 6 and 71 months compared to non vaccinated children (absolute efficacy) and to children immunized with seasonal non adjuvanted vaccines (relative efficacy). Immunogenicity has also been assessed across all the studies and the effect of repeated immunizations with one exploratory study. The observations collected in studies on the pandemic vaccine H5N1 Aflunov are also reported as supportive data.

Overall in the clinical development of Fluad in children from 6 months to 8 years two phase 2 studies (V70P2, V70P6), one pivotal phase 3 study and one exploratory study on seasonal re-vaccination study were conducted.

Additionally results for Fluad in paediatric population 6 months to 17 years are available from 2 supportive studies [V87P6 (safety of 2 doses of H5N1-Focetria in 334 children 6 months to 17 years compared to 137 recipients of Fluad of the same age) and V7P29 (immunogenicity and safety of 1 dose of Fluad in 116 children 9 to 17 years of age)].

Table 2.7.3.3.1-4 Inclusion of Subjects in the Immunogenicity Analysis – Phase 2 Studies

Age range	6 to <36 months						36 to <72 months				9 to 17 years	
Study	V70P2		V70P2E1[a]		V70P6[d]		V70P2E1[b]		V70P6[c,d]		V7P29	
Vaccine group	Fluad	Vaxigrip	Fluad	Vaxigrip	Fluad	Fluzone	Fluad	Vaxigrip	Fluad	Fluzone	Fluad	Fluogen/ Flushield
Total vaccinated	130	139	25	23	136	132	18	23	44	48	116	100
Immunogenicity PP Population (%)	104 (80)	118 (85)	23 (92)	20 (87)	97 (71)	102 (77)	18 (100)	20 (87)	23 (52)	20 (42)	106 (91)	92 (92)

[a] actual age 16 to <36 months; [b] actual age 36 to <48 months; [c] actual age 36 to <60 months
[d] As the difference between the PP and FAS populations was >10%, a supplementary analysis was performed on the FAS; these data are provided in the CSR for V70P6 in Section 5.3.5.1.
Source: V70P2 CSR Table 14.1.1.1 and Table 14.1.1.3.2; V70P6 CSR Table 14.1.1.1.2; V7P29 CSR Table 12.2

Dose-response studies and main clinical studies

Each adult dose of Fluad (licensed for use in elderly) contains 15µg of hemagglutinin (HA) from the H1N1, H3N2 and B strains and MF59 (squalene content of 9.75 mg per dose) in a total volume of 0.50 ml.

Specific studies aimed to establish the optimal amount and proportion of antigens and adjuvant for paediatric population have not been performed. In the development of the pandemic vaccine different amounts of antigen were explored but with a fixed amount of adjuvant. That approach was accepted under the special circumstances of licensure and use of the vaccine.

For the seasonal trivalent vaccine the content and mode of use proposed by the Applicant are simply in line with the current practice of not-adjuvanted product, which may not be fully appropriate.

Results from retrospective effectiveness studies with not-adjuvanted vaccines (Allison 2006, Ritzwoller 2005), a case control study (Shuler 2007) and immunogenicity studies (Neuzil 2006, Walter 2006, Englund 2006) indicate that antibody responses are substantially higher when young children are given 2 doses. They are the basis for the recommendation that all children aged 6 months to 8 years who are being vaccinated for the first time should receive 2 vaccine doses separated by ≥4 weeks.

The Applicant has provided data supporting the acceptability of the chosen dose, proposed dose schedule, and formulation of the final product with the following considerations:

i) Immunogenicity against CHMP criteria. CHMP criteria were met with the proposed posology used in the paediatric studies. Results from studies V70P2, V70P6 and the pivotal efficacy study showed that

two vaccinations with Fluad were needed to meet all CHMP criteria for the B-strain in unprimed (seronegative at baseline) children 6 months to <36 months and 36 months to <72 months of age (results are presented in Section 2.7.2.3.1). In two out of three studies with data on immunogenicity Fluad was significantly better than non-adjuvanted influenza comparator following two doses. In study V70P6 actually the advantage of Fluad over the comparator in subjects seronegative at baseline was limited or absent. In the pivotal efficacy study, superiority for all 3 strains in immunogenicity was only clearly met after 2 doses. This was particularly evident for the B strain responses.

ii) Demonstration of efficacy using the proposed posology in the pivotal efficacy study. The absolute vaccine efficacy was estimated from one study to be 81.36% (95% CI: 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, although increased reactogenicity, in both age groups. The efficacy was significantly higher relative to non-adjuvanted influenza vaccine control.

The clinical data from a total of five randomized, controlled, observer-blind studies are submitted in support of an indication for the use of Fluad in infants and children from 6 months to 8 years of age.

All studies enrolled children in general good health, as determined by medical history and physical examination at study entry. Children with a serious disease (e.g. 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 to be enrolled. In response to the LoQs the Applicant reported that some children enrolled were affected by medical conditions and additional analyses were provided. Children were not to have been administered licensed vaccines within a 4-week period prior to enrollment; this was shortened to 14 days for licensed inactivated vaccines in the pivotal efficacy study and in study V70P6. In the pivotal efficacy study the inspection reported that most enrolled children received Prevenar but no systematic recording of the vaccinations and of the date of administration was performed.

Overall in the presented studies a total of 5849 children 6 months to <18 years of age were enrolled. Of these, 2,498 were enrolled to receive Fluad and 3,356 to receive control vaccine (either licensed influenza vaccine [2,317 subjects] or non-influenza control [1,039 subjects]).

During the assessment of the pivotal study the need to exclude at least one specific study site were data were suspected to be false further lower the amount of observations for the safety database, whose size is becoming critically small.

Summary of main efficacy results

Main results on immunogenicity
Summary of immunogenicity Results Against Homologous Strains

Children 6 to <36 months of age
A higher immune response to Fluad than to a non-adjuvanted influenza vaccine was already evident at 4 weeks after the first vaccination (i.e. study day 29) with higher GMTs and GMRs observed, especially for the two A influenza strains. Nevertheless, immunogenicity data in children of this age showed that, particularly for the B-strain immune response after 1 vaccination was not sufficient to meet all 3 CHMP criteria. In studies V70P2 and in the pivotal efficacy study no CHMP criterion was met for any of the vaccines for the B strain and in study V70P6 only CHMP criterion for GMR after Fluad vaccination was met for the B-strain for details refer to Section 2.7.2.3.1of the Fluad dossier.

Upon CHMP request, data on immunogenicity obtained by the two phase II studies and by the pivotal one were re-analyzed using the same age groups.

A selection of the comparative data on subjects seronegative at baseline from the three studies are shown below:

Figure 45-7

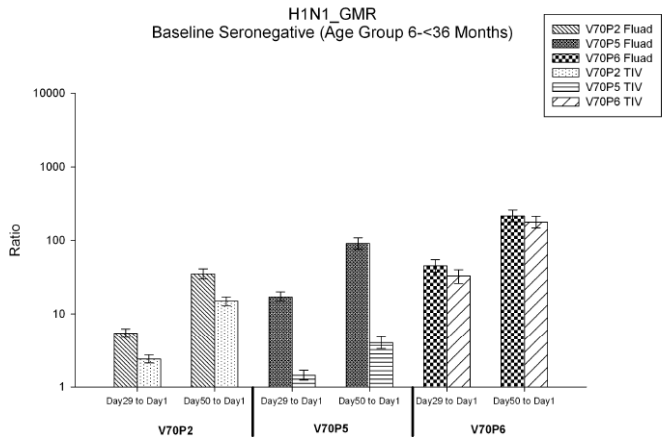


Figure 45-8

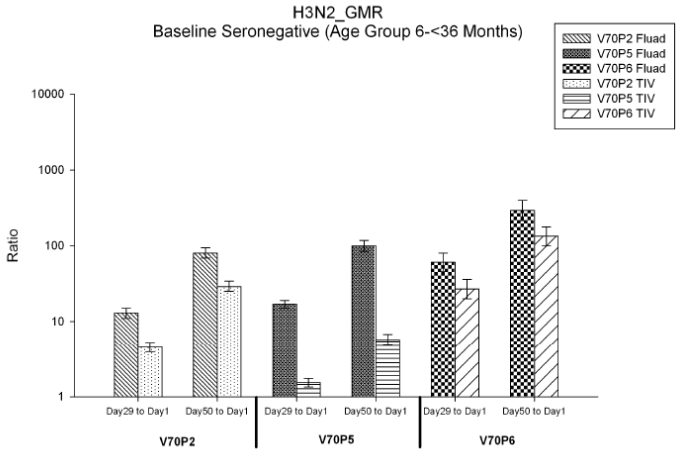
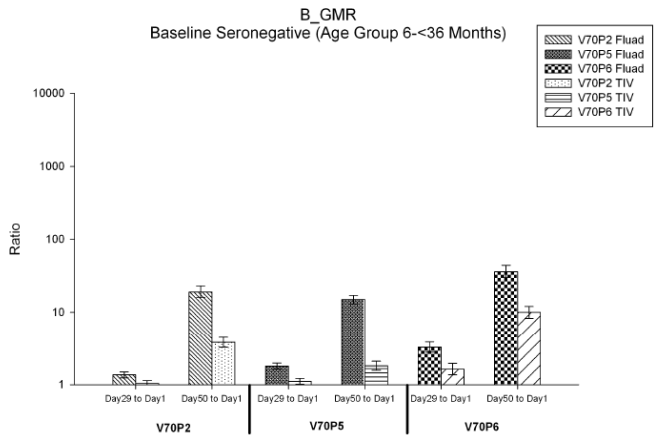


Figure 45-9



When considering GMR across the three studies it is evident that the largest difference in favour of FLUAD has been obtained in the pivotal efficacy study which is pivotal also for immunogenicity evaluation. In study V70P6 limited or no advantage is observed at day 50 for A viral antigens of FLUAD compared to TIV in each of the two age-groups

Similar graphs have been provided for seroconversion and seroprotection and the differences between adjuvanted and TIV products are mostly obtained by the pivotal study while V70P6 is not indicating clear advantages of FLUAD in seroprotection or seroconversion against H1N1 or H3N2 antigens.

Figure 45-13

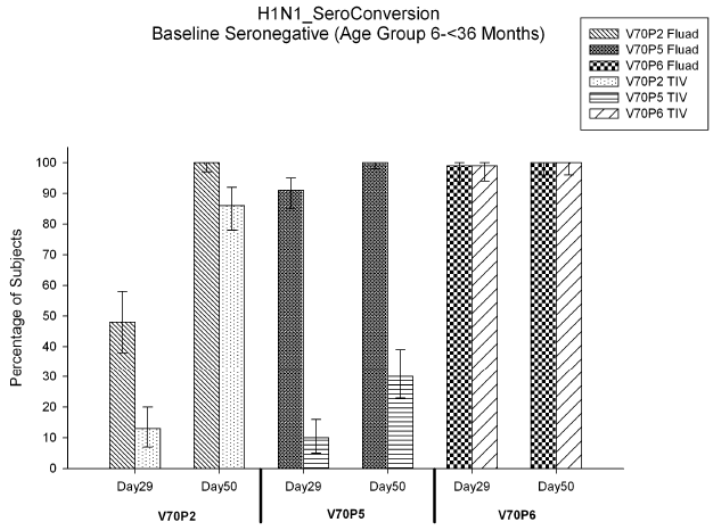


Figure 45-14

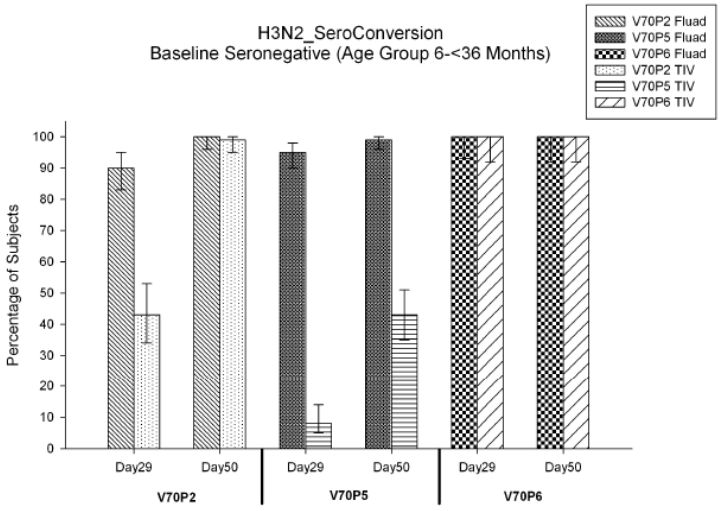


Figure 45-15

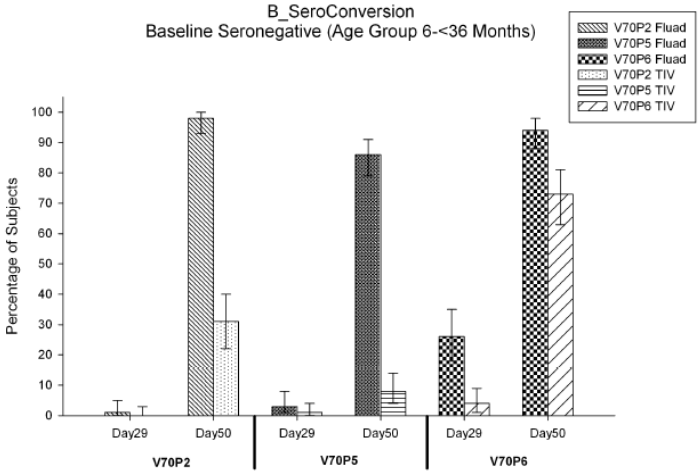


Figure 45-19

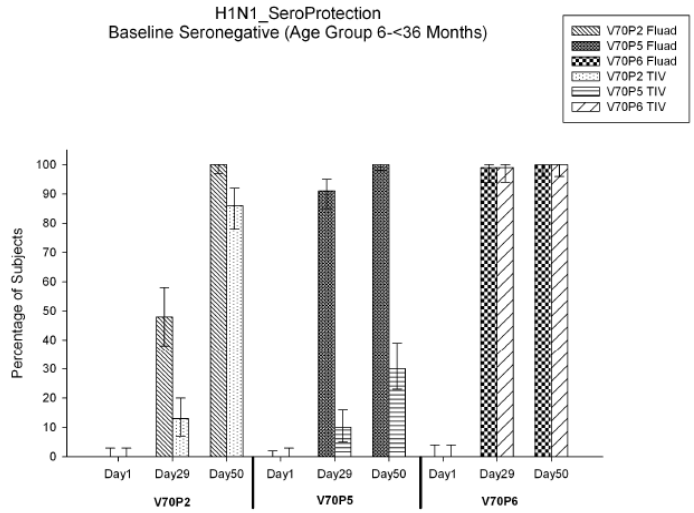


Figure 45-20

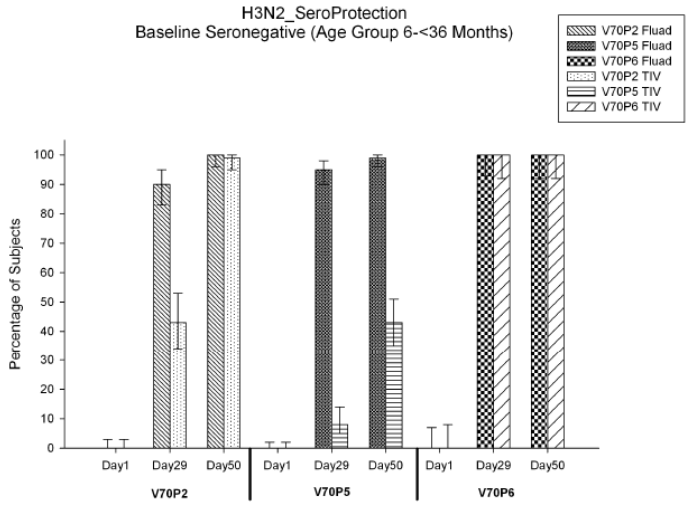
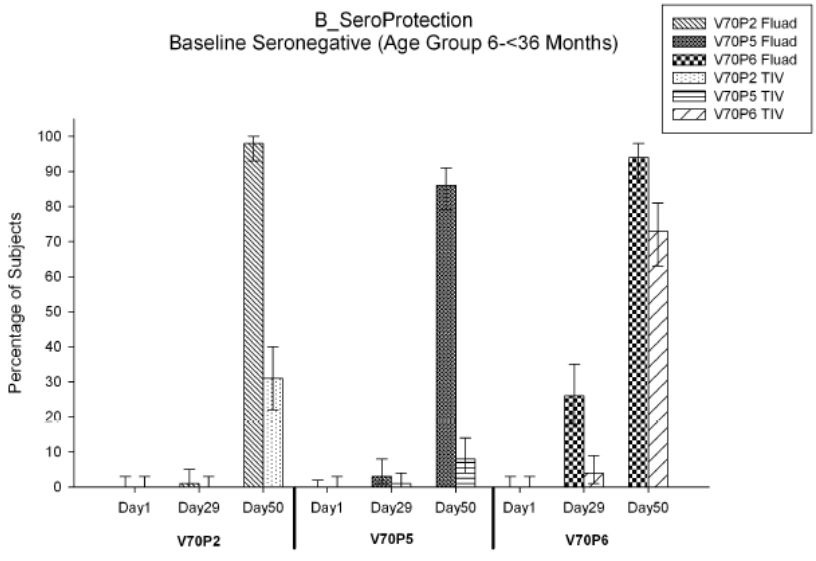


Figure 45-21



Children 36 to <72 months of age

A comparative analysis for subjects seronegative at baseline is presented as already explained above for children 6-36 months of age. Results are similar.

Figure 45-10

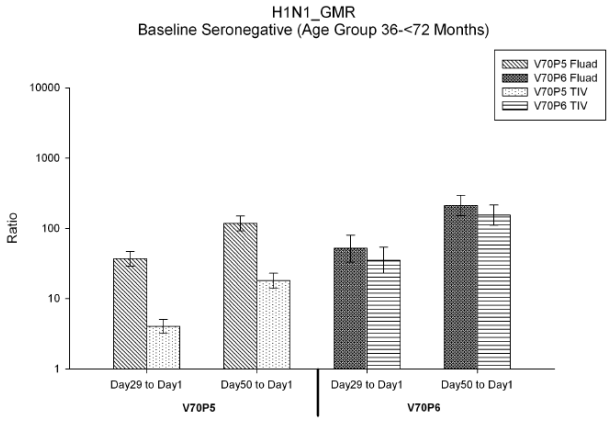


Figure 45-11

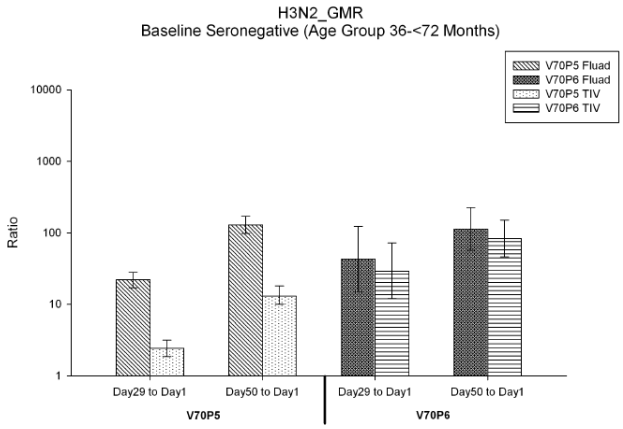


Figure 45-12

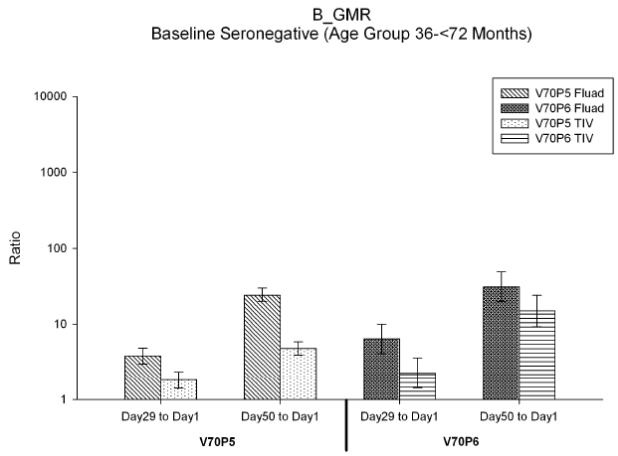


Figure 45-16

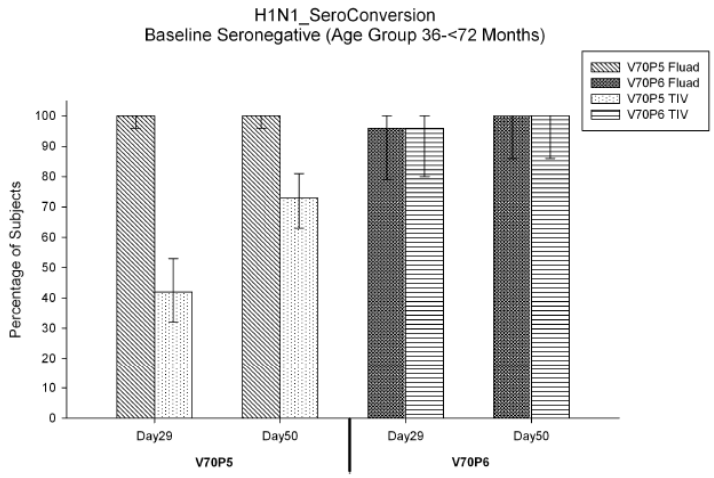


Figure 45-17

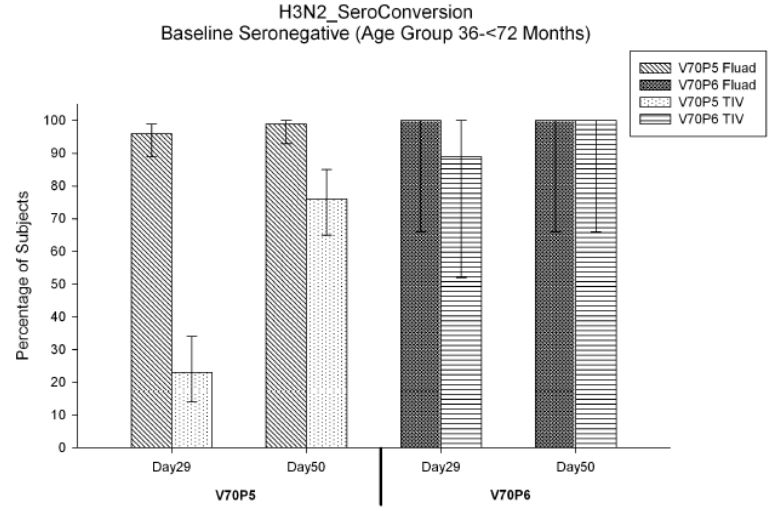


Figure 45-18

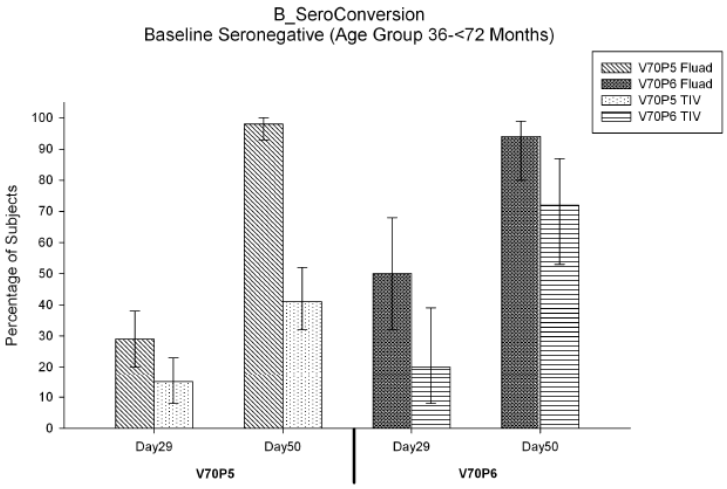


Figure 45-22

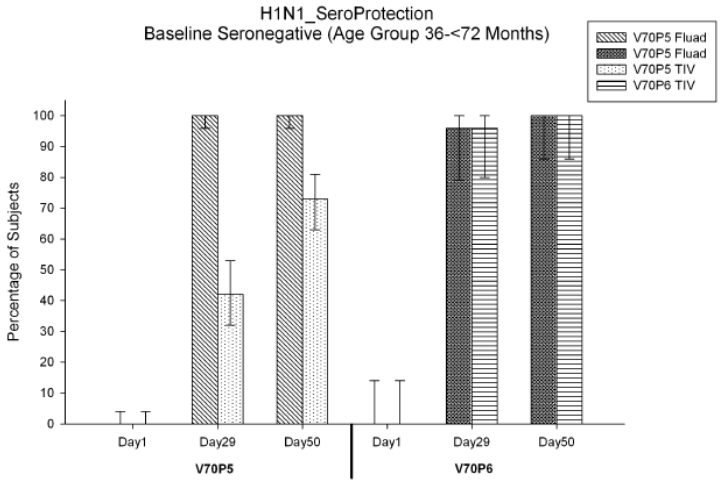


Figure 45-23

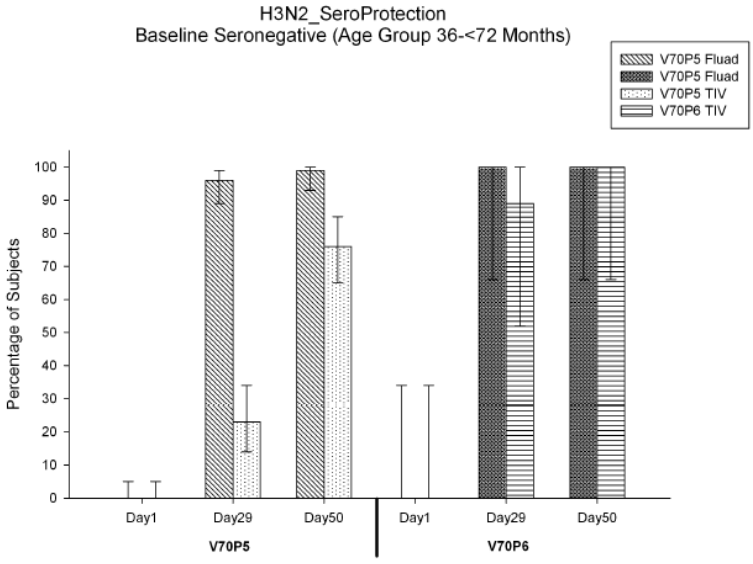
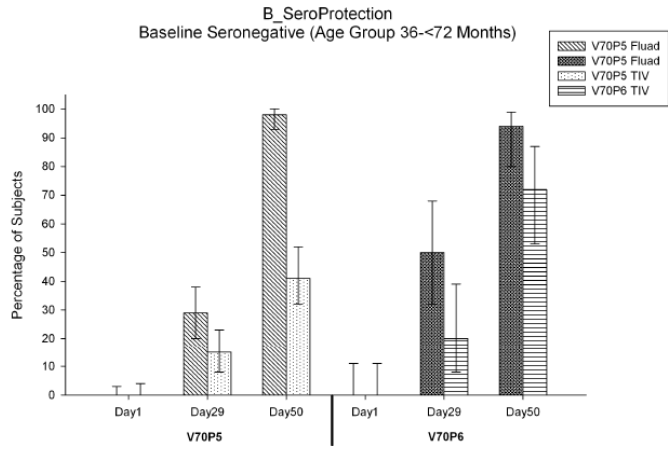


Figure 45-24



Pivotal efficacy phase III study

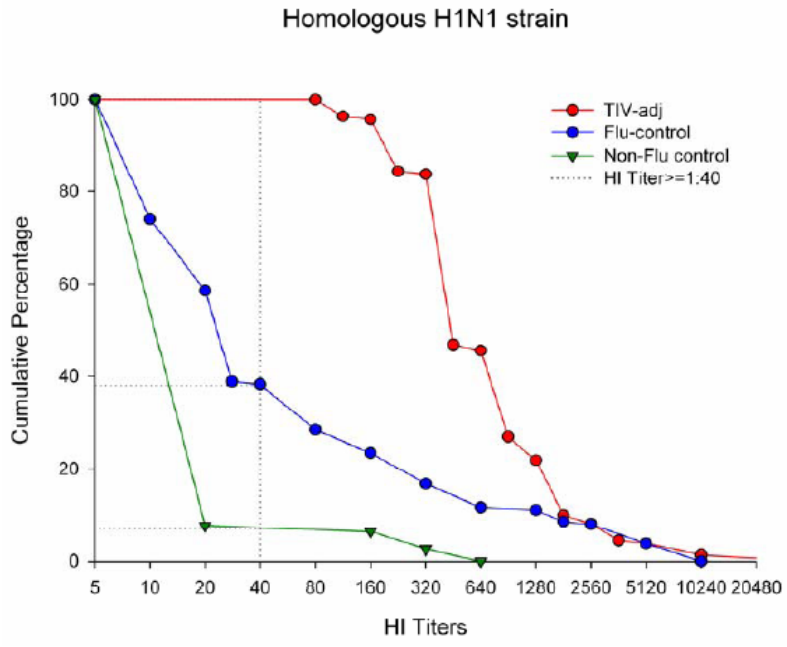
Immunogenicity after 2 half doses (0.25mL) of Fluad in previously unvaccinated children 6 to <36 months of age

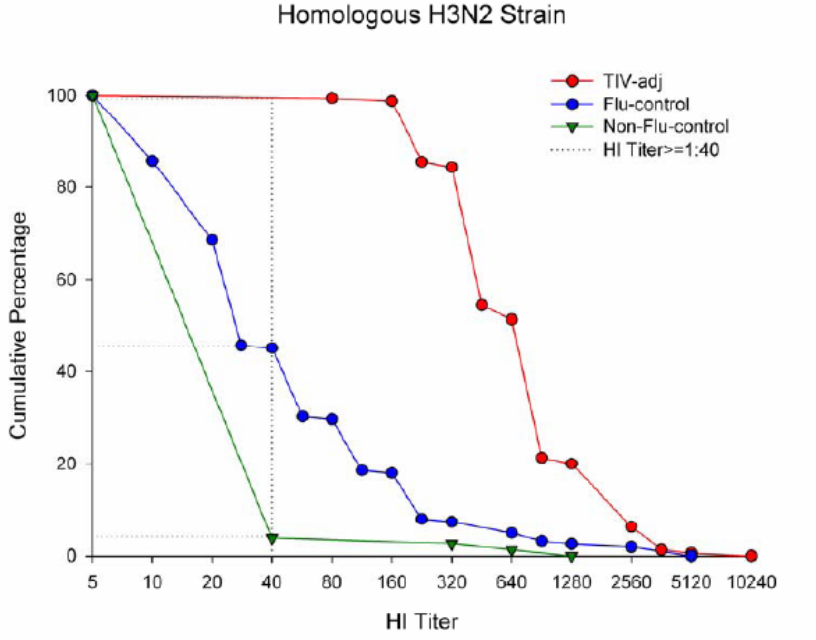
Independent from the assay (HI or SRH) all 3 CHMP criteria defined for adults were met 3 weeks after 2 vaccinations with 0.25mL of Fluad (Tables 2.7.3.3.2.2-1 and 2.7.3.3.2.2-2). After 2 vaccinations with 0.25mL Influsplit (flu control) with HI assay 1 out of 3 CHMP criteria was met for H1N1, 2 out of 3 CHMP criteria were met for H3N2 and no CHMP criterion was met for the B-strain.

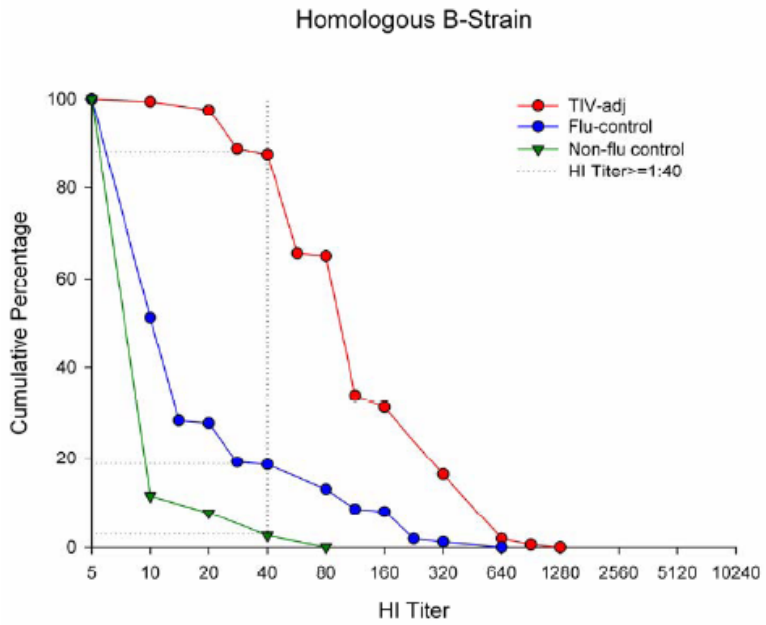
With SRH assay 2 out of 3 CHMP criteria were met for H1N1 and no criterion was met for H3N2 and B strain. Immunogenicity of Fluad in this age group was significantly higher than immunogenicity of Influsplit. The lower limit of 2-sided 95% CI for vaccine group ratios Fluad to Influsplit of HI and MN GMTs/SRH GMAs and GMRs was above 1 for all 3 strains (Table 2.5.4.5.1-1). The lower limit of the 2-sided 95% CI for vaccine group differences for seroprotection (HI), percentages of subjects with MN titer ≥1:80, seroconversion/significant increase (HI) and at least 4 fold increase of MN titer were far above 0.

The figures below show reverse cumulative distribution of HI titers from the pivotal efficacy Study.

Figure 11.4.1.6-1: Reverse Cumulative Distribution of HI Titers Against Homologous Strains at Day 50 in 6 to <36 Months Age Group-Season 2008/09







As shown by the reverse cumulative distribution of HI titers, response to the B antigens are lower compared to A antigens. By applying the cut-off indicated by the Applicant for H3N2 (HI>320) to predict a VE of 80%, it is noted that very few subjects reach the threshold indicating VE towards the B strain.

Children 36 to <72 months of age

Similar to the younger age group also in children 36 to <72 months the higher immunogenicity of Fluad compared with non adjuvanted influenza vaccines was already evident 4 weeks after the first vaccination (day 29) with higher GMTs and GMRs observed, especially for the two A influenza strains. Nevertheless due to the low immunogenicity in the B-strain particularly regarding seroprotection in unprimed children only 1 vaccination is also considered as not sufficient in unprimed children of this age group (for details refer to Section 2.7.2.3.1).

Immunogenicity after 2 doses (0.5mL) of Fluad

Independent of the assay (HI or SRH) all CHMP criteria defined for adults were met 3 weeks after 2 vaccinations with 0.25mL of Fluad (Tables 2.7.3.3.2.2-1 and 2.7.3.3.2.2-2).

After 2 vaccinations with 0.25mL Influsplit (flu control) with the HI assay all CHMP criteria were met for the 2 A strains and 2 out of 3 CHMP criteria were met for the B strain (seroprotection criterion was not met). With the SRH assay 2 out of 3 CHMP criteria were met for H1N1 (seroprotection criterion was not met) and all criteria were met for H3N2 and B strain. Even though the differences between vaccination groups were slightly smaller in this age group compared with the younger children, the immunogenicity of Fluad in this age group was still significantly higher than the immunogenicity of Influsplit as measured with the HI and MN assays. The lower limit of the 2-sided 95% CI for vaccine group ratios Fluad to Influsplit of GMTs and GMRs was above 1 for all 3 strains (Table 2.5.4.5.1-1). The lower limit of the 2-sided 95% CI for vaccine group differences for seroprotection (HI), percentages of subjects with MN titer ≥1:80, seroconversion/significant increase (HI) and at least 4 fold increase of MN titer were above 0. Due to the small sample size (22 subjects in the Fluad group and 15 subjects in the Influsplit group) results with SRH should be interpreted carefully.

Table 2.5.4.5.1-1 Vaccine group ratios or differences Fluad to Influsplit on Day 50 – pivotal trial FAS-season 2008/2009

Age group		6 to < 36 months[d]			36 to <72 months[e]		
		HI	SRH	MN	HI	SRH	MN
H1N1	GMT ratios (95% CI)	**15 (11-21)**	**2.48 (1.45-4.24)**	**15 (8.78-26)**	**4.16 (2.94-5.89)**	1.88 (0.9-3.89)	**3.51 (1.72-7.17)**
	GMR[a] ratios (95% CI)	**18 (14-23)**	**2.61 (1.55-4.39)**	**18 (12-26)**	**3.59 (2.84-4.54)**	1.58 (0.73-3.43)	**4.18 (2.73-6.4)**
	% SP[b] differences (95% CI)	**62% (54-69)**	**32% (2-56)**	**71% (58-81)**	**18% (12-25)**	**30% (3-57)**	**32% (18-45)**
	% SC[c] differences (95% CI)	**62% (55-69)**	23% (-7-47)	**64% (52-74)**	**18% (12-25)**	**30% (3-57)**	**18% (10-30)**
H3N2	GMT ratios (95% CI)	**16 (12-20)**	**3.82 (2.42-6.03)**	**17 (11-26)**	**3.72 (2.56-5.39)**	**1.74 (1.03-2.94)**	**4.15 (2.11-8.15)**
	GMR[a] ratios (95% CI)	**16 (12-19)**	**2.38 (1.44-3.92)**	**17 (12-23)**	**3.39 (2.45-4.68)**	1 (0.52-1.93)	**2.99 (1.77-5.03)**
	% SP[b] differences (95% CI)	**54% (47-62)**	**68% (44-84)**	**74% (63-83)**	**10% (5-17)**	**27% (9-52)**	**26% (14-40)**
	% SC[c] differences (95% CI)	**54% (46-62)**	**64% (40-80)**	**50% (38-62)**	**12% (6-19)**	**47% (25-70)**	**21% (7-34)**
B	GMT ratios (95% CI)	**6.99 (5.72-8.53)**	**2.17 (1.2-3.92)**	**15 (9.04-24)**	**3.39 (2.71-4.23)**	0.87 (0.5-1.52)	**4.45 (2.69-7.37)**
	GMR[a] ratios (95% CI)	**6.97 (5.9-8.24)**	**3.1 (1.8-5.35)**	**15 (9.8-22)**	**3.69 (3.06-4.45)**	0.65 (0.33-1.3)	**5.15 (3.32-7.99)**
	% SP[b] differences (95% CI)	**69% (60-76)**	**48% (16-71)**	**64% (50-75)**	**39% (31-47)**	17% (-8-44)	**30% (18-43)**
	% SC[c] differences (95% CI)	**69% (60-76)**	**48% (16-71)**	**52% (40-63)**	**40% (32-48)**	10% (-13-37)	**12 (2-24)**

Source: Section 2.7.3 Tables 2.7.3.3.2.2-1, 2.7.3.3.2.2-2, 2.7.3.3.2.2-3; Bold font: If difference between vaccine groups were statistically significant: i.e. 95% CIs of vaccine group ratio do not include 1; 95% CIs of vaccine group difference do not include 0; [a]GMR = geometric mean ratio of GMTs/GMAs (day 50/day 1); [b]SP = seroprotection = HI titer ≥ 1:40, SRH area ≥25mm^2, MN titer ≥1:80; [c]SC = seroconversion or significant increase = for HI: the percentage of subjects achieving a rise from <1:10 (seronegative pre-vaccination) to ≥1:40 or at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (≥10); for SRH: percentage of subjects achieving a rise from <25 mm^2 (seronegative pre-vaccination) to ≥25 mm^2 or at least a 4-fold increase in SRH diameter from a seropositive pre-vaccination titer (≥25 mm^2) ; for MN: SC=seroconversion = the percentage of subjects achieving at least a 4-fold increase in MN titer; [d]HI: Fluad N=160; Influsplit N=162; SRH: Fluad N=15; Influsplit N=22; MN: Fluad N=56; Influsplit N=66; [e]HI: Fluad N=150; Influsplit N=147; SRH: Fluad N=22; Influsplit N=15; MN: Fluad N=48; Influsplit N=56;

CHMP and CBER criteria met by Fluad, a non adjuvanted influenza vaccine and a non influenza vaccine from the pivotal efficacy Study are summarized in the table below

Table 11.4.7-1: CHMP and CBER Criteria at Day-50 Against the Homologous Strains in Subjects Aged 6 to <36 Months for Combined Seasons-FAS

		A/H1N1			A/H3N2			B		
		TIV-Adj	Flu-control	Non-flu control 1	TIV-Adj	Flu-control 1	Non-flu control 1	TIV-Aadj	Flu-control 1	Non-flu control 1
	HI Assay									
CHMP	HI titer≥1:40	+	-	-	+	-	-	+	-	-
CHMP	Seroconversion	+	-	-	+	+	-	+	-	-
CHMP	GMR	+	+	-	+	+	-	+	-	-
CBER	HI titer≥1:40	+	-	-	+	-	-	+	-	-
CBER	Seroconversion	+	-	-	+	-	-	+	-	-
	SRH Assay									
CHMP	HI titer≥1:40	+	-	-	+	-	-	+	-	-
CHMP	Seroconversion	+	+	-	+	-	-	+	-	-
CHMP	GMR	+	+	-	+	-	-	+	-	-

Source: Table 14.2.1.3.1; Table 14.2.1.1.1; Table 14.2.1.2.1; Table 14.2.1.13.1; Table 14.2.1.14.1; Table 14.2.1.15.1

Table 11.4.7-2: CHMP and CBER Criteria at Day-50 Against the Homologous Strains in Subjects Aged 6 to <72 Months for Combined Seasons-FAS

		A/H1N1			A/H3N2			B		
		TIV-Aadj	Flu-control 1	Non-flu	TIV-Adj	Flu-control 1	Non-flu	TIV-Adj	Flu-control 1	Non-flu
	HI Assay									
CHMP	HI titer≥1:40	+	-	-	+	-	-	+	-	-
CHMP	Seroconversion	+	+	-	+	+	-	+	-	-
CHMP	GMR	+	+	-	+	+	-	+	+	-
CBER	HI titer≥1:40	+	-	-	+	-	-	+	-	-
CBER	Seroconversion	+	-	-	+	-	-	+	-	-
	SRH Assay									
CHMP	HI titer≥1:40	+	-	-	+	+	+	+	+	-
CHMP	Seroconversion	+	+	-	+	+	-	+	+	-
CHMP	GMR	+	+	-	+	+	-	+	+	-

Source: Table 14.2.1.3; Table 14.2.1.1; Table 14.2.1.2; Table 14.2.1.13; Table 14.2.1.14; Table 14.2.1.15

Immunogenicity after 2 half doses (0.25mL) of Fluad in Phase 2 studies in children not previously vaccinated

Children 3 years to <18 years

Immunogenicity after 1 dose (children 9 to <18 years) or 2 doses (children 3 to <9 years) of Fluad (0.5mL) in Phase 2 studies

In the age group 9 to <18 years for the 2 A strains immunogenicity was similar for Fluad and non-adjuvanted flu control vaccines. For the B-strain the immune response with Fluad (GMR of 18) was higher than after flu vaccine control (GMR was 10). All CHMP criteria were met for all strains in both vaccination groups (Table 2.7.3.3.2.2-4).

Limited data are available for the age sub-group 6-9 years.

Immunogenicity after third consecutive dose in primed children

Very few primed children in study V70P2E1 have received a third dose in a consecutive season which has been defined as an exploratory study. Fluad induced noteworthy higher GMTs against all three vaccine antigens with respect to Vaxigrip (Table 11.4.1.2.1-1).

Table 11.4.1.2.1-1 Summary of Percentages of Subjects Achieving Seroprotection and Seroconversion or Significant Increase in HI Titres, by Age Group

		Number of Subjects (%) and (95% CI)					
		A/H1N1		A/H3N2		B	
		Fluad	Vaxi[a]	Fluad	Vaxi[a]	Fluad	Vaxi[a]
Overall		N=41	N=40	N=41	N=40	N=41	N=40
	SP[b] (day 1)	6(15%) (6-29)	2(5%) (1-17)	36(88%) (74-96)	16(40%) (25-57)	4(10%) (3-23)	0(0%) (0-9)
	SP[b] (day 22)	41(100%) (91-100)	40(100%) (91-100)	41(100%) (91-100)	40(100%) (91-100)	41(100%) (91-100)	27(68%) (51-81)
	Serocon. rate[c] (day 22)	39(95%) (83-99)	38(95%) (83-99)	40(98%) (87-100)	34(85%) (70-94)	40(98%) (87-100)	27(68%) (51-81)
<36 months		N=23	N=20	N=23	N=20	N=23	N=20
	SP[b] (day 1)	2(9%) (1-28)	1(5%) (0-25)	22(96%) (78-100)	10(50%) (27-73)	1(4%) (0-22)	0(0%) (0-17)
	SP[b] (day 22)	23(100%) (85-100)	20(100%) (83-100)	23(100%) (85-100)	20(100%) (83-100)	23(100%) (85-100)	9(45%) (23-68)
	Serocon. rate[c] (day 22)	23(100%) (85-100)	19(95%) (75-100)	23(100%) (85-100)	17(85%) (62-97)	22(96%) (78-100)	9(45%) (23-68)
≥36 months		N=18	N=20	N=18	N=20	N=18	N=20
	SP[b] (day 1)	4(22%) (6-48)	1(5%) (0-25)	14(78%) (52-94)	6(30%) (12-54)	3(17%) (4-41)	0(0%) (0-17)
	SP[b] (day 22)	18(100%) (81-100)	20(100%) (83-100)	18(100%) (81-100)	20(100%) (83-100)	18(100%) (81-100)	18(90%) (68-99)
	Serocon. rate[c] (day 22)	16(89%) (65-99)	19(95%) (75-100)	17(94%) (73-100)	17(85%) (62-97)	18(100%) (81-100)	18(90%) (68-99)

Source: Table 14.2.1.1.1, Table 14.2.1.1, Table 14.2.1.2.1, and Table 14.2.1.2; ; [a] = Vaxigrip; [b]Seroprotection HI titers ≥40; [c] seroconversion rate: seroconversion and/or significant increase; Seroconversion - negative pre-vaccination serum (i.e., HI titer <10) and post-vaccination HI titer ≥40 and Significant increase - at least a 4-fold increase in HI titers in subjects who were positive pre-vaccination (i.e., HI titer ≥10).

Table 2.7.3.3.2.2-5 Immunogenicity of Fluad After a Third Consecutive Dose in Children in the Phase 2 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[d]	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.
[d] 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
Source: V70P2E1 CSR Table 14.2.1.1.1, Table 14.2.1.2.1, Table 14.2.1.3.1 and Table 14.2.1.3.4.1

Both vaccines induced high seroconversion rates against both A homologous strains, with more children achieving seroconversion or significant increase in Fluad recipients against B strain.

Immunogenicity Results against Heterologous Strains

Previously Unvaccinated Children 6 to <36 months

In the pivotal efficacy study HI antibody levels after 2 doses were higher in the Fluad group with respect to the flu vaccine control group for each of the heterologous strains tested. The difference was statistically significant as the lower limit of the 2-sided 95% CI of vaccine group ratio between Fluad and flu vaccine control of GMTs and GMRs was above 1 for all 3 strains (Table 2.5.4.5.2-1). Nevertheless immune response for the heterologous B strain was relatively weak in both vaccination groups (Table 2.7.3.3.2.3-1). Similar results were obtained in the Phase II trials; the response to the heterologous A strains was stronger than the response observed to the heterologous B strains (Table 2.7.3.3.2.3-2).

Previously Unvaccinated Children 36 months and above

Similar results as in the younger age group above were obtained in this age group in the pivotal efficacy study (Tables 2.5.4.5.2-1 and 2.7.3.3.2.3-1). A strong immune response to heterologous strains was also observed in the Phase 2 study V70P6 (Table 2.7.3.3.2.3-2), with similar results in this study for Fluad and the comparator vaccine (Fluzone).

Pivotal Efficacy Study: immunogenicity results against heterologous strains

Table 11.4.1.6-2: Percentage (95% CI) of Subjects Aged 6 to <36 Months with HI titer ≥1:40 in Season 2008/09 HI Assay- FAS (Heterologous Strains)

		TIV-adj	Flu-control	Non-flu control	TIV-adj - Flu-control	TIV-adj - Non-flu Control	Flu-control- Non-flu Control
A/Solomon Islands/2006 (A/H1N1)		**N=166**	**N=165**	**N=83**			
	Day 1	5%(3-10)	11%(7-17)	5%(1-12)	-5% (-12-0)	1% (-7-6)	6% (-2-13)
	Day 29	15%(10-21) N=165	13%(9-20) N=163	5%(1-12) N=82	1% (-7-9)	**10% (2-17)**	**9% (1-16)**
	Day 50	[ab]95%(90-98) N=160	24%(18-31) N=162	5%(1-13) N=78	**71% (63-78)**	**90% (82-94)**	**19% (10-27)**
	Day 181	61%(53-68) N=161	19%(13-26) N=163	5%(1-12) N=80	**42% (32-51)**	**56% (46-64)**	**14% (6-22)**
A/Wisconsin/2009 (A/H3N2)		**N=166**	**N=165**	**N=83**			
	Day 1	4%(1-8)	5%(2-9)	2%(0-8)	-1% (-6-3)	1% (-5-6)	2% (-4-7)
	Day 29	37%(30-45) N=165	6%(3-10) N=163	2%(0-9) N=82	**31% (23-40)**	**35% (26-43)**	3% (-3-8)
	Day 50	[ab]100%(98-100) N=160	30%(23-37) N=162	4%(1-11) N=78	**70% (63-77)**	**96% (89-99)**	**26% (17-34)**
	Day 181	[ab] 99%(97-100) N=161	42%(34-50) N=163	23%(14-33) N=80	**58% (50-65)**	**77% (67-85)**	**19% (7-30)**
B/Brisbane/2008		**N=166**	**N=165**	**N=83**			
	Day 1	0%(0-2)	0%(0-2)	0%(0-4)	0%(-2-2)	0%(-4-2)	0% (-4-2)
	Day 29	1%(0.015-3) N=165	0%(0-2) N=163	0%(0-4) N=82	1%(-2-3)	1%(-4-3)	0% (-4-2)
	Day 50	5%(2-10) N=160	0%(0-2) N=162	0%(0-5) N=78	**5%(3-10)**	5%(0-10)	0% (-5-2)
	Day 181	0%(0-2) N=161	1%(0.016-3) N=163	6%(2-14) N=80	-1%(-3-2)	-6%(-14--3)	-6% (-13--2)

Source: Table 14.2.1.7.1; a: CBER criterion for HI titer≥1:40 met; b: CHMP criterion for HI titer≥1:40 met; bold font: vaccine group difference statistically significant as 95% CIs do not include 0.

Table 11.4.1.6-8: Percentages of Subjects With HI Titers ≥ 40 and Vaccine Group Differences in Subjects 6 to <72 Months of Age for Season 2008/09 (Heterologous Strains) HI Assay-FAS

		TIV-adj	Flu-control	Non-flu control	TIV-adj - Flu-control	TIV-adj - Non-flu Control	Flu-control-Non-flu Control
A/Solomon [illegible]		N=319	N=316	N=158			
	Day 1	21% (16-26)	22% (17-27)	18% (12-25)	-1% (-8-5)	3% (-5-10)	(4%) (-4-11)
	Day 29	32% (27-38) N=316	24% (20-29) N=313	18% (12-25) N=156	**8% (1-15)**	**14% (6-22)**	(6%) (-2-14)
	Day 50	[ab]96% (94-98) N=310	45% (39-51) N=309	18% (12-25) N=150	**51% (46-57)**	**78% (71-84)**	(27%) (18-35)
	Day 181	[a] 72% (67-77) N=309	34% (29-40) N=310	18% (12-25) N=151	**38% (31-45)**	**55% (46-62)**	(16%) (8-24)
A/Wisconsin/2009 (A/H3N2)		N=319	N=316	N=158			
	Day 1	25% (21-31)	25% (20-30)	21% (15-28)	0% (-6-7)	5% (-4-12)	(4%) (-4-12)
	Day 29	60% (54-66) N=316	29% (24-34) N=313	21% (14-28) N=156	**31% (24-39)**	**40% (31-47)**	(8%) (0-16)
	Day 50	[ab] 100% (98-100) N=310	54% (48-59) N=309	21% (15-29) N=150	**46% (41-52)**	**78% (71-84)**	(32%) (23-41)
	Day 181	[ab] 100% (98-100) N=309	63% (57-68) N=310	43% (35-51) N=151	**37% (32-42)**	**57% (49-64)**	(20%) (10-29)
B/Brisbane/2008		N=319	N=316	N=158			
	Day 1	0% (0-1)	0% (0-1)	1% (0.016-3)	0% (-1-1)	-1% (-3-1)	(-1%) (-3-1)
	Day 29	3% (2-6) N=316	1% (0-3) N=313	1% (0.016-4) N=156	2% (0-5)	3% (0-6)	(1%) (-2-3)
	Day 50	10% (7-14) N=310	3% (1-5) N=309	0% (0-2) N=150	**7% (4-12)**	**10% (7-14)**	(3%) (0-5)
	Day 181	3% (1-5) N=309	3% (1-5) N=310	5% (2-10) N=151	0% (-3-3)	-3% (-8-1)	(-3%) (-8-1)

Source: Table 14.2.1.7; a: CHMP criterion for percentage of subjects with HI titer≥1:40 achieved; b: CBER criterion for percentage of subjects with HI titer≥1:40 achieved; Bold font: vaccine group difference statistically significant as 95% CIs do not include 0

Table 2.5.4.5.2-1 Vaccine group ratios or differences (HI assay) Fluad to Influsplit for heterologous strains on day 50 – pivotal efficacy study FAS- season 2008/2009

Age group		6 to < 36 months[d]	36 to <72 months[e]
A/H1N1/Solomon Islands/2006	GMT ratios (95% CI)	7.54 (5.33-11)	3.84 (2.4-6.15)
	GMR[a] ratios (95% CI)	9.32 (7.69-11)	3.31 (2.71-4.05)
	% SP[b] differences (95% CI)	71% (63-78)	30% (23-38)
	% SC[c] differences (95% CI)	71% (63-78)	30% (23-38)
A/H3N2/ Wisconsin/2009	GMT ratios (95% CI)	13 (10-16)	3.84 (2.48-5.93)
	GMR[a] ratios (95% CI)	14 (12-17)	3.57 (2.79-4.57)
	% SP[b] differences (95% CI)	70% (63-77)	19% (13-26)
	% SC[c] differences (95% CI)	73% (66-79)	25% (17-33)
B/Brisbane/2008	GMT ratios (95% CI)	1.74 (1.57-1.92)	1.84 (1.57-2.15)
	GMR[a] ratios (95% CI)	1.74 (1.58-1.93)	1.85 (1.59-2.14)
	% SP[b] differences (95% CI)	5% (3-10)	10% (3-17)
	% SC[c] differences (95% CI)	5% (3-10)	10% (3-17)

Source: Section 2.7.3 Table 2.7.3.3.2.3-1; Vaccine group ratio were statistically significant as 95% CIs do not include 1; Vaccine group difference were statistically significant as 95% CIs do not include 0; [a]GMR = geometric mean ratio of GMTs (day 50/day 1); [b]SP = seroprotection = HI titer ≥1:40; [c]SC = seroconversion or significant increase = the percentage of subjects a rise from <1:10 (seronegative pre-vaccination) to ≥1:40 or achieving at least a 4-fold increase in HI titer from a seropositive pre-vaccination titer (≥1:10); [d]HI: Fluad N=160; Influsplit N=162; [e]HI: Fluad N=150; Influsplit N=147;

Children Vaccinated in the Previous Influenza Season

For both age cohorts in study V70P2E1 for all three heterologous strains, the immune response after vaccination with Fluad was similar to, or higher than, that observed after vaccination with Vaxigrip. Differences between vaccination groups were more pronounced in children 6 to <36 months than in children 36 months and above.

Table 11.4.1.2.2-3 Summary of CHMP Criteria[a] Met After Fluad or Vaxigrip Vaccination Against Mismatched Strains – PP Population

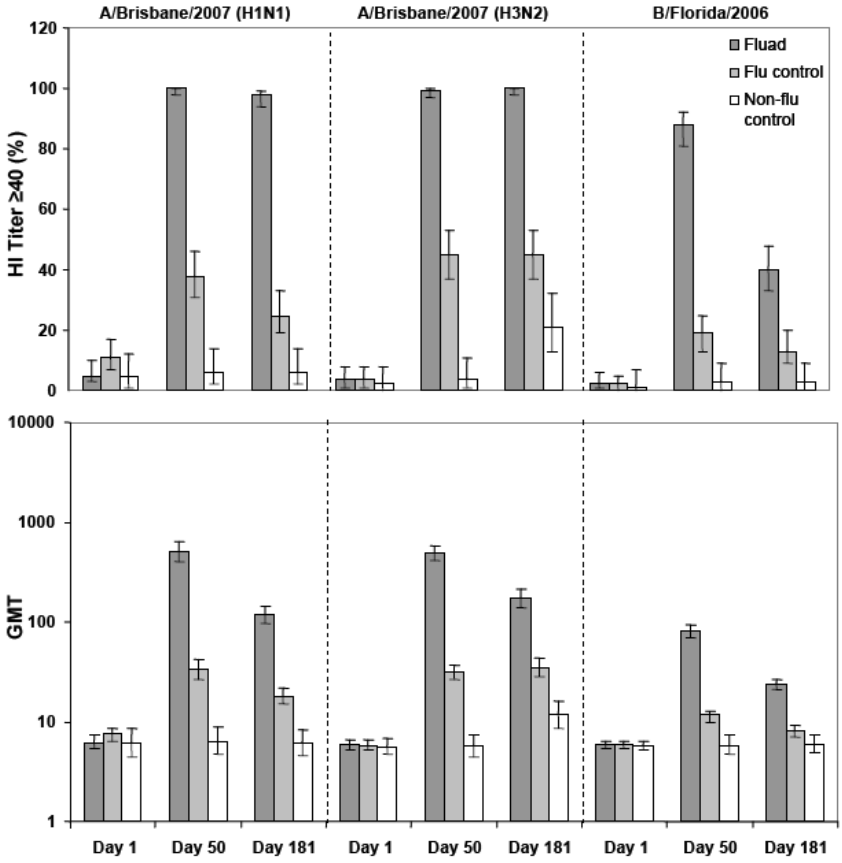
Serological Criteria to meet CPMP/BWP/214/96 requirements	A/H1N1		A/H3N2		B	
	Fluad	Vaxigrip	Fluad	Vaxigrip	Fluad	Vaxigrip
Overall	**N=41**	**N=40**	**N=41**	**N=40**	**N=41**	**N=40**
Seroprotection[b] >70%	+	+	+	+	-	-
GMR[c] >2.5	+	+	+	+	+	-
Seroconversion[d] or significant increase[e] >40%	+	+	+	+	-	-
<36 months	**N=23**	**N=20**	**N=23**	**N=20**	**N=23**	**N=20**
Seroprotection[b] >70%	+	+	+	+	-	-
GMR[c] >2.5	+	+	+	+	+	-
Seroconversion[d] or significant increase[e] >40%	+	+	+	+	-	-
≥36 months	**N=18**	**N=20**	**N=18**	**N=20**	**N=18**	**N=20**
Seroprotection[b] >70%	+	+	+	+	-	-
GMR[c] >2.5	+	+	+	+	+	-
Seroconversion[d] or significant increase[e] >40%	+	+	+	+	-	-

[a] CHMP criteria for healthy adults (18 to 60 years of age) were used for assessing immunogenicity in the age groups under evaluation. [b] Seroprotection is defined as an HI titer ≥ 40; [c] GMR = ratios of day 22/day 1 geometric mean HI titers; [d] Seroconversion is defined as negative pre-vaccination serum (i.e., HI titer <10) and post-vaccination HI titer ≥ 40; [e] Significant increase is defined at least a 4-fold increase from non-negative (≥ 10) pre-vaccination HI titer; Mismatched strains tested: A/Brisbane/59/2007- H1N1 like; A/Brisbane/10/2007- H3N2 like; B/Florida/4/2006-like.

Antibody Persistence

The pivotal efficacy Study examined the persistence of HI antibodies against both homologous and heterologous strains over a period of approximately 6 months. About 6 months after the vaccination in both age groups (6 to <36 months and 36 to < 72 months) for all homologous strains and heterologous A-strains considering non-overlapping 2-sided 95% CIs, GMTs were significantly higher in the Fluad group compared to the flu vaccine control group and a significantly higher percentage of subjects had HI titers ≥1:40. Almost all of the subjects in the Fluad group 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 for the homologous B-strains at Study Day 181. As discussed in the previous sections, the immune response following vaccination with non-adjuvanted flu-control vaccine was weaker than that induced by Fluad. As a consequence, the levels of antibodies at Day 181 in flu-control vaccine recipients were below those of the Fluad recipients (Figures 2.7.3.3.5-1, 2.7.3.3.5-2, 2.7.3.3.5-3 and 2.7.3.3.5-4).

Figure 2.7.3.3.5-1 Antibody persistence following vaccination in pivotal trial (PP population; subjects aged 6 to <36 months) - HI assay (Homologous strains) – season 2008/2009)



Source: V70P5 CSR Table 14.2.1.1.1 and Table 14.2.1.3.1

Study V70P2

The results from study V70P2 (age cohort: 6-36 months of age) are consistent with those obtained in the pivotal efficacy study (see below). At day 209, 180 days after the second dose, 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.

Pivotal Efficacy Clinical phase 3 study

The study is phase III, observer-blind, randomized controlled multi-centre study was intended to be conducted over three consecutive influenza seasons 2007/2008, 2008/2009 and 2009/2010. In practice, enrollment of the first season started very late was prematurely interrupted. In the third season the occurrence of the pandemic caused the interruption of the study. Data collected across different periods and study sites are presented as a single study. During the Season 2008/2009, sample collection from subjects with ILI was performed in different manner and a different relative proportion of subjects across the study groups was enrolled. The involved sites were: in season 2007/08, 28 sites all located in Germany; in season 2008/09 83 sites plus 1 coordinating site in Germany and 15 sites in Finland; in season 2009/10, 15 sites in Finland and 2 sites in Italy. Assuming that the sites in Germany and in Finland were the same the study included data from 101 different study centre. The enrolled sample by centre was very variable with 10 centres enrolling only one or two children.

Efficacy evaluation has been performed on data obtained only from the first two seasons, due to the overcoming pandemic in 2009. Observations from the first season were limited and most of the efficacy inferences are based on the 2008-9 season.

Methods

Study Participants

The study included previously unvaccinated healthy children aged 6 to <72 months in the first two seasons and children aged 6 to <36 months for the third season.

In a convenience subset of subjects only in Finland blood samples were drawn at baseline (day 1), prior to and 21 days after second vaccination (day 29 and 50) and about 6 months after first vaccination for evaluating the immunogenicity against the test vaccines.

Table 11.1-1 Overview of the Populations Analyzed in Subjects 6 to <36 Months Age- All Seasons

	TIV-adj	Flu-Control	Non-flu Control
	Season-2007/08		
Enrolled Set (N)	188	94	97
Randomized	188 (100%)	94 (100%)	97 (100%)
Efficacy-FAS	187 (99%)	93 (99%)	97 (100%)
Efficacy-PPS	166 (88%)	87 (93%)	89 (92%)
	Season-2008/09		
Enrolled Set (N)	917	902	469
Randomized	917 (100%)	902 (100%)	469 (100%)
Efficacy-FAS	916 (100%)	902 (100%)	469 (100%)
Efficacy-PPS	858 (94%)	843 (93%)	436 (93%)
Immunogenicity-FAS[a]	166 (18%)	165 (18%)	83 (18%)
Immunogenicity-PPS[a]	98 (11%)	106 (12%)	47 (10%)
	Season-2009/10		
Enrolled Set (N)	78	76	41
Randomized	78 (100%)	76 (100%)	41 (100%)
Immunogenicity-FAS[a]	11 (14%)	7 (9%)	6 (15%)
Immunogenicity-PPS[a]	6 (8%)	3 (4%)	1 (2%)

Source: Table 14.1.1.1.2; a: Immunogenicity was analyzed on a subset of subjects; percentages here are given with respect to the enrolled set

Table 11.1-2 Overview of the Populations Analyzed in Subjects 6 to <72 Months Age- by Seasons

	TIV-adj	Flu-Control	Non-flu Control
	Season-2007/08		
Randomized	325	165	164
Efficacy-FAS	323 (99%)	164(99%)	164 (100%)
Efficacy-PPS	298 (92%)	154 (93%)	151 (92%)
	Season-2008/09		
Randomized	1616	1608	829
Efficacy-FAS	1614 (100%)	1608 (100%)	829 (100%)
Efficacy-PPS	1521 (94%)	1509 (94%)	775 (93%)
Immunogenicity-FAS	319 (20%)	316 (20%)	158 (19%)
Immunogenicity-PPS	199 (12%)	196 (12%)	87 (10%)

Source: Table 14.1.1.1.1

Treatments

In each study period, the subjects were randomized to three vaccine groups, TIV-adj, Flu-control and Non-flu-control vaccine. The relative proportion across the study groups varied between the first two seasons.

Each subject received two doses of the study vaccines given about 4 weeks apart (on study days 1 and 29). In the third season the subjects were offered an egg-based H1N1sw pandemic vaccine, Focetria about 3 weeks after the second study vaccination.

Assuming a naïve status in the subjects, the dosage of the influenza vaccines followed the recommendation for trivalent inactivated influenza vaccines in this age group:

The flu-control vaccines (Agrippal S1 in season 2007/08; Influsplit SSW in seasons 2008/09 and 2009/10) and the TIV-adj (Fluad) were administered as 2 doses of 0.25mL for subjects aged 6 to <36 months and 2 doses of 0.5mL for subjects aged 36 to <72 months.

The non-flu vaccine controls, Menjugate/ Encepur Children were administered across the three seasons. For Menjugate, two 0.5mL doses are recommended for the subjects under the age of 12 months; for Encepur Children, two 0.25mL priming doses are recommend, followed by a booster dose at approximately 9-12 months after priming.

Vaccines	Active Ingredients and Antigen Content			Vol injected
	2007/08	2008/09	2009/10	
Flu-control	Agrippal (Lot #070602B): A/Solomon Islands/3/2006 (H1N1)- 15µg HA A/Wisconsin/67/2005 (H3N2)- 15µg HA B/Malaysia/2506/2004- 15µg HA	Influsplit (Lot #: Influsplit AFLUA 351 AA): A/Brisbane/59/2007 (H1N1)- 15 µg of HA A/Brisbane/10/2007 (H3N2)- 15 µg of HA B/Florida/4/2006- 15 µg of HA	Influsplit: A/Brisbane/59/2007 (Lot #: Influsplit AFLUA 446A) (H1N1)- 15 µg of HA A/Brisbane/10/2007 (H3N2)- 15 µg of HA B/Brisbane/60/2008- 15 µg of HA	0.25mL/0.5mL
Non-flu control (Menjugate)	*Neisseria meningitidis* strain C11 oligosaccharide (10µg) conjugated to CRM-197 protein (*12.5-25.0* µg) (LOT #: Menjugate XA 2076 AC Menjugate 161011D; Menjugate 161011C (Season-2008/09); Menjugate 266011 I (Season 2009/10)			0.5mL
Non-flu control (Encepur)	Inactivated TBE virus / strain K23 adjuvanted with Aluminum hydroxide (LOT #: Season- 2007/08:Encepur children 072041A; Season 2008/09: Encepur children 091011A; Season 2009/10: Encepur Children 100031A)			0.25mL

Other treatments and vaccinations:

Although the Applicant stated that all prescription medication, including non-study vaccines, being taken by the subjects on entry to the study and all prescription medication given in addition to the study vaccine during this clinical trial were regarded as concomitant medication and were documented on the "Prior and Concomitant Medications" CRF, the performed inspection at the site in Finland revealed that the administration of Prevenar vaccine was not systematically recorded. In contrast, the Applicant has stated that all relevant medication (including vaccinations and relevant medication prescribed to the subject within 4 weeks prior to the start of the study) was entered on the "Prior and Concomitant Medications" CRF. The following concomitant treatments were discouraged and, if used, lead to a major protocol violation according to the medical judgment of the Novartis Vaccines Medical Monitor (see exclusion criteria, Section 9.3.2 in the dossier).

- Systemic steroids
- Other immunosuppressive agents
- Blood or plasma derivatives including immunoglobulin
- Non-study vaccines (with the exception of post-exposure vaccinations in a medical emergency e.g. hepatitis, rabies, tetanus).

Objectives

Primary objectives:

- Safety: To demonstrate the safety and tolerability of one or two 0.25mL IM doses of Fluad (TIV-adj) in unprimed children aged 6 to <36 months, compared with Agrippal S1 and/or with Influsplit SSW (Flu vaccine control) in terms of any solicited local and systemic reactions (combined) reported within 7 days after any vaccination.
- Absolute efficacy: To demonstrate protection provided by two 0.25mL intramuscular (IM) doses of Fluad (TIV-adj) in unprimed children aged 6 to <36 months, compared with Menjugate/ Encepur Children (Non-flu vaccine control), against influenza illness1 caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine.

Secondary objectives (extract):

- Absolute efficacy: To demonstrate protection provided by two 0.25mL or 0.5mL IM doses of Fluad, compared to non-flu vaccine control, against influenza illness caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine, in children aged 6 to <72 months.

The primary objective is to show safety and efficacy on children aged 6-35 months. The per protocol study population in this age-group accounts for 1024 recipients of FLUAD and 795 recipients aged 36-71 months.

Secondary Objectives are listed in the table below:

Table 2-2: Secondary Objectives- Efficacy

Absolute Efficacy				
Objective	**Age Group (months)**	**Vaccines administered**	**Doses**	**Against influenza Strain**
Demonstrate protection	6 to <72	Fluad versus non-flu control	2 doses of 0.25mL or 0.5mL	Homologous
Evaluate protection	6 to <36; 6 to <72	Fluad versus non-flu control	2 doses of 0.25mL or 0.5mL	Heterologous
Evaluate protection	6 to <36; 6 to <72	Fluad versus non-flu control	2 doses of 0.25mL or 0.5mL	Any strain (Homologous and Heterologous combined)
Relative Efficacy				
Evaluate protection	6 to <36; 6 to <72	Fluad versus flu-vaccine control	2 doses of 0.25mL or 0.5mL	Homologous
Evaluate protection	6 to <36; 6 to <72	Fluad versus flu-vaccine control	2 doses of 0.25mL or 0.5mL	Heterologous
Evaluate protection	6 to <36; 6 to <72	Fluad versus flu-vaccine control	2 doses of 0.25mL or 0.5mL	Any strain (Homologous and Heterologous combined)

Table 2-3: Secondary objectives- ILI

Objectives	Age group (months)	Vaccines administered	Parameters
Number of cases	6 to <36; 6 to <72	Fluad versus non-flu control	all-cause hospitalizations; hospitalizations due to confirmed influenza; all-cause outpatient medical visits; outpatient medical visits due to influenza illness or influenza symptoms
		Fluad versus flu-control	
Number of days	6 to <36; 6 to <72	Fluad versus non-flu control	Loss of days of usual activity due to ILI in subjects direct caregivers
		Fluad versus flu-control	
Indirect protective effect (2007/08)	6 to <36; 6 to <72	Fluad versus non-flu control	In household-contact persons with ILI
		Fluad versus flu-control	
Incidence rate of the 2009-2010 H1N1 pandemic	6 to <36	Egg derived H1N1 sw vaccine	
Number of cases	6 to <36	Egg derived H1N1 sw vaccine	All-cause hospitalizations; hospitalizations due to confirmed influenza; all-cause outpatient medical visits and outpatient medical visits due to influenza illness or influenza symptoms in H1N1 pandemic period.

Secondary objectives related to ILI were not pursued.

- **Outcomes/endpoints**

Efficacy against PCR-confirmed influenza was evaluated over the first two years (seasons 2007/08 and 2008/09) of the planned three year surveillance (for details refer to Section 2.7.3.1 of the dossier). The evaluation of efficacy against seasonal strains was not carried out during the third year (season 2009/10) due to the occurrence of the H1N1 pandemic. (It should be noted that children enrolled during this season were offered vaccination against the pandemic strain).

For assessing the efficacy of the vaccines administered, from 01 Dec2007/ 2008/ 2009 to the end of surveillance period (approximately determined by the surveillance organizations of the countries where the trial was conducted; Robert Koch Institute (RKI) for Germany, European Influenza Surveillance Scheme, renamed as EISN as part of ECDC for Finland) for the respective season, completely vaccinated study subjects (from 3 weeks after second vaccination) with influenza symptoms (based on CDC criteria for 'influenza like illness', ILI) were asked to come to the study site to be evaluated for for influenza infection. Nasopharyngeal specimens were to be collected within 24 hours of the onset of symptoms (for details refer to Section 2.7.3.1).

During the Season 2007/2008, rapid tests were performed at the study sites on swabs from subjects with ILI, but these tests did not have any screening purpose and were only used for the diagnostic benefit of the study subjects. According to the Applicant all respiratory samples collected at study sites were sent to a first laboratory (C) independent of the outcome of the rapid test and were analyzed by a multiplex RT-PCR assay which at the inspection was found to be different from the assay described in the application. For those testing positive, RNA was extracted from a portion of the clinical sample and sent to the Department of Virology in a University Hospital for the study efficacy assessment.

During the Season 2008/2009, sample collection from subjects with ILI was performed in a different manner. A sample was collected on which the rapid test was performed at the site for diagnostics purposes, and independent of the test outcome, all samples were sent to the first laboratory (C) in

order to be analyzed by multiplex RT-PCR. In addition, for those subjects whose rapid test was positive, a second sample was taken and sent directly to the Dept. of Virology. For samples that were negative in the rapid test but positive in the multiplex RT-PCR at the first laboratory, (C) an RNA extract was sent to the Dept. of Virology.

In the documentation provided the procedure for classifying laboratory confirmed cases was not presented and was clarified only after the inspection.

Related to assessment of Efficacy (Section 5.3.5 CSR pivotal efficacy trial), efficacy was calculated on PCR confirmed cases.

For the following endpoints, efficacy of Fluad was to be evaluated both in previously unvaccinated children aged 6 to <36 months and in the overall age cohort (children aged 6 to <72 months) compared to Non-flu vaccine control.

To evaluate protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine.

Relative efficacy:
For the following end points, efficacy of Fluad was evaluated compared to Flu vaccine control (Agrippal S1 and/or Influsplit SSW):

proportion of prevented cases against influenza illness caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine by two 0.25mL and/or 0.5mL IM doses of Fluad.

protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine.

Immunogenicity:
For the following end points, vaccine's immunogenicity will be evaluated both in previously unvaccinated children aged 6 to <36 months and in the overall age cohort (children aged 6 to <72 months).

superiority of immunogenicity of two 0.25mL or 0.5mL IM doses of Fluad, compared to Influsplit SSW, in terms of post-immunization geometric mean titers (GMTs), as measured by haemagglutination inhibition (HI) assay.

- **Sample size**

This overall study (spanning three seasons) was powered to demonstrate the primary safety objective. In fact, with 2000 (2500) evaluable subjects in the TIV-adj group and 2000 (2500) evaluable subjects in the flu vaccine control group this study has ca. 90% (95%) power, including adjustment for multiple testing among the two primary objectives (Bonferroni).

The study also has sufficient ability to show absolute efficacy of TIV-adj. In fact, with 2000 (2500) evaluable subjects in the TIV-adj group and 1000 (1250) evaluable subjects in the non-flu vaccine control group this study has ca. 70% (80%) power to demonstrate the absolute efficacy of TIV-adj, again including adjustment for multiple testing among the two primary objectives (Bonferroni).

For further illustration Table 9.7.2-1 shows the number of evaluable subjects necessary to have a power of at least 80% considering different attack rates, always assuming an efficacy of 70% for TIV-adjuvanted and a two-sided alpha of 2.5%.

Table 9.7.2-1

Attack Rate (%) Menjugate/Encepur Children	Attack Rate (%) FLUAD	Total sample size to obtain 80% power* (ratio 2:1)
1%	0.3%	14,979
3%	0.9%	4,993
5%	1.5%	2,996
7%	2.1%	2,140
9%	2.7%	1,664

* Poisson method; Blackwelder, Stat Med 1993

Results

Conduct of the study

For evaluating the efficacy of the vaccines administered, the subjects were monitored for the influenza symptoms during the active surveillance periods of the influenza seasons 2007/2008, 2008/2009 and 2009/2010. All the subjects who were fully vaccinated for that season were asked to visit the site if they had experienced the influenza symptoms (observation period from 3 weeks after the second vaccination). Nasopharyngeal secrete/swab specimens were targeted for collection within 24 hours of onset of symptoms (with a window of up to 72 hours). According to the submitted initial documentation clinical specimens were sent to a specialized laboratory for PCR testing for confirmed diagnosis and for further evaluation for subtype (A/H3N2, A/H1N1, or B). Upon receipt of additional clarifications highlighted by the Inspection Reports it was clear that the methods described and those used were different. Also, the decision process used to finally assign influenza cases was not described in the MAA.

Clinical specimens were sent to a specialized laboratory for PCR testing for confirmed diagnosis and for further evaluation for subtype (A/H3N2, A/H1N1, or B). If the PCR assay tests were positive for Influenza A or B, viral culture confirmation had to follow.

Viral culture was not performed and cases were classified according to an unreported algorithm based on a different laboratory.

For the season 2007/08, participation per subject was approximately 6 months; for season 2008/09, participation per subject was approximately 12 months (1 influenza season + long-term safety follow-up); for season 2009/10, participation per subject was for at least 6 months or until the end of the surveillance period for influenza, whichever is longer. In practice data from season 1 did not contribute to VE because of late start and season 3 neither was used because of the pandemic.

Study sites contributing to VE and safety evaluation were in Germany and in Finland.

Overall 98 sites (plus one coordinating centre) were included. Sample size in each site was highly variable ranging between 217 and 1. In particular 10 sites had only one or two children enrolled.

Background epidemiological data in Germany and Finland in the pivotal season for VE 2008-9 and accrual rate in the study

Season 1

Only sites in Germany participated in the first season, but because of delayed approval by local health authorities and ethical committees, only 654 subjects were recruited.

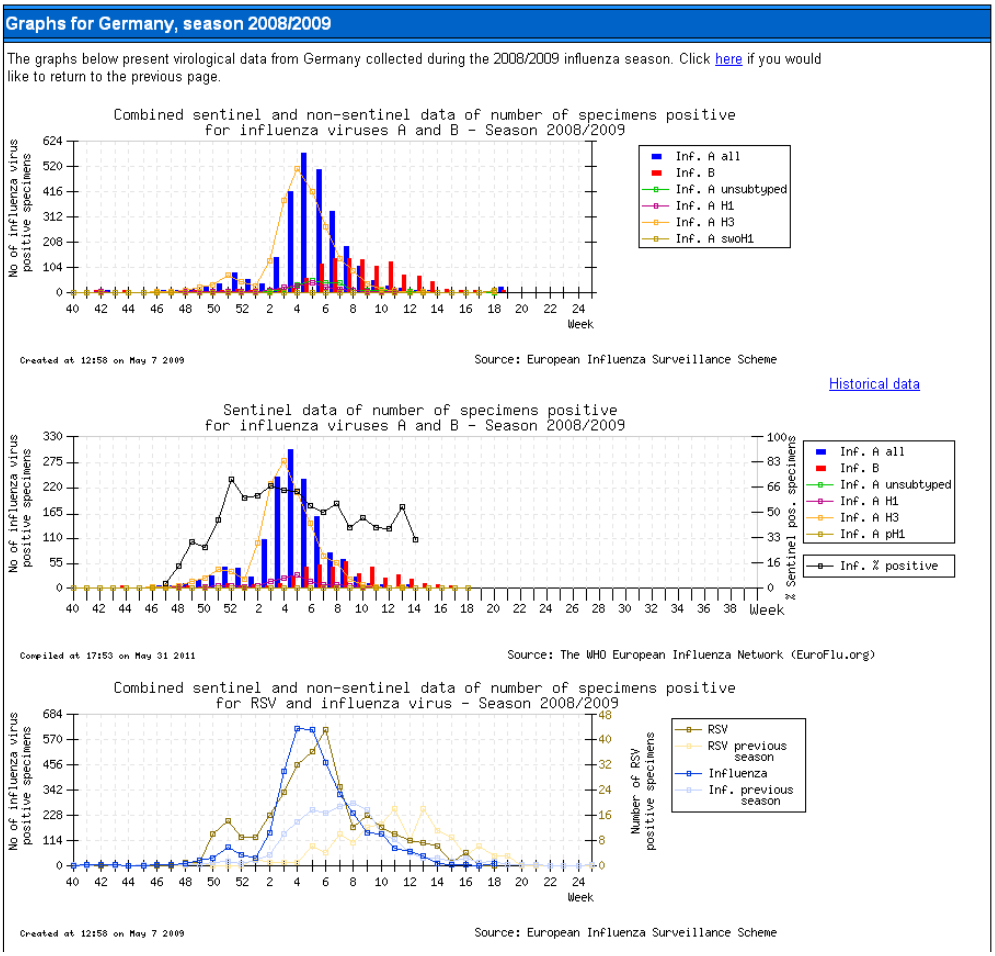
Season 2

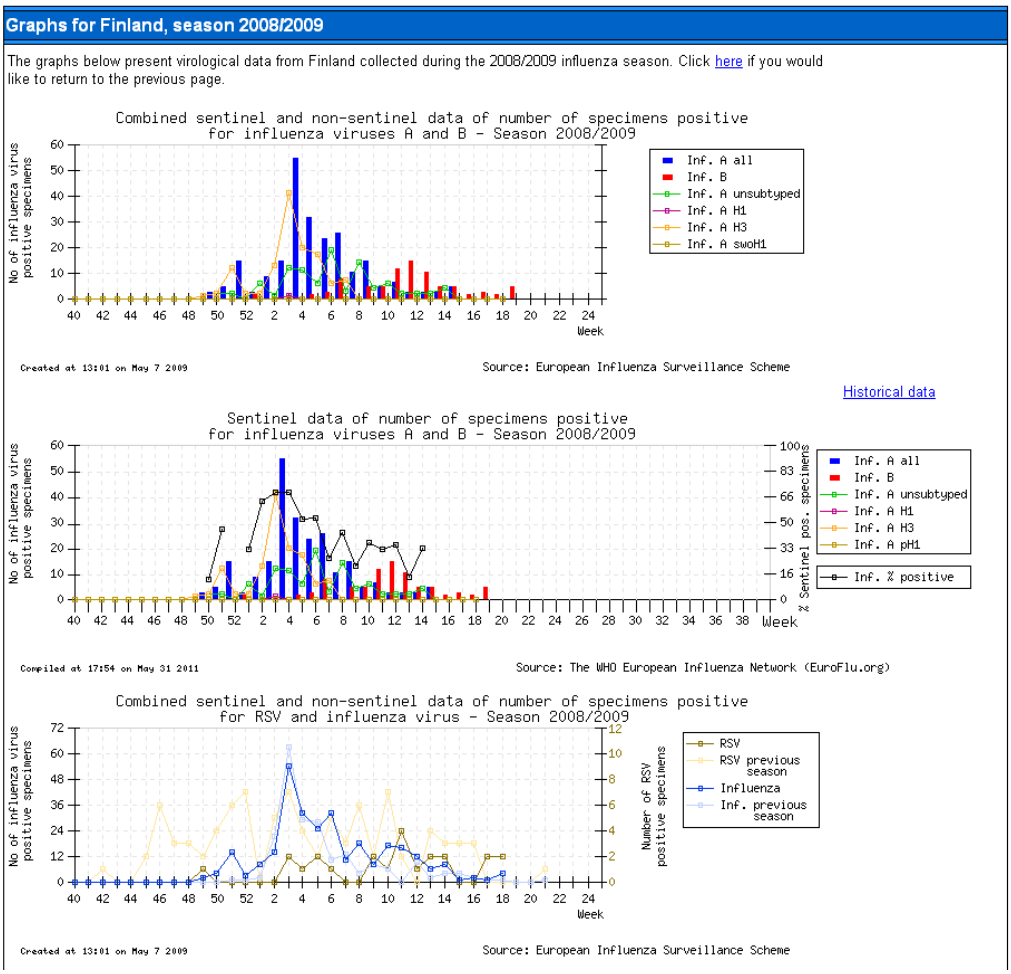
During 2008-09, 82% of subjects were recruited.

Season 3

During season 3, the H1N1 pandemic occurred and the study was discontinued after only 193 subjects had been recruited.

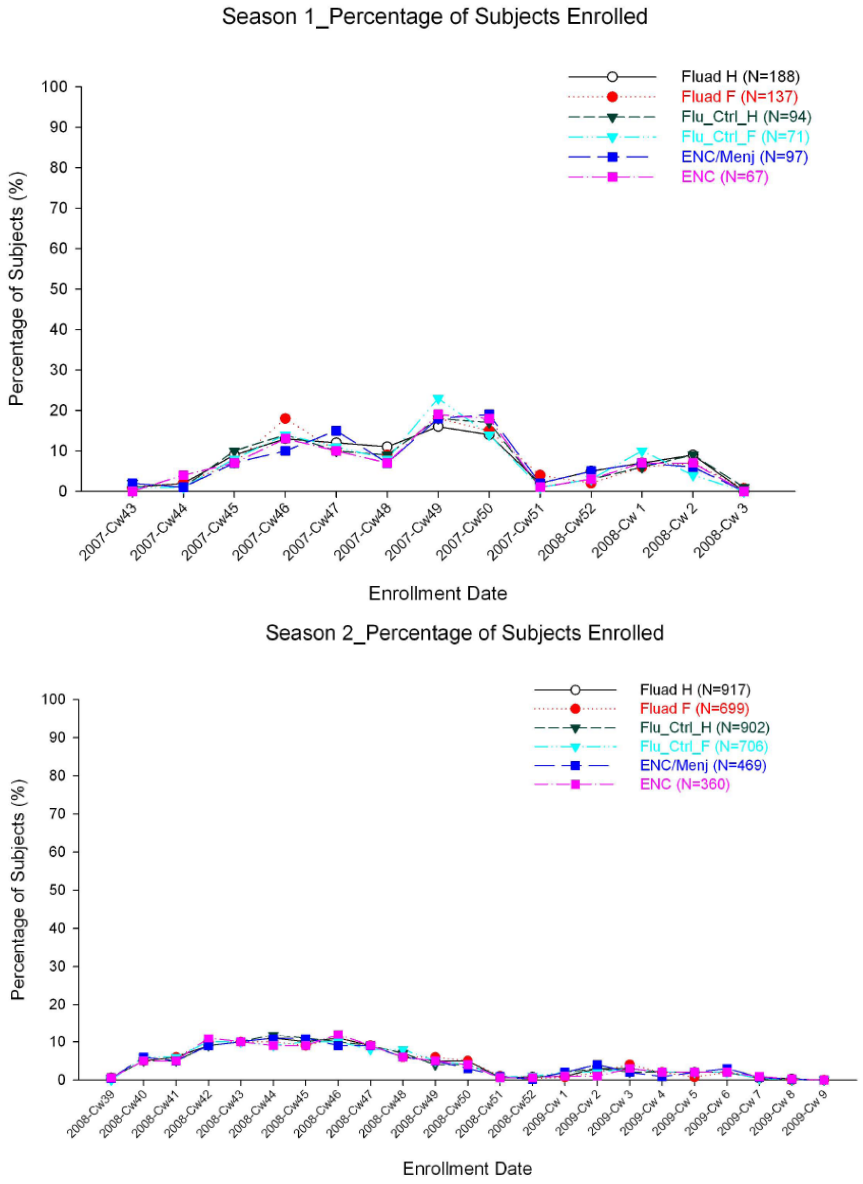
Figure 63-9. Proportion of Influenza-Positive Samples by Week of Reporting, Week 40/2008–20/2009, Germany and Finland





Sample size in each site was highly variable in the 98 sites included in season 2 in the study ranging between 217 and 1. In particular 10 sites had only one or two children enrolled.

Compared to the above reported seasonal influenza epidemic, below the enrolment rate in the pivotal study by week is shown.



Baseline/Background data

The degree of susceptibility of enrolled subjects can be inferred from the serology status at baseline in the following table

Table 2.7.3.3.1-8 Baseline Immune status (HI, SRH and MN assays) Immunogenicity FAS of Pivotal phase II study (season 2008/09)

Age range		6 to <36 months			36 to <72 months		
Vaccine group		Fluad	Influsplit SSW	Menjugate/Encepur	Fluad	Influsplit SSW	Encepur
		HI assay					
N subjects at Day 1		N=166	N=165	N=83	N=153	N=151	N=75
H1N1	GMT (95% CI)	6.21 (5.33-7.24)	7.52 (6.45-8.76)	5.93 (4.8-7.33)	16 (13-21)	14 (11-19)	16 (12-24)
	% SP [a] (95% CI)	5 (3-10)	11 (7-17)	5 (1-12)	36 (28-44)	32 (25-41)	29 (19-41)
H3N2	GMT (95% CI)	5.85 (5.13-6.67)	5.8 (5.09-6.6)	5.66 (4.73-6.77)	27 (20-37)	25 (18-34)	25 (16-39)
	% SP [a] (95% CI)	4 (1-8)	4 (1-8)	2 (0-8)	44 (36-52)	42 (34-50)	40 (29-52)
B	GMT (95% CI)	6.01 (5.59-6.45)	6 (5.59-6.44)	5.87 (5.32-6.47)	6.8 (6.2-7.46)	7.31(6.65-8.03)	7.07 (6.21-8.04)
	% SP [a] (95% CI)	2 (1-6)	2 (0-5)	1 (0.03-7)	1 (0-5)	3 (1-7)	7 (2-15)
		SRH assay					
N subjects at Day 1		N=15	N=22	N=12	N=22	N=15	N=13
H1N1	GMT (95% CI)	5.88 (3.89-8.89)	6.32 (4.53-8.8)	6.75 (4.23-11)	8.39 (5.36-13)	7.14 (4.18-12)	10 (5.73-18)
	% SP [a] (95% CI)	7 (0-32)	5 (0-23)	8 (0-38)	18 (5-40)	13 (2-40)	15 (2-45)
H3N2	GMT (95% CI)	11 (7.94-15)	6.69 (5.24-8.53)	6.8 (4.83-9.57)	14 (8.97-21)	9.05 (5.41-15)	14 (8.11-24)
	% SP [a] (95% CI)	0 (0-22)	0 (0-15)	0 (0-26)	23 (8-45)	20 (4-48)	38 (14-68)
B	GMT (95% CI)	4.66 (3.18-6.83)	6.66 (4.9-9.06)	5.86 (3.8-9.03)	8.68 (5.73-13)	6.75 (4.11-11)	9.75 (5.8-16)
	% SP [a] (95% CI)	0 (0-22)	9 (1-29)	0 (0-26)	14 (3-35)	7 (0-32)	15 (2-45)

		MN assay					
N subjects at Day 1		N=58	N=67	N=35	N=49	N=57	N=30
H1N1	GMT (95% CI)	5.58 (4.51-6.91)	6.55 (5.38-7.97)	6.34 (4.81-8.35)	13 (8.7-19)	16 (11-22)	11 (7.26-18)
	% ≥80 (95% CI)	3 (0-12)	6 (2-15)	9 (2-23)	10 (3-22)	16 (7-28)	17 (6-35)
H3N2	GMT (95% CI)	5.95 (4.66-7.58)	5.92 (4.73-7.4)	6.1 (4.45-8.36)	21 (12-37)	17 (10-27)	23 (13-43)
	% ≥80 (95% CI)	3 (0-12)	4 (1-13)	6 (1-19)	37 (23-52)	30 (18-43)	37 (20-56)
B	GMT (95% CI)	6.51 (5.32-7.97)	6.5 (5.39-7.83)	6.98 (5.37-9.08)	7.2 (5.6-9.27)	7.78 (6.18-9.8)	7.39 (5.53-9.87)
	% ≥80 (95% CI)	2 (0.044-9)	3 (0-10)	6 (1-19)	2 (0.052-11)	2 (0.044-9)	3 (0.084-17)

[a] SP = seroprotection = HI titer ≥ 40 or SRH area ≥25 mm²
Source: V70P5 CSR Table 14.2.1.1.3, Table 14.2.1.3.3, Table 14.2.1.13.1, Table 14.2.1.15.1, Table 14.2.1.16.1 and Table 14.2.1.18.1

- **Numbers analysed**

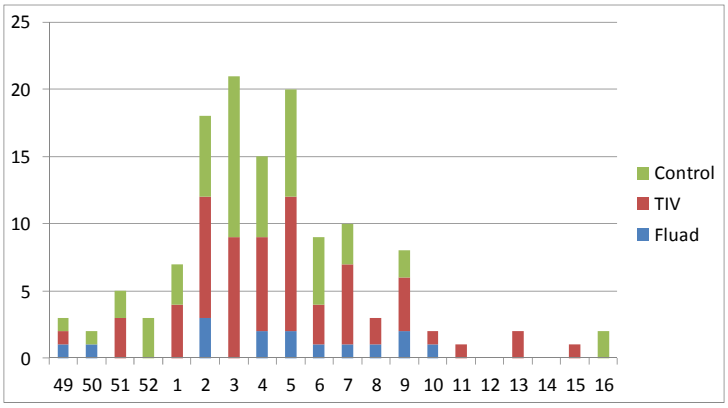
		Enrolled		Efficacy and Safety			Immunogenicity	
		Planned	Analyzed	Planned	FAS	Safety	Planned	FAS
2007/08	TIV-adj	2200	325	2200	323	323	a	0
	Flu-control	1100	165	1100	164	164	a	0
	Non-flu control	1100	164	1100	164	162	a	0
2008/09	TIV-adj	2200	1616	2200	1614	1609	332	319
	Flu-control	2200	1608	2200	1608	1607	332	316
	Non-flu control	1100	829	1100	829	827	166	158
2009/10	TIV-adj	1400	78	1400	b	78	220	11
	Flu-control	1400	76	1400	b	76	220	7
	Non-flu control	700	41	700	b	41	110	6

Source: Table 14.1.1.1.1 (for number of subjects analyzed); study protocol for the planned number of subjects; a: a total of 830 subjects were planned for season 2007/08; b: all available samples were included in efficacy robustness analysis.

Summary of Main Efficacy Results

Overall, during Seasons 2007/2008 and 2008/2009, 1216 samples were collected from 979 subjects with ILI. In 37 sites out of 98 no single ILI was detected or investigated.

Laboratory confirmed influenza-like-illness,
2008-2009 season, by week of onset and treatment,
Finland, Germany



Of 153 positive respiratory samples sent from the first laboratory (C) to the Dept. of Virology, 84 were confirmed influenza cases and included in the efficacy analysis. Among the remaining 69 samples (153 minus 84) not included in the efficacy analysis:

- 40 samples were not confirmed influenza positive at the Dept. of Virology (D);
- 25 samples were confirmed influenza positive at the Dept. of Virology (D), but fell within the 3 weeks interval between vaccination and ILI sampling, defined in both the Study Protocol and SAP as implausible for the purpose of the efficacy analysis;
- 4 samples were duplicates, none of which were double counted in the analysis as they had the same subject code number. These duplicates resulted from sampling of subjects with ILI on different dates, however close one to another (range 5-9 days).

Analysis of Efficacy

All the efficacy analyses were primarily performed on the Full Analysis Set (FAS). The primary and secondary end-points for evaluating the efficacy of the test vaccine TIV-adj when compared with the placebo (Non-flu control) and Flu-control, were analyzed based on the symptomatic, PCR-confirmed influenza cases recorded only 3 weeks after the second vaccination in each season (2007/08 and 2008/09).

Table 2.7.3.3.2.1-1 Efficacy of Fluad in children in the pivotal efficacy study – Subjects with PCR-confirmed influenza 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	1103	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%

[a] details on the subjects included in the efficacy analysis are provided in Table 2.7.3.3.1-3.
Source: V70P5 CSR Table 14.4.1.2.1, Table 14.4.1.2.1.1, Table 14.4.1.2.5, Table 14.4.1.2.5.1, Table 14.4.1.3.1, Table 14.4.1.3.1.1, Table 14.4.1.3.5 and Table 14.4.1.3.5.1

Subjects of 6 to <36 Months Age

During the season-2007/08 the incidence of influenza (Influenza A or B) cases in 6 to <36 months age cohort was low across all the vaccine groups, with only two subjects, both from placebo group (Non flu-control) diagnosed with symptomatic PCR confirmed influenza (Table 11.4.1.1-1).

During the season -2008/09 the incidence of influenza cases was relatively higher with, a higher number of cases being recorded in the Non-flu control and the Flu-control groups (3% to 4%) than in the TIV-adj group (<1%). Most of these cases were caused by influenza strains matching the vaccines administered in the TIV-adj and Flu-control groups.

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.

The point estimate of the absolute efficacy of Fluad vaccine (i.e., vs. the non-flu control vaccine) against matched strains was 89.07%. The point estimate of the relative efficacy (i.e. vs. the flu control vaccine) was calculated as 80.17%. The lower limits of the 2-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.

A total of 110 PCR-confirmed cases of influenza due to any strain (matched and mismatched) were considered as laboratory confirmed 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).

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, i.e., regardless of the antigenic match with the strains, was 86.17%, with the lower limit of the 2-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%.

Due to the findings reported in the inspection report on the quality of the management of laboratory specimens and assays, the biological samples collected during the study were re-tested. The number of positive specimens slightly changed with an apparent increase in the number of positive specimens among the recipients of control vaccines or a decrease in the vaccine recipients.

The estimates of VE have therefore re-computed accordingly with an increase in the vaccine efficacy reported. Vaccine efficacy was also recomputed excluding subjects with unblinded conditions.

All these approaches were performed with the attempt to clarify the dubious quality of the study which cannot be corrected during the analysis.

The original data are reported below.

Absolute efficacy

Across the two seasons the number of subjects who experienced influenza was higher in the placebo group (Non-flu control) group (3% to 4% of subjects) than in the test vaccine (TIV-adj) group (<1% of subjects).The absolute efficacy of the TIV-adj vaccine against the antigenically matched strains was high (81.36%) with the lower bound of 2-sided 97.66% CI at 49% (Table 11.4.1.1-1). These results show that the primary objective/criterion of absolute efficacy was achieved.

Similarly the test vaccine (TIV-adj) was shown to be highly efficacious with respect to the protection provided against influenza strains regardless of the antigenic match, with the absolute efficacy of the test vaccine against infection from any influenza strain at 79% (Table 11.4.1.1-1).

The incidence of the influenza cases due to non-matching viral strains was low across the three vaccine groups (Appendix 16.2.6.2) Analysis of the vaccine efficacy in the subjects with influenza caused due to mismatching strains was not carried out due to the insufficient number of such cases and as such analysis would not yield informative efficacy results. The number of swabs that could not be sub-typed and strain specified additionally impedes interpretation of results related to non-matching strain influenza cases. Overall, there are only isolated (i.e. one to two) definitely non-matching cases in that age cohort in each of the treatment groups besides a similar number of cases with not determinable match.

Relative efficacy

Spanning the two seasons the number of subjects who experienced influenza was higher in the Flu-control group (2.2% and 2.5%) that received non-adjuvanted trivalent seasonal vaccines, than in the test vaccine group that received adjuvanted trivalent seasonal vaccine (TIV-adj) (<1%; Table 11.4.1.1-1). The relative efficacy of the TIV-adj vaccine with respect to the Flu-control vaccines in terms of the frequency of subjects affected by the matching influenza strain was 68% (Table 11.4.1.1-1).

The test vaccine was also found to be more efficacious than the Flu-control vaccines in providing protection against influenza regardless of the antigenic strain match with the relative efficacy being 64% (Table 11.4.1.1-1).

Overall, spanning the two influenza seasons (2007/08 and 2008/09) TIV-adj had significantly lower incidence of influenza cases (with or regardless of strain match) than the placebo (Non-flu control) and non-adjuvanted Flu-control groups and therefore showed a high absolute and relative efficacies. All the estimates were statistically significant.

Flu-control versus Placebo (Non-flu control):

The incidence of the influenza cases caused due to any strain (regardless of the antigenic match), in the Flu-control and placebo groups spanning the two influenza seasons (2007/08 and 2008/09) was comparable (2.5% versus 3.8%); the efficacy of the Flucontrol group in comparison with the placebo was low (40% with 95% CI of 6%-66%; Table 14.4.1.4.5.1). Most of the influenza cases were caused due to the antigenically matching strains (Table 11.4.1.1-1).

Table 11.4.1.1-1: Percentage of Subjects Aged 6 to <36 Months with Virus-Confirmed Influenza and Efficacy (Poisson) of the Vaccines Administered-FAS

	TIV-adj	Non-flu Control	VE (in % and 95% CI) Absolute[a]	Flu Control	VE (in %, 95% CI) Relative[b]
	Season-2007/08				
	N=187	**N=97**		**N=93**	
Matched strain	0	0	-	0	-
Any strain	0	2 (2%)		0	-
	Season-2008/09				
	N=916	**N=469**		**N=902**	-
Matched Strain	7 (0.76%)	19 (4%)	-	22 (2%)	-
Any strain	9 (0.98%)	20 (4%)	-	25 (3%)	-
	Combined Seasons-2007/08 and 2008/09				
	N=1103	**N=566**		**N=995**	
Matched Strain	7 (0.6%)	19 (3.3%)	**81.36 [c](49.24-93.16)**	22 (2.2%)	68.42 [d](26.59-86.41)
Any strain	9 (0.8%)	22 (3.8%)	79.18 (54.78-90.42)	25 (2.5%)	64.16 (23.21-83.28)

Source: Table 14.4.1.2.1.1; Table 14.4.1.2.5.1; Table 14.4.1.3.3.1; Table 14.4.1.3.5.1 a: TIV-adj versus Non-flu Control; b: TIV-adj versus Flu Control; c: 2-sided 97.66% CI; d: by CMH method; **Bold font**: Primary objective.

Subjects 6 to <72 Months of Age

In the season 2007/08, the incidence of the PCR-confirmed influenza cases in 6 to <72 months age cohort was low across all the vaccine groups, with <1% cases been recorded in TIV-adj and Flu-control groups. A higher number of cases were recorded in the placebo (Non-flu control) group (2.4% of subjects). None of the cases recorded during this season were diagnosed to be caused by the matching influenza strains included in the vaccine administered (Table 11.4.1.2-1). In the Season 2008/09, most of the cases recorded in 6 to <72 months age cohort across the vaccine groups had PCR confirmed influenza due to the strains matching the influenza strains included in the vaccines. The incidence was lower in the TIV-adj group than in the Flu-control and placebo (Non-flu control) groups.

Absolute efficacy

Spanning the two seasons, the influenza attack rate regardless of the antigenic match with the strains included in the vaccines, was significantly lower in the TIV-adj vaccine group (<1%) than in the

placebo group (Non-flu control) (about 5%; Table 11.4.1.2-1). The observed attack rate in the placebo (Non-flu control) group was similar to the range expected for baseline attack rate (Section 9.7.2). The absolute efficacy of the test vaccine was high against the matching strain (about 89%) as well as against any influenza strains regardless of antigenic match (86%) (Table 11.4.1.2-1).

Relative efficacy

Across the two seasons the influenza attack rate was higher in the Flu-control group that received non-adjuvanted seasonal influenza (2% to 3% across matched and any strains) vaccines than in the test vaccine (TIV-adj) group (<1%). The test vaccine was shown to be highly efficacious relative to the Flu-control vaccine against the influenza caused by the matching strains (80%) as well as against influenza caused by any strain, regardless of the antigenic match (75%) (Table 11.4.1.2-1).

Flu-control versus Placebo (Non-flu control):

Spanning the two influenza seasons (2007/08 and 2008/09), the incidence of the influenza cases (regardless of the antigenic match) in the overall age group of 6 to <72 months was comparable between the Flu-control group and placebo group (3% versus 5%; Table 11.4.1.2-1). The efficacy of the Flu-control group when compared with the placebo was low (43% with 95% CI of 15%- 61%; Table 14.4.1.4.5).

Table 11.4.1.2-1: Percentage of Subjects Aged 6 to <72 Months with Virus-Confirmed Influenza and Efficacy (Poisson) of the Vaccines Administered-FAS

	TIV-adj	Non-flu Control	VE (in %) Absolute[a]	Flu Control	VE (in %) Relative[b]
	Season-2007/08				
	N=323	N=164		N=164	
Matched strain	0	0	-	0	-
Any strain	1 (0.3%)	4 (2.4%)	-	0	-
	Season-2008/09				
	N=1614	N=829		N=1608	
Matched Strain	9 (0.5%)	41 (4.9%)	-	44 (2.7%)	-
Any strain	12 (0.7%)	43 (5%)	-	50 (3%)	-
	Combined Seasons-2007/08 and 2008/09				
	N=1937	N=993		N=1772	
Matched Strain	9 (0.46%)	41 (4.1%)	89.07 (78-95)	44 (2.4%)	80.17 (59-90)
Any strain	13 (0.67%)	47 (4.7%)	86.17 (74-93)	50 (2.8%)	75.49 (55-87)

Source: Table 14.4.1.2.1; Table 14.4.1.2.5; Table 14.4.1.3.1; Table 14.4.1.3.5; a: TIV-adj versus Non-flu Control; b: TIV-adj versus Flu Control.

Table 2.7.3.3.2.1-2 Absolute and relative efficacy of Fluad in children in the pivotal study (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)

[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
Source: V70P5 CSR Table 14.4.1.2.1, Table 14.4.1.2.1.1, Table 14.4.1.2.5, Table 14.4.1.2.5.1, Table 14.4.1.3.1, Table 14.4.1.3.1.1, Table 14.4.1.3.5 and Table 14.4.1.3.5.1,

Influenza like illnesses, hospitalizations, and school/work days lost

6 to <36 Months Age group

Spanning the two influenza seasons (2007/08 and 2008/09), 25% to 28% of subjects across the vaccine groups reported Influenza Like Illnesses (ILIs). Though there was no substantial difference among the vaccine groups with ILIs, there was a trend of slightly lower proportion of such cases in the TIV-adj group when compared to the Flu-control and placebo (Non-flu control) groups (25% versus 27% and 29%; Table 11.4.1.5-1).

Table 11.4.1.5-1: Influenza Like Illnesses, in the 6 to <36 Months Age Cohort for Combined Seasons 2007/08 and 2008/09-Efficacy FAS

	Combined Seasons-2007/08 and 2008/09		
	TIV-adj	Flu-control	Non-flu control
	N=1103	N=995	N=566
Subjects with ILI[a]	280 (25%)	272 (27%)	163 (29%)
Mean ILI Events	1.3±0.5	1.3±0.5	1.3±0.6
Mean bed days	2.0±2.5	1.8±2.4	2.1±2.4
Median (bed days)	1.0	1.0	1.0
Mean inactive days	2.9±3.3	2.6±3.3	3.0±3.6
Median (inactive days)	2.0	1.0	2.0
Seek medical care	204 (73%)	198 (73%)	123 (75%)
Outpatient visits			
No	45 (16%)	50 (18%)	34 (21%)
Any	192 (69%)	183 (67%)	113 (69%)
Not available	43 (15%)	39 (14%)	16 (10%)
Inpatient visits			
No	224 (80%)	215 (79%)	134 (82%)
Any	13 (5%)	19 (7%)	14 (9%)
Not available	43 (15%)	38 (14%)	15 (9%)
Outcome			
Recovered	269 (96%)	267 (98%)	159 (98%)
Alive with sequelae	5 (2%)	2 (<1%)	2 (1%)
Lost to follow-up	3 (1%)	1 (<1%)	0
ILI persisting	3 (1%)	1 (<1%)	2 (1%)
Not available	0	1	0

Source: Table 14.4.1.1.6.1; Table 14.1.1.1.2 (Source for number of subjects in efficacy FAS); a: Percentage of subjects with respect to FAS; All other percentage are with respect to the subjects reporting ILIs.

The general condition of the subjects was assessed by the physician to be either very good/good/poor/very poor based on a brief physical evaluation. Among the subjects reporting ILIs, in a low proportion of subjects (8% to 11%) the condition was assessed to be "poor" and <1% of subjects were assessed to be in "very poor" condition; all other subjects were reported to be in "good" to "very good" condition (Table 14.4.1.1.6.1 of the dossier).

A large proportion of the subjects with ILIs had inactive bed days in all the vaccine groups and 73% to 75% of the subjects with ILIs sought medical care. More than half of the subjects with ILIs in each vaccine group had at least one outpatient visit (67% to 69%).

Across the vaccine groups a low proportion of subjects with ILIs reported hospitalizations and the TIV-adj group had a lower percentage of such reports (5% versus 7% in the Flu control group and 9% in the placebo [Non-flu control] group). The majority of subjects had an outcome of complete recovery from the ILIs (96% to 98%).

6 to <72 Months Age Group:
Influenza like illnesses (ILIs) were analyzed in the overall age cohort (6 to <72 months age) spanning two influenza seasons 2007/08 and 2008/09. The percentage of subjects reporting ILIs in the overall age cohort were low and there was a trend towards a slightly lower incidence of such cases in the TIV-adj group when compared with Flu-control and placebo (Non-flu control) groups (22% to 25%; Table 11.4.1.5-2).

Table 11.4.1.5-2: Influenza Like Illnesses (ILIs) in the 6 to <72 Months Age Cohort for Combined Seasons 2007/08 and 2008/09- Efficacy FAS

	Combined Season-2007/08 and Season-2008/09		
	TIV-adj	Flu-control	Non-flu control
	N=1937	N=1772	N=993
Subjects with ILI[a]	425 (22%)	436 (25%)	253 (25%)
Mean ILI Events	1.2±0.5	1.2±0.5	1.3±0.6
Mean bed days	1.9±2.3	1.9±2.4	2.3±2.7
Median (bed days)	1.0	1.0	2.0
Mean inactive days	3.1+3.3	2.9+3.7	3.3+3.5
Median (Inactive days)	3.0	2.0	2.0
Seek medical care	310 (73%)	316 (72%)	186 (74%)
Outpatient visits			
No	76 (18%)	79 (18%)	50 (20%)
Any	290 (68%)	293 (67%)	174 (69%)
Not available	59 (14%)	64 (15%)	29 (11%)
Inpatient visits			
No	346 (81%)	347 (80%)	206 (81%)
Any	20 (5%)	26 (6%)	19 (8%)
Not available	59 (14%)	63(14%)	28 (11%)
Outcome			
Recovered	414 (97%)	431 (99%)	248 (98%)
Alive with sequelae	5 (1%)	2 (<1%)	2 (<1%)
Lost to follow-up	3 (<1%)	1 (<1%)	0
ILI persisting	3 (<1%)	1 (<1%)	3 (1%)
Not available	0	1 (<1%)	0

Source: Table 14.4.1.1.6.2; Table 14.1.1.1.1 (Source for the number of subjects in efficacy FAS) a: Percentage of subjects with respect to FAS; All other percentages are with respect to the subjects reporting ILIs

The general condition was considered "good" to "very good" in most of the subjects (about 90%) and was assessed to be "poor" or "reduced" in about 10% subjects (Table 14.4.1.1.6.2). Among the subjects with ILIs a large proportion of subjects had inactive bed days and majority of these subjects had received medical care (72% to 74%).

Most of these subjects had reported outpatient visits (67% to 69%) and across the vaccine groups a low percentage of subjects reported hospitalization; as observed with the 6 to <36 months age group, the TIV-adj group reported slightly lower percentage of subjects with hospitalization (5% versus 6% in the Flu control group and 8% in the placebo [Nonflu control] group; Table 11.4.1.4-2). A vast majority of the subjects with ILIs had recovered from the illness (97% to 99%).

Lack of any substantial difference in the incidence of ILI cases among the adjuvanted, non-adjuvanted and placebo groups could be due to the fact that the symptoms of ILIs, fever (≥37.8°C), cough or sore throat can have multiple etiologies especially in the subjects of this age group. Among the subjects reporting ILIs, a low proportion of subjects had laboratory confirmed influenza across the vaccine groups and the incidence of confirmed influenza cases was lower in the TIV-adj group (reported by 1% of subjects; 13 out of 1103 subjects) than in the Flu-control (by 5% of subjects; 50 out of 995 subjects) and placebo groups (by 8% of subjects; 47 out of 566 subjects) (Section 11.4.1.1 and Section 11.4.1.2).

No effect on ILI occurrence was shown in the study.

Sub-analyses relevant to efficacy estimate

Efficacy Robustness Analysis- Across Three Seasons

Efficacy robustness analysis was performed on all the subjects with symptomatic PCR-confirmed influenza, in the 2007/08, 2008/09 and 2009/10 influenza seasons; this analysis also included subjects with early influenza diagnosis from 3 weeks after first vaccination to 3 weeks after the second vaccination. Influenza cases recorded prior to 3 weeks after the first vaccination were excluded from all the efficacy analyses.

Across the age cohorts (overall 6 to <72 and 6 to <36 months) the pooled analysis spanning the three influenza seasons (2007/08; 2008/09 and 2009/10) shows that the incidence of influenza cases was significantly lower in the adjuvanted TIV-adj group (<1% subjects) when compared with the Placebo (Non-flu Control group; 4% to 5%) or with the non-adjuvanted Flu-control group (2% to 3%; Table 11.4.1.3-1), therefore with a significantly high absolute and relative efficacy estimates. The vaccine efficacy of the Flu-control group when compared to the placebo (Non-flu control) was also low (VE: 40% to 48% across the age groups and matched or any strains; Table 14.4.1.4.2; Table 14.4.1.4.2.1; Table 14.4.1.4.6; Table 14.4.1.4.6.1). Hence, the efficacy results spanning the three influenza seasons (2007/08; 2008/09 and 2009/10) confirm the results spanning two seasons (2007/08 and 2008/09; primary and secondary end-points), thereby establishing the robustness of the results from primary and secondary efficacy analyses

Table 11.4.1.3-1: Absolute and Relative Efficacy (Poisson) Spanning the Three Seasons and Age Cohorts -FAS

Combined Seasons-2007/08; 2008/09 and 2009/10					
[a]All Age Cohorts					
	TIV-adj	Non-flu Control	VE (in %) Absolute[a]	Flu Control	VE (in %) Relative
	N=2015	N=1034		N=1846	
Matched Strain	10 (<1%)	50 (5%)	[b]89.76 (80-95)	54 (3%)	[b]81.6 (64-91)
Any strain	16 (<1%)	56 (5%)	85.68 (75-92)	62 (3%)	76.1 (59-86)
6 to <36 Months					
	N=1181	N=607		N=1069	
Matched Strain	8 (<1%)	26 (4%)	[b]84.28 (66-93)	26 (2%)	[b]69.5 (33-86)
Any strain	10 (<1%)	29 (5%)	c	31 (3%)	69.3 (38-85)

Source: Table 14.4.1.2.2; Table 14.4.1.2.2.1; Table 14.4.1.2.6; Table 14.4.1.2.6.1; Table 14.4.1.3.2; Table 14.4.1.3.2.1; Table 14.4.1.3.6; Table 14.4.1.3.6.1; a: combined subjects: 6 to <72 years for season 2007/08 + 6 to <72 years for season 2008/09 + 6 to <36 for season 2009/10; b: by CMH method; c: Not determined as the algorithm did not converge.

Subjects Aged 6 to <24 months and 24 to <72 months

Efficacy of the test vaccine (TIV-adj) was also evaluated by sub-grouping the subjects (aged 6 to <72 months) into alternative age groups of 6 to <24 months and 24 to <72 months and the influenza cases recorded during the span of two influenza seasons-2007/08 and 2008/09 were analyzed.

6 to <24 Months Age:

The incidence of the influenza cases in 6 to <24 months age group was low in the influenza season 2007/08, with overall 2 cases recorded only in the placebo (Non-flu control) group. In the influenza season 2008/09, a low percentage of cases were recorded in the test vaccine group (adjuvanted TIV-adj group) than in the placebo and nonadjuvanted Flu-control groups (Table 11.4.1.4-1).

Therefore spanning the two influenza seasons (2007/08 and 2008/09) the TIV-adj was found to be highly efficacious when compared with the placebo (Non-flu control) and Flu-control vaccine with high absolute and relative efficacies against both, the influenza strains matching the strains included in the influenza vaccine administered as well as against all strains regardless of the antigenic match.

Flu-control versus Placebo (Non-flu control): In the age group of 6 to <24 months, the incidence of the influenza cases was similar between the Flu-control and Non-flu control groups (Table 11.4.1.4-1); therefore the non-adjuvanted Flu-control was not found to be efficacious when compared with the placebo (VE: 1.5% Table 14.4.1.4.4).

24 to <72 Months Age:

In the influenza season 2007/08, the incidence of influenza cases in 24 to <72 age group was low with three cases of influenza were recorded across the vaccine groups; two in the placebo group and one in the TIV-adj group. In the influenza season 2008/09, the incidence of influenza cases was high in all the vaccine groups. Across the vaccine groups the test vaccine (adjuvanted TIV-adj) group reported lowest incidence of the influenza cases (by <1% of subjects); highest rate of influenza was recorded in the placebo group (by 7% of subjects) and the Flu-control group reported relatively lower number of such

cases (by 3% of subjects) (Table 11.4.1.4-1).

Overall, after pooling the influenza cases across the two influenza seasons (2007/08 and 2008/09) in the subjects aged 24 to <72 months, the test vaccine TIV-adj was found to have a high absolute (versus placebo) and relative efficacies (versus Flu-control) against both matching as well as any influenza strains.

Flu-control versus Placebo (Non-flu control): The non-adjuvanted Flu-control vaccine showed a better response in the older age group, 24 to <72 months when compared with the 6 to <24 months age group. The incidence of the influenza cases was lower in the Flucontrol group than in the placebo group (3% versus 6%; Table 11.4.1.4-1) with the vaccine efficacy of 55% (95% CI of 27%-73%; Table 14.4.1.4.4).

Table 11.4.1.4-1: Absolute and Relative Efficacy (CMH) in Subjects Aged 6 to <24 and 24 to <72 Months -FAS

		TIV-adj	Non-flu Control	VE (in %) Absolute	Flu Control	VE (in %) Relative
6 to <24 Months			Season 2007/08			
		N=131	N=61		N=63	
	Matched strains	0	0	-	0	-
	Any Strain	0	2 (3%)	-	0	-
			Season 2008/09			
		N=689	N=340		N=643	
	Matched strains	4 (<1%)	8 (2%)	-	15 (2%)	-
	Any Strain	5 (<1%)	9 (3%)	-	18 (3%)	-
			Combined Seasons (2007/08 and 2008/09)			
		N=820	N=401		N=706	
	Matched strains	4 (<1%)	8 (2%)	75% (20-92)	15 (2%)	75% (25-91)
	Any Strain	5 (<1%)	11 (3%)	77% (37-92)	18 (3%)	73% (29-90)
24 to <72 Months			Season 2007/08			
		N=192	N=103		N=101	
	Matched strains	0	0	-	0	-
	Any Strain	1 (<1%)	2 (2%)	-	0	-
			Season 2008/09			
		N=925	N=489		N=965	
	Matched strains	5 (<1%)	33 (7%)	-	29 (3%)	-
	Any Strain	7 (<1%)	34 (7%)	-	32 (3%)	-
			Combined Seasons (2007/08 and 2008/09)			
		N=1117	N=592		N=1066	
	Matched strains	5 (<1%)	33 (6%)	92% (80-97)	29 (3%)	82% (54-93)
	Any Strain	8 (<1%)	36 (6%)	88% (75-95)	32 (3%)	75% (45-89)

Source: Table 14.4.1.2.4; Table 14.4.1.2.8; Table 14.4.1.3.4; Table 14.4.1.3.8.

Efficacy by serostatus at baseline

Response to the vaccines administered was analyzed by classifying the subjects based on baseline immune status into subjects who were seronegative at baseline (HI titer <1:10) and subjects who were seropositive at baseline (HI titer ≥1:10).

Table 11.4.2.8-1: Efficacy of Vaccines Administered in Subjects Seronegative at Baseline Season- 2008/09 - FAS

	TIV-adj	Non-Flu Control (Placebo)	VE (Absolute) TIV-adj : Non-flu Control	Flu-control	VE (Relative) TIV-adj :Flu control
Subjects 6 to <72 Months Age					
	N=246	N=127		N=247	
Matched strain (H3N2)	3 (1%)	6 (5%)	74.07 (0-93.39)	14 (6%)	78.74 (27-94)
Any strain(H3N2)	3 (1%)	6 (5%)	74.07 (0-93.39)	14 (6%)	78.74 (27-94)

Source: Table 14.4.1.2.4.1; Table 14.4.1.2.8.1; Table 14.4.1.3.4.1; Table 14.4.1.3.8.1

Evaluation of a Serological Predictor of Protection against Influenza

An HI titer of 1:40 has been widely used as a correlate of protection in children. However, this antibody level was estimated from studies in adult subjects (>18 years) and not in children. Therefore, the subset of subjects with immunogenicity data was used to evaluate the relationship between antibody levels 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.

As detailed in section 11.4.1.6, the immunogenicity subset was confined to season 2008/09. The present analyses included a total of 311, 313 and 153 subjects (6 to<72 months age group) in the TIV-adj, Flu-control (non-adjuvanted) and the Non-flu control (placebo) group respectively with antibody titers against the A/H3N2 strain at day 50.

The present analyses also included the subjects, in whom baseline titer was not measured, thus explaining slightly higher sample sizes. Day 50 geometric mean titer (GMTs) including 2-sided 95% confidence interval is summarized in the Table 11.4.1.8-1 below:

Table 11.4.1.8-1: A/Brisbane/2007 (A/H3N2) Geometric Mean Titer and Percentages of Subjects With HI Titer ≥ 1:40 in Subjects 6 to <72 Months of Age for Season 2008/09

A/Brisbane/2007 (A/H3N2)	TIV-adj	Flu-control	Non-flu control
Day 50	N=311	N=313	N=153
GMT	746 (661-843)	92 (74-115)	12 (9.0-15.4)

Source: Appendix 16.1.9.8.1

Six subjects from Non-flu control group, 14 subjects from Flu-control group and only two subjects from TIV-adj group experienced influenza caused due to A/H3N2 strain in the immunogenicity subset. The distribution of influenza cases by day 50 HI titer is shown in Table 11.4.1.8-2 below.

Table 11.4.1.8-2: Distribution of Culture-Confirmed Influenza Cases by Titer of HI Antibodies to A/Brisbane/2007 (A/H3N2) in Subjects 6 to <72 Months of Age for Season 2008/09

A/Brisbane/2007 (A/H3N2) Titer	Non-flu control n/N (%)	Flu-control n/N (%)	TIV-adj n/N (%)
5	6/119 (5.04)	2/25 (8.00)	0/4
10	-	2/36 (5.56)	-
20	0/2	4/47 (8.51)	-
28	-	0/1	-
40	0/1	2/42 (4.76)	0/1
57	-	0/1	-
80	0/4	4/28 (14.29)	0/1
113	-	0/1	-
160	0/7	0/32	0/21
226	-	0/1	0/2
320	0/13	0/17	0/63
453	0/1	-	0/7
640	0/4	0/16	1/76 (1.32)
905	-	0/2	0/4
1280	-	0/35	1/63 (1.59)
1810	-	0/4	0/4
2560	0/1	0/19	0/46
3620	0/1	0/2	0/9
5120	-	0/4	0/10

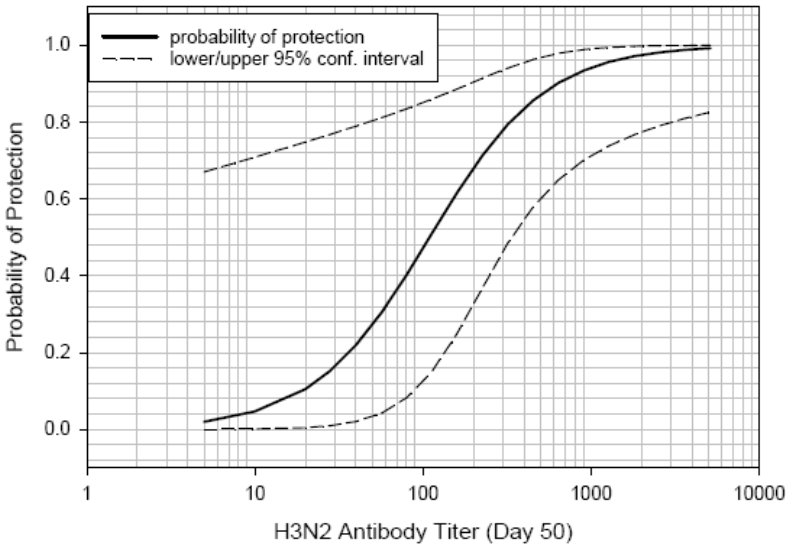
The Prentice criterion (Prentice 1989) is generally utilized to determine whether an immunologic correlate of protection can be determined. The criterion requires that the observed vaccine effect can be completely explained in a statistical model using immunologic data. In practice, this requires that the immunologic data be highly correlated with the observed vaccine effect and also that when the immunologic data is included in the model, the effect of vaccine group is no longer significant. Accordingly, 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 log2 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 (Table 11.4.1.8-3). Thus, according to the Prentice criterion, antibody titer can be considered as correlate of protection.

Having established that antibody titer may serve as a correlate of protection, an antibody cut-off level for clinical protection against H3N2 associated influenza was determined. In the past, usually this level has been defined as the antibody level at which the probability of clinical protection is 50% (Nauta JJP et al, 2009). However, since 50% protection is lower than the desired public health effect, further analyses were conducted to determine the level of antibody associated with 60%, 70%, 80%, and 90% protection

The probability between occurrence of influenza and H3N2 antibody titer level was evaluated using a model advocated by Dunning AJ (2006) that accommodates both antibody titers and factors independent of antibody titers. In this model the probability that a subject develops influenza is the probability that the subject is susceptible multiplied by the probability that susceptible individuals develop disease. Susceptibility is characterized by the probability λ and the probability that a subject with titer t is protected is represented by a 2-paramter logit function, with α and β denoting the location and the scale parameters of interest.

Fitting the data to the H3N2 antibody levels and the respective influenza cases observed in the immunogenicity subset (across all three vaccine groups) parameter estimates (shown in the Table 11.4.1.8-4 of the study report) have been obtained and the result of the model is shown below:

Figure 11.4.1.8-1: Probability of Protection by A/Brisbane/2007 (A/H3N2) Titers at Day 50 in 6 to <72 Months Age Group



Titer values at which 50%, 60%, 70%, 80% and 90% of subjects are protected can be derived from the model (Table 11.4.1.8-5).

Table 11.4.1.8-5: Antibody Titer Levels by Protection Rates in Subjects 6 to <72 Months of Age for Season 2008/09

Probability of Protection	H3N2 Antibody Titer Level
50%	1:110
60%	1:151
70%	1:215
80%	1:330
90%	1:629

Source: Appendix 16.1.9.8.3

The conventional 1:40 antibody level is only associated with 22% protection from clinical infection.

Summary of main studies

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Pivotal Efficacy for trial

Title: A Phase III, randomized, observer-blind, controlled, multi-center clinical study to evaluate the efficacy, safety and immunogenicity of one and two intramuscular doses of FLUAD® versus control vaccines in unprimed healthy subjects aged 6 to <72 months.			
Study identifier	Pivotal Efficacy Trial		
Design	randomized, observer-blind, controlled, multi-center clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 years 10 months not applicable not applicable
Hypothesis	Non inferiority for safety		
Treatments groups	FLUAD		Fluad, 28 days, 2019
	Unadjuvanted seasonal influenza vaccine		Agrippal (07/08) Influsplit (08/09 & 09/10). 28 days, 1849
	Non influenza control vaccine		Menjugate/ Encepur 28 days, 1034
Endpoints and definitions	Primary	Primary endpoint 1	To demonstrate the safety and tolerability of one or two 0.25mL IM doses of Fluad (TIV-adj) in unprimed children aged 6 to <36 months, compared with Agrippal S1 and/or with Influsplit SSW (Flu vaccine control) in terms of any solicited local and systemic reactions (combined) reported within 7 days after any vaccination.
	Primary	Primary endpoint 2	To demonstrate protection provided by two 0.25mL intramuscular (IM) doses of Fluad (TIV-adj) in unprimed children aged 6 to <36 months, compared with Menjugate/ Encepur Children (Non-flu vaccine control), against influenza illness caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine.

	Secondary	Secondary Endpoint 1	To demonstrate the safety and tolerability of one or two 0.25mL or 0.5mL IM doses of Fluad in unprimed children aged 6 to <72 months, compared to flu vaccine control, in terms of any solicited local and systemic reactions (combined) reported within 7 days after any vaccination.
	Secondary	Secondary Endpoint 2	To demonstrate protection provided by two 0.25mL or 0.5mL IM doses of Fluad, compared to non-flu vaccine control, against influenza illness caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine, in children aged 6 to <72 months.
	Secondary	Secondary Endpoint 3	To evaluate protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine in unprimed children aged 6 to <36 months compared to Non-flu vaccine control.
	Secondary	Secondary Endpoint 4	To evaluate protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine in unprimed children aged 6 to <72 months and in the overall age cohort compared to Non-flu vaccine control.
	Secondary	Secondary Endpoint 5	To evaluate protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine in unprimed children aged 6 to <36 months compared to Flu vaccine control. . (Agrippal S1 and/or Influsplit SSW).
	Secondary	Secondary Endpoint 5	To evaluate protection provided by two 0.25mL and/or 0.5mL IM doses of Fluad against influenza illness caused by virus-confirmed community-acquired influenza wild type strains, regardless of antigenic match to those contained in the vaccine in unprimed children aged 6 to <72 months and in the overall age cohort compared to Flu vaccine control. (Agrippal S1 and/or Influsplit SSW).

	Secondary	Secondary Endpoint 6	To demonstrate superiority of immunogenicity of two 0.25mL or 0.5mL IM doses of Fluad, compared to Influsplit SSW, in terms of post-immunization geometric mean titers (GMTs), as measured by haemagglutination inhibition (HI) assay in unprimed children aged 6 to <36 months and in the overall age cohort
	Secondary	Secondary Endpoint 7	To demonstrate superiority of immunogenicity of two 0.25mL or 0.5mL IM doses of Fluad, compared to Influsplit SSW, in terms of post-immunization geometric mean titers (GMTs), as measured by haemagglutination inhibition (HI) assay in unprimed children aged 6 to <72 months and in the overall age cohort
Database lock	September 2010		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set, 1 year post vaccination/subject			
Descriptive statistics and estimate variability	Treatment group	FLUAD	Unadjuvanted seasonal influenza vaccine	Non influenza control vaccine
	Number of subject	1937	1772	973
	age (Mean)	32.1	34.2	33.2
	Standard Deviation	18.8	19.7	19.6
	Male gender (count)	830(51%)	803(50%)	435(52%)
		N/A	N/A	N/A
	Caucasian Race (count)	1569(97%) N/A	1538(96%) N/A	792(96%) N/A

Effect estimate per comparison	Primary endpoint (risk for local and systemic reactions)	Comparison groups	FLUAD vs. Flu control
		Relative risk	1.03
		97.66% CI	0.98-1.09
		P-value	>0.05
	Primary endpoint (Efficacy)	Comparison groups	FLUAD vs. Flu control vs. Non-Flu control
		ILI Incidence	0.46% vs. 2.4% vs. 4.1%
		None	N/A

		P-value	N/A
	Secondary endpoint 1	Comparison groups	FLUAD vs. Flu control
		Relative risk	1.0832
		95% CI	1.046-1.121
	Secondary endpoint 2	Comparison groups	FLUAD vs. Non-Flu control
		Vaccine Efficacy	89.76%
		95% CI	80-95%
	Secondary endpoint 3	Comparison groups	FLUAD vs. Non-Flu control
		Vaccine Efficacy	84.28%
		95% CI	66-93%
	Secondary endpoint 4	Comparison groups	FLUAD vs. Flu control
		Vaccine Efficacy	81.6%
		95% CI	64-91%
	Secondary endpoint 5	Comparison groups	FLUAD vs. Flu control
		Vaccine Efficacy	69.5%
		95% CI	33-96%
	Secondary endpoint 6	Comparison groups	FLUAD vs. Flu control
		% Difference in Titer >1:40 at Day 50: H1N1, H3N2, B	62%; 54%; 69%
		95% CI: H1N1, H3N2, B	54-69; 47-62; 60-76
	Secondary endpoint 7	Comparison groups	FLUAD vs. Flu control
		% Difference in Titer >1:40 at Day 50: H1N1, H3N2, B	41%; 33%; 55%
		95% CI: H1N1, H3N2, B	36-46; 28-39; 48-61
	7-day observation window are presented along with the severity of each reaction. The differences among the vaccine groups with respect to the primary safety endpoint are analyzed by means of confidence intervals for the relative risk calculated by the CMH method. All the adverse events occurring during the study, judged either as related to vaccination or not by the investigator, were to be recorded. The adverse events were then grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported adverse events, as well as adverse events at least possibly related to study vaccine, were summarized according to system organ class and preferred term within system organ class. These summaries were presented by vaccination group.		

Clinical studies in special populations

No clinical study in special population has been conducted.

Analysis performed across trials (pooled analyses AND meta-analysis)

No analysis across trials was provided for immunogenicity.

Supportive study(ies)

Study V70P6

It is a Phase II, Observer-Blind, Randomized, Multi-center Study to Evaluate the Safety and immunogenicity of Two 0.25 mL or 0.5 mL Doses of Fluad and Fluzone Influenza Vaccines in Healthy Children Aged 6 to <60 Months, conducted in 2008 in Guatemala. The study was performed between January and October and overlapped with the local influenza season. The Applicant has suggested that results on immunogenicity may have been affected by the natural circulation of seasonal influenza.

The table below shows the planned and (actual) numbers of subjects enrolled.

Age / Vaccine	6 to <12 months	12 to <18 months	18 to <24 months	24 to <30 months	30 to <36 months	36 to <60 months	Total
Fluad	26 (23)	26 (35)	26 (24)	26 (23)	26 (31)	45 (44)	175 (180)
Fluzone	26 (21)	26 (35)	26 (28)	26 (20)	26 (28)	45 (48)	175 (180)
Total	52 (44)	52 (70)	52 (52)	52 (43)	52 (59)	90 (92)	350 (360)

Finally, a total of 180 subjects were enrolled into each of the two treatment arms:
Fluad: 136 subjects of 6 to < 36 months of age; 44 subjects of ≥ 36 months of age.
Fluzone: 132 subjects of 6 to < 36 months of age; 48 subjects of ≥ 36 months of age.

The immunogenicity of the two vaccines was evaluated considering the following measurements according to the CBER criteria for the paediatric population:

- The lower bound of the two-sided 95% confidence interval (CI) for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 40%.
- The lower bound of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥40 should meet or exceed 70%.

The per protocol (PP) population comprised 120 subjects in the Fluad group (97 in 6 to < 36 months and 23 in 36 to < 60 months of age group) and 122 subjects in the Fluzone group (102 in 6 to < 36 months and 20 in 36 to < 60 months of age group). PP and FAS populations differed by more than 10% for both vaccine groups. Influenza A circulation was reported in the study area during the active phase of the study, coinciding with the immunizations and day-50 blood sampling period. Since the immune response to infection and to vaccination cannot be distinguished, the immunogenicity results for the influenza A strains are to be interpreted in the light of this epidemic.

Immunogenicity results in 6 to < 36 months of age group (PP Population)

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 seroprotction 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 also consistently 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.

In study V70P6 limited or no advantage is observed at day 50 for A viral antigens of FLUAD compared to TIV in each of the two age-groups

Similar graphs have been provided for seroconversion and seroprotection and study V70P6 does not indicate clear advantages of FLUAD in seroprotection or seroconversion against H1N1 antigens.

Study V7P29

The supportive Fluad study V7P29 investigated immunogenicity and safety of 1 dose of Fluad in children 9 years to 17 years of age. It was conducted in 1996-7 and enrolled 217 subjects, of whom 117 received Fluad. Fluad vaccine was different from the current presentation as the adjuvant was in a separate vial. No superiority of Fluad compared to non-adjuvanted comparators was shown.

The value of the present study is very limited as it include a study product different from the present one, also the comparator vaccine is not on the market and results do not show any advantage.

Study Synopsis Table C
Geometric mean titers and ratios, percentages of subjects with a fourfold increase in titers, and percentages of subjects with a postimmunization titer of at least 160, 28 days after immunization

	Age	9-12 Years		13-17 Years	
HI Titer Variable	**Antigen**	FLUAD n=51	FLUOGEN/ FLUSHIELD n=40	FLUAD n=55	FLUOGEN/ FLUSHIELD n=52
Day-28 GMT	B	471	441	322	251
	A/H3N2	665	763	468	361
	A/H1N1	833	1014	730	631
Day-28 to day-0 GMR	**B	23	13	14	8.4
	A/H3N2	18	19	14	9.7
	A/H1N1	20	18	17	18
Percentage of subjects with ≥4-fold increase from day 0 to day 28	*B	92%	85%	95%	75%
	A/H3N2	92%	95%	95%	81%
	A/H1N1	96%	98%	95%	90%
Percentage of subjects with titer ≥160 at day 28	B	96%	93%	89%	83%
	A/H3N2	100%	100%	96%	92%
	A/H1N1	96%	98%	95%	96%

*$P<0.05$; **$P<0.01$; for vaccine group difference.

Discussion on clinical efficacy

Fluad was developed in late 90's and since the year 2000 it has been used in many EU countries following a Mutual Recognition Procedure (with Italy as reference member state) for seasonal vaccination of elderly population.

The use of adjuvanted influenza vaccine for younger age groups has been promoted in response to the threat of pandemic and, a vaccine using the same type and amount of adjuvant (Focetria) but lower protein content, has been authorised for use during the 2009 pandemic.

It is relevant to underline that the safety and vaccine efficacy of any influenza vaccine for paediatric use has to be proven within clinical studies, as the serologic correlate for protection used for adults are of unknown relevance in children.

The current application, although related to a product developed more than 15 years ago and authorized for use in elderly, includes as pivotal only one study addressing clinical vaccine efficacy and two phase II studies. One exploratory study on re-vaccination on a limited sample size has been also included.

Design and conduct of clinical studies

The clinical developmental program for Fluad paediatric encompassed 4 randomized, active controlled observer blind clinical studies in the paediatric population (6-72 months): 1 pivotal phase 3 trial

assessing both immunogenicity, and clinical efficacy and safety, and 3 phase 2 immunogenicity studies.

In addition, 2 supportive phase 2 randomized controlled observer-blind immunogenicity studies in children aged 6 months to 18 years, were carried out. One additional supportive study, randomised observer blind multicenter incomplete factorial design phase 1b study on the adjuvant dose, was carried out.

As serologic criteria were recognized to be of unknown relevance for paediatric population, the conduct of efficacy trial is crucial. In the present application, only one efficacy study was included and its quality has been questioned by the performed GCP Inspection.

The selected patient population was limited to healthy children who do not represent the recommended target population of influenza seasonal vaccination in most EU countries.

The lack of the inclusion of the at-risk population for influenza complications, i.e. children with chronic morbidities, greatly limits the external validity of the study results for the clinical practice.

According to VWP, efficacy data in healthy children may be considered relevant to immunocompetent children with underlying chronic diseases but may not be relevant to immunocompromised children. Immunogenicity data in immunocompromised children should be obtained at least as post-approval.

It is also noted that, so far no timetable or even protocol for the planned studies has been submitted. Following specific request, the Applicant has provided an interim analysis on a sub-sample of the study V70_29 investigating the efficacy and safety of Fluad in subjects at-risk for influenza complications, and conducted outside EU. Full results of the ongoing study should be submitted as soon as they are available. However, the majority of subjects included in study V70_29 are immunocompetent. It is thus considered mandatory, in case the CHMP agrees with granting a MA, that the Applicant commits to address the efficacy and safety of Fluad paediatric in immunocompromised children through a post-approval study.

In addition, very limited efficacy and safety data are available in children aged 6-9 years. Only supportive studies (e.g. the immunogenicity study V7P29 conducted in 1996 and V87P6 including H5N1 vaccine in subjects 9-17 years old) have included subjects older than 6 years of age. Of note, these studies showed that the adjuvanted vaccine did not perform better than the non-adjuvanted one.

The peculiarity of Fluad paediatric is the expected advantage it may confer, compared to current available non-adjuvanted influenza vaccines, being potentially able to induce an immune priming effect, by stimulating immune memory in otherwise naïve subjects. This is the rational of studying the vaccine in the very young population. The potential for inducing a strong immune response was also the reason for which the same Fluad vaccine has been already licensed in EU only in subjects above 65 years of age. The adjuvanted vaccine was in fact considered able to re-enforce the immune response in already primed subject who are likely, due to old age and partial decrease in immune competence, to have a sub-optimal immune response to non-adjuvanted seasonal vaccines. On the contrary, it was considered, that in the broad adult population, there was a clear trend towards increased reactogenicity following the administration of the adjuvanted Fluad vaccine as compared to not adjuvanted TIVs and no clear evidence of additional advantages in terms of increased efficacy. On the basis of these considerations, it was decided not to grant a MA for Fluad in the adult population and to limit its use to the elderly population. The same approach should be applied when reviewing the data for Fluad paediatric. The potential advantage conferred by the use of the adjuvanted vaccine in children has to be carefully assessed in different age groups and weighted with the unfavorable effect of increased reactogenicity. This is considered necessary also because it ensures uniformity and consistency with the criteria applied for the granting of the MA in the elderly population.

Table 31-4-6 from Study V111_03, submitted by the Applicant in response to the CHMP question, shows an increased local and systemic reactogenicity after the booster dose of the H1N1 Focetria vaccine. This suggests that a similar increased or higher reactogenicity is to be expected with the seasonal vaccination with Fluad paediatric that contains the same amount of adjuvant but six or more fold protein content. To this respect, the Applicant proposal to extrapolate immunogenicity data from other age cohorts in order to approve the use of Fluad paediatric also in children aged 6 to 8 years is not considered acceptable. If data extrapolation were considered acceptable, the logic corollarium would be to extend the use of Fluad paediatric to any adolescent and adult age. A comparison between specific safety and immunogenicity data of vaccination with Fluad paediatric and non adjuvanted TIVs, in the age-group 6-9, is considered necessary in order to clearly show the benefit of Fluad paediatric in this age-group.

Limited data are available on the efficacy of influenza vaccines in the paediatric population. Most of the presented data are based on assessment of serologic immune response in 317 subjects aged 6-36 months and 194 subjects aged 36-72 months vaccinated with influenza vaccines. A serological correlate of protection in the childhood population has not been identified yet, and the CHMP and CBER serological criteria for the assessment of vaccine immunogenicity in adults are borrowed for the evaluation of vaccine immunogenicity in the paediatric population. The choice of serological CHMP and CBER criteria, used in the adult population, as primary endpoints in most of the submitted studies, is thus appropriate in the absence of validated alternatives. However, the lack of validated serological correlates associated with clinical protection makes difficult to formulate a judgement about the clinical advantage provided by vaccination in the paediatric population.

Immunogenicity results were obtained mainly from a sample of subjects derived from the pivotal efficacy study. The sample was defined in the dossier as a "convenience sample". In the course of the reviewing process, the Applicant has clarified that the immunogencity analysis of the pivotal efficacy study included subjects from only one season and only from Finland (i.e. none of the children enrolled in Germany was analyzed to assess vaccine-induced immunogenicity).

The novelty of the present application is represented by the assessment, in the pivotal phase 3 study, of the absolute vaccine efficacy, evaluated by PCR-confirmed influenza like illness (ILI) cases in vaccinated subjects. The choice of this primary endpoint is appropriate and of interest as usually vaccine efficacy is derived only from immunogenicity data, for which no demonstration of a statistical association with clinical protection achieved in children is available at present.

However, absolute vaccine efficacy was investigated only for subjects between 6 and 72 months and only from one epidemic season due to the overcome of the 2009-10 pandemic influenza which swept out all the other circulating strains. The sensitivity of diagnostic methods is crucial to determine vaccine efficacy.

At Day 120 of the reviewing process, The Applicant has been requested to provide clarifications on the PCR method validation, handling of PCR samples, and on the general conduct of the PCR test. The answers provided by the Applicant did not solve the issues highlighted by the CHMP, but rather raised further serious concerns on the reliability of overall PCR data, and thus of the influenza cases detected by PCR. In addition, results from the GCP inspection revealed that the Central laboratory (C) where all 1216 nasal samples were analyzed by PCR to identify those containing influenza virus, besides having no quality system in place did not implement any control on the quality and validity of the PCR test used. As a consequence of the deficiencies in the PCR analysis highlighted by the inspectors, the Applicant has decided to retest, using a third different PCR method, the nasal samples in a third new laboratory (E) (However, as detailed in the GCP section of the present AR, due to several critical issues identified in the conduct of the retesting, the fact that degradation upon storage of the PCR samples and/or cross-contamination or mislabeling of the samples that underwent retesting cannot be

excluded, and the lack of a correct validation of the new PCR test, overall PCR results from the pivotal study are not considered reliable, and thus cannot be used to assess vaccine efficacy.

Although in the introduction it is stated that also transmissibility from the infected child is a public health problem, the study does not measure either the vaccine efficacy in preventing secondary household cases (although planned among the secondary objectives in the pivotal efficacy study), or vaccine efficacy by severity of cases.

From the description provided, the time of follow-up after vaccination for detection of incident influenza cases was variable across the study centres in different countries.

The Applicant should provide additional information on the distribution of individual duration of follow-up vaccination for detection of incidence of influenza cases, stratified by study centre, since from the description provided this time was variable across the study centres in different countries.

The methodology used in the pivotal efficacy study has some issues to be clarified mainly linked to the incomplete blinding of participating subjects (reported only in one amendment to the protocol and not discussed in the final report) and to the relatively low number of PCR confirmed cases.

The lack of double blindness (parents and guardians were aware of the treatment received by their children) may have in fact introduced a bias related to ILI detection as parents or guardians of children recipients of Fluad paediatric may have been less keen to consult the study site for ILI. This might have resulted in incomplete detection of all ILI cases and/or different timing of ILI assessment in subjects vaccinated with Fluad paediatric. The clarification submitted by the Applicant on the definition of observer blinded study do not solve the issue. The actual extension of unblinding seems to be higher than the 186 subjects in Germany and 104 in Finland previously reported in the original MA dossier. In such conditions it is difficult to understand the real extension of unblinding and the potential effects on the safety and on the VE.

As regards the issue of incomplete detection of all ILI cases and/or different timing of ILI assessment, it has been clarified that enrolment in Finland was completed earlier in the season compared to Germany. A not negligible proportion of children in Germany was enrolled in the latest weeks of 2008 and the beginning of 2009 when the seasonal flu and the at-risk period was likely to be more intense. These subjects are likely to have contributed with shorter observation time to the estimate of VE as cases detected and laboratory confirmed soon after vaccination were discarded. The concern of an incomplete detection of ILI cases has not been relieved.

Seasonal influenza vaccination is routinely performed every year in the same subject. It is thus important to evaluate the benefit/risk of a yearly administration of an adjuvanted vaccine in the paediatric population considering the relative mildness of influenza in healthy subjects. Long-term studies, designed to allow the evaluation of the benefit/risk of subsequent vaccinations in an adequate number of children, for at least two influenza seasons, are thus advisable. Study V70P2E1 is the only extension study addressing the efficacy and safety of re-vaccination with Fluad paediatric, one year after the first vaccination. However, re-vaccination was evaluated only on 41 subjects. The limited number of subjects enrolled in this study significantly hampers the correct interpretation of the results. As also recommended by the VWP, since the SmPC of Fluad claims that the vaccine is for routine yearly vaccination, adequate data have to be provided regarding safety and immunogenicity upon repeated vaccination with Fluad paediatric before approval.

The paediatric population, in particular children in the first two years of age, is exposed to a number of recommended vaccinations. No study has been designed to address the effect of Fluad paediatric administration on other vaccinations due at the same age.

Efficacy data and additional analyses

Overall, immunogenicity results show that two doses of Fluad paediatric induce higher immune response compared to non-adjuvanted seasonal vaccines. These findings are clinically relevant as the immune system of infants and toddlers is partially developed and non-adjuvanted vaccines do not appear to induce satisfactory protective antibodies in unprimed children. This trend appears particularly evident for the influenza B strain, versus which conventional non-adjuvanted vaccines constantly showed, with the exception of study V70P6, lower immunogenicity than versus influenza A antigens, not meeting CHMP and CBER criteria in the pivotal efficacy study, V70P2 and its extension. Instead all 3 CHMP criteria were met after 2 vaccinations with 0.25 ml of Fluad paediatric in all clinical studies (Pivotal efficacy trial, V70P2, V70P2E1 and V70P6).

It is noted that the increase in immunogenicity in patients treated with Fluad paediatric was variable depending on the trial and, in fact, in one of the trials (V70P6) the non adjuvanted vaccine actually performed better than Fluad paediatric (for the H3 antigen, in the age group >36 months).

When considering GMR across the three studies it is evident that the largest difference in favour of FLUAD has been obtained in the the pivotal efficacy study which is pivotal also for immunogenicity evaluation. In study V70P6 limited or no advantage is observed at day 50 for A viral antigens of Fluad paediatric compared to TIV in each of the two age-groups.

Similar graphs have been provided for seroconversion and seroprotection and the differences between adjuvanted and TIV products are mostly obtained by the pivotal efficacy study while V70P6 is not indicating clear advantages of FLUAD in seroprotection or seroconversion against H1N1 antigens.

The Applicant failed to prove that results of the three studies presented on immunogenicity consistently show the same degree of advantage of the adjuvanted vaccine compared to the TIV in subjects seronegative at baseline. In particular, one out of the three studies V70P6 show very little advantage. The Applicant suggests that such lack of difference may be attributable to the conduct of the study during to the influenza season and to the fact that naturally acquired infection in any study group would have masked actual differences between vaccines. Such hypothesis questions the validity of the entire V70P6 and its value. The Applicant has to assess the reliability of results on comparative immunogenicity from V70_P6 and comment on the observed inconsistency across the presented studies on the advantage of Fluad compared to TIVs.

Immunogenicity versus heterologous strains, was generally lower than versus homologous strains for both Fluad paediatric and non-adjuvanted vaccines. In the pivotal efficacy study, irrespectively of the age group, most subjects from Fluad paediatric group achieved seroprotection against the A strains. Instead CHMP/CBER criterion for seroprotection was not met in the non-adjuvanted influenza vaccine group. The response against the heterologous B strain was weak not meeting the CHMP and CBER criteria. Immunogenicity results at day 181 mirrored results at day 50 against homologous and heterologous A strains. However, seroprotection was not achieved for the B strains for both adjuvanted and non-adjuvanted vaccines.

Upon request, an overall assessment of consistency across all studies has been provided by a meta-analysis resulting in a plot showing the relative ratio of GMTs, SPs and SRs of vaccinated versus unvaccinated children, taking into account the size of the study. However, the results from the meta-analysis are strongly influenced by the results of study V70_P5 the entire validity of which is questioned. Thus consistency for serological data among all studies cannot be claimed.

As far as the incidence of influenza is concerned, it is noted that study V70_P5 was a large multicenter study, involving, in the season 2008-2009, 99 centres. The size of the sample enrolled in the centres is extremely variable (217-1) and many centre did contributed only with 1-2 children.

Overall, during Seasons 2007/2008 and 2008/2009, 1216 samples were collected from 979 subjects with ILI. In 37 sites out of 98 no single ILI was detected or investigated.

In the entire study a total of 43 confirmed cases were detected in the unvaccinated group, 50 in the recipients of non adjuvanted influenza vaccine and only 12 in subjects vaccinated with Fluad paediatric. However, due to the critical issues affecting the reliability of overall PCR data, no sound conclusion may be drawn on the influenza cases detected by PCR, and thus on vaccine efficacy.

Efficacious vaccination against influenza is expected to produce a tangible benefit in terms of the proportion of children not experiencing influenza symptoms. Although influenza-like syndrome can be caused by a variety of agents, during the seasonal epidemics a large part of ILI is attributed to influenza. Therefore, the benefit of influenza vaccination should be reflected in a decreased percentage of ILIs, at least during the seasonal epidemic. Such aspect is particular relevant in the risk-benefit evaluation of the vaccine and on the expected effect of its introduction in large scale immunization programs. Almost no difference has been observed in the frequency of ILI and in outcomes associated to severity of the clinical picture, as hospitalization. It is also observed that:

1. In one centre in Germany enrolling a high number of children (B) no ILI cases were ever detected and inspectors raised doubts about incorrectness of data on safety collected there.
2. In one centre in Finland 30 (A) ILI cases were detected but none was laboratory investigated as swabs were not taken.
3. The entire system for ILI detection and influenza confirmation changed across the trial with relevant differences across the intended length of the study.

Compared to the frequency of ILI and to the expected attack rate of influenza (both approx 20%), the overall number of PCR-confirmed cases is low (incidence in the age-group 6-72 months is 0.45%) and vaccine efficacy estimates have wide CIs.

Despite randomization, some residual confounding factors can occur due to other factors associated with the risk of acquiring influenza (i.e. family size, day-care centre, geographic location, etc) and unevenly distributed across study groups. Stratified analyses are usually performed to assess the effect of such factors. However, the Applicant has clarified that such variables were not collected and no additional analyses can be performed.

No established serological correlates for protection are available for children, therefore evidence for

vaccine efficacy is considered a requirement, at least at licensure, to define the benefit provided by vaccination. Immunogenicity results for Fluad paediatric have shown a lower immune response against B strain and two doses were needed to comply with CHMP criteria. For a TIV, estimate of the protection conferred against each of the three matched strains would be ideal. However, the difficulty in obtaining strain specific vaccine efficacy is acknowledged, due to the actual circulating strain in each season and to the impossibility to show efficacy against non-circulating strains. Such constraint is usually addressed by studies conducted across different seasons, when different strains may circulate.

In the pivotal efficacy study, vaccine efficacy has been obtained essentially in one influenza season and has been shown for A/H3N2 strain. No estimates were obtained for H1N1 or B strains. According to the VWP opinion, the extrapolation of VE obtained with one strain (A or B) is not acceptable if not adequately supported by data. Epidemiological data from the seasonal surveillance in Germany and in Finland suggest that B viruses did indeed circulate. However, the proportion of identified B viruses compared to A viruses in the pivotal trial is very low and the VE estimates for B viruses are very imprecise. Data related to the H1N1 vaccine Focetria are supportive but not completely pertinent as related to a monovalent vaccine.

Upon request, the Applicant has supported the claim of VE against different strains with data on immunogenicity based on SRH and MN assays.

Supportive studies are intended to show the advantage of the use of an adjuvanted influenza vaccine in children and adolescents of 9-17 years of age. However, they add limited knowledge to the current application.

Study V7P29, performed in 1996-1997, used a different presentation and schedule (one single dose) of the Fluad paediatric vaccine.

Study V87P6 was related to the H5N1 pandemic mock-up file. The study compared Fluad paediatric vaccine with a H5N1 pandemic vaccine (Aflunov) that includes a different amount of antigen and a different viral strain, the immunogenic characteristics of which are very different from the seasonal strains.

Conclusions on clinical efficacy

The dossier includes data on immunogenicity of two doses of Fluad paediatric in healthy population aged 6-72 months, suggesting a positive effect of the vaccine administration, although some inconsistency about the advantage of use of adjuvanted vaccine are observed. Most of the immunogenicity results derive from Study V07P5 and are obtained from a sub-sample of children. The validity of those results rely upon the decision on the acceptability of the entire study which presented various flaws in quality. As immunogenicity is concerned for example the lack of systematic recording of other administered vaccines to study children may represent a limit.

In addition, in the context of the pivotal efficacy study, the Applicant has assessed VE by evaluating virus infection in vaccinated children by PCR analysis and detecting influenza symptoms by monitoring of ILI cases. In the absence of identified serologic correlates for protection in this age-group, the Applicant has performed one trial on clinical efficacy on healthy children which is crucial to the entire evaluation. On the reliability of the trial results the entire Application is based. Regrettably the Inspection performed has put in evidence many relevant failures and the final report recommended not to accept the trial results due to the lack of compliance with GCP. The absence of the Sponsor's effective monitoring of the conduct and quality of the study, does not allow to exclude that the same or different critical flaws may have happened also in other study centres not subjected to the GCP inspection. Moreover, critical findings, questioning the validity of the PCR analysis, were discovered in the central laboratory that analysed all nasal swab samples collected in all study centres. The retesting of PCR samples performed by the Applicant bears the same bias as the previous original testing. Thus, the critical findings highlighted by the inspectors cannot be solved by the exclusion of some questioned data from the final analysis. The GCP Inspection found not only a lack of GCP compliance in the inspected sites but also identified a number of issues, regarding the clinical efficacy data from the pivotal trial, that were inaccurately stated in the first dossier submitted by the Applicant. This greatly impacts the reliability of overall study results.

In case the corrective actions proposed by the Applicant are considered sufficient to validate the data from the pivotal study, the efficacy results obtained are encouraging, but still some important areas are to be studied.

The dossier does not provide any evidence related to other issues that should be addressed in the evaluation of the benefit/risk balance of an adjuvanted seasonal influenza vaccination in young children:

- vaccine efficacy in sub-groups to whom the vaccination is offered as primary target (especially children with chronic co-morbidities). In most EU countries, according to public health recommendation, only at-risk children because of underlying health condition, currently receive seasonal influenza vaccine, but in the clinical programs only healthy children aged between 6 months and 6 years have been included. Final data from the on-going clinical trial V70_29 are

awaited, together with the Applicant's commitment to perform a post-approval trial in immunocompromised children.
- demonstration of vaccine efficacy towards the B strain,
- efficacy and safety of repeated yearly administrations,
- data on possible interactions with concomitant or consequent immunisations with other vaccines usually recommended in the paediatric population,
- efficacy and safety data in the age group 6-9.

Clinical safety

Patient exposure

The safety data of Fluad paediatric come from 6 clinical trials (4 main studies and 2 supportive studies) performed in children (ages 6 months to <18 years).

Two phase 2 studies (V70P2, V70P6), one pivotal phase III study and one extension study were conducted. Additionally results for Fluad paediatric in paediatric population aged from 6 months to <18 years are available from 2 supportive studies (V87P6 and V7P29).

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 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 pivotal phase 3 study was designed to demonstrate:

a. the safety and tolerability of one or two doses of Fluad paediatric in previously unvaccinated children aged 6 to <36 months, compared with Flu vaccine control in terms of any solicited local and systemic reactions (combined) reported within 7 days after any vaccination.
b. absolute efficacy in terms of protection provided by two doses of Fluad paediatric in previously unvaccinated children aged 6 to <36 months, compared with Non-flu vaccine control, against influenza illness1 caused by virus-confirmed community-acquired influenza wild type strains matching with those contained in the vaccine.

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 supportive study V87P6 was conducted for the development of the H5N1 pandemic vaccine. Fluad paediatric 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. The supportive Fluad paediatric study V7P29 was designed to investigate the immunogenicity and safety of 1 dose of Fluad in children 9 to <18 years of age.

Table 2.7.4-1: Overview of the Main and Supportive Studies with Fluad in the Paediatric Population (6 Months to <18 Years): Safety Population

Study	Extension Study	Number of Vaccinations [1] (Dose-level [2])	Timing of 2nd or 3rd Vaccination	Age Group	Number of Subjects Vaccinated [3]	
					Fluad	Control Vaccine [4]
Main Studies for Safety of Fluad in Paediatric Populations						
V70P2	no	2 (7.5µg)	4 weeks apart	6 to <36 months	130	139
V70P2E1 (extension to V70P2)	yes	1 (7.5µg)	~12 months after 2nd injection in study V70P2	6 to <36 months	25	23
	yes	1 (15µg)		≥ 36 months	18	23
V70P6 [5]	no	2 (7.5µg)	4 weeks apart	6 to <36 months	136	132
	no	2 (15µg)		3 to <5 years	44	48
V70P5 [6, 7]	no	2 (7.5µg)	4 weeks apart	6 to <36 months	1178	1068
		2 (15µg)		3 to <6 years	834	778
Supportive Studies for Safety of Fluad in Paediatric Populations						
V87P6	no	2 (7.5µg)	3 weeks apart [8]	6 to <36 months	56	145
	no	2 (15µg)		3 to <9 years	40	96
	no	2 (15µg)		9 to <18 years	41	93
V7P29	no	1 (15µg)	NA	9 to <18 years	116	100

Source: ISS Table 1.5.2 (all subjects with safety data post Day 22/28).

[1]: Vaccination with Fluad, a MF59-adjuvanted trivalent subunit (A/A/B) seasonal influenza vaccine, or control vaccine

[2]: Dose level of HA antigen for each of the 3 seasonal influenza strains (as per WHO recommendation).

[3]: Subjects that received at least one vaccination (Safety Population); for more details and total number of subjects by age group, please see Section 2.7.4.1.2, (Tables 2.7.4.1.2-1 and 2.7.4.1.2-2).

[4]: Control influenza vaccines were: Vaxigrip (non-adjuvanted seasonal flu vaccine) for V70P2 and V70P2E1; Fluzone (non-adjuvanted seasonal flu vaccine) for V70P6; Agrippal® S1 (non-adjuvanted seasonal flu vaccine) for Part I of V70P5, Influsplit SSW® (non-adjuvanted seasonal flu vaccine) for Part II and Part III of V70P5; PanH5N1 (MF59-adjuvanted pandemic influenza vaccine) for V87P6; Fluogen/Flushield (non-adjuvanted seasonal flu vaccine) for V7P29.

NOTE: NOT included in the Pooled Safety Analyses were the Menjugate® and Encepur® Children vaccines used as efficacy control in all three parts of V70P5 (for details refer to Table 2.7.4-2 below) and the PanH5N1 used in study V87P6 (pandemic flu vaccine development program) for which Fluad was used as a safety control. Due to the premature termination of V70P5 study Part III (see Table 2.7.4-2 below), a small number of subjects from Part III was included in the Pooled Safety Analyses of unsolicited AEs (Section 2.7.4.2.1.1.2).

[5]: in V70P6: 8 children <36 months of age (6 Fluad, 2 Fluzone) were erroneously randomized to age group 36 to <60 months, and are presented as randomized (in the 6 to <36 months group) and not as treated.

[6]: in V70P5: a few children were erroneously randomized to the wrong age or vaccine group, and for the ISS analyses they are presented as treated. However, in the clinical study report (CSR) V70P5 (Section 5.3.5), subjects are presented as randomized and thus numbers in this table do not match the CSR.

[7]: Extension study planned and initiated, no data available as of October 2010 (cut-off for this document).

[8]: The control PanH5N1 vaccine group received a 3rd vaccination ~12 months after 2nd injection.

Demographic and other baseline characteristic were balanced between vaccination groups, within each age group, and the majority of subjects were Caucasian; mostly Hispanic children (N=369, safety population, Table 2.7.4.1.3-1) were participating in study V70P6 conducted in Guatemala.

Table 2.7.4.1.3-1 Demographics and Other Baseline Characteristics in the Pooled Safety Population

Demographic and Other Baseline Characteristics	6 to <36 Months		3 to <9 Years*		9 to <18 Years	
	Fluad	Flu-Control [1]	Fluad	Flu-Control [1]	Fluad	Flu-Control [1]
	N=1500	N=1339	N=918	N=826	N=157	N=100
Age (months): Mean (SD)	17.8 (8.7)	18.1 (8.7)	–	–	–	–
Age (years): Mean (SD)	–	–	4.0 (0.9)	4.0 (0.8)	12.8 (2.5)	13.0 (2.4)
Sex:						
Male	776 (52%)	695 (52%)	498 (54%)	422 (51%)	82 (52%)	50 (50%)
Female	724 (48%)	644 (48%)	420 (46%)	404 (49%)	75 (48%)	50 (50%)
Race:						
Asian	16 (1%)	9 (<1%)	13 (1%)	14 (2%)	2 (1%)	0
Black	13 (<1%)	7 (<1%)	8 (<1%)	3 (<1%)	16 (10%)	22 (22%)
Caucasian	1311 (87%)	1157 (86%)	838 (91%)	741 (90%)	136 (87%)	77 (77%)
Hispanic	138 (9%)	138 (10%)	44 (5%)	49 (6%)	0	0
Other	22 (1%)	28 (2%)	15 (2%)	19 (2%)	3 (2%)	1 (1%)
Weight (kg): Mean (SD)	11.26 (3.21) (N=1498)	11.25 (2.50) (N=1338)	18.50 (3.61)	18.27 (3.35) (N=825)	54.44 (17.45)	55.05 (17.69)
Height (cm): Mean (SD)	81.07 (9.06) (N=1495)	81.10 (8.75) (N=1338)	107.12 (8.02) (N=917)	106.57 (8.01) (N=825)	159.09 (14.71)	159.44 (14.38)
BMI: Mean (SD)	17.03 (3.97) (N=1495)	16.98 (1.73) (N=1338)	16.02 (1.69) (N=917)	16.01 (1.74) (N=825)	20.99 (4.05)	21.24 (4.48)
Inclusion Criteria fulfilled:						
Yes	1490 (99%)	1330 (99%)	913 (99%)	824 (100%)	155 (99%)	99 (99%)
No	10 (<1%)	9 (<1%)	5 (<1%)	2 (<1%)	2 (1%)	1 (1%)

Source: ISS Table 1.2.3 (all subjects with safety data post Day 22/28).
(N=…): actual N given only if N was smaller than indicated in the column-heading.
[1]: Flu-Control vaccines were: Vaxigrip for V70P2, Fluzone for V70P6, Agrippal S1 for Part I of V70P5 and Influsplit SSW for Part II and Part III of V70P5, none for V87P6, and Fluogen/Flushield for V7P29.
*: Upper age limit lower than <9 years for all Fluad main-studies: V70P2 = <36 months, V70P6 = <60 months (5 years), and V70P5 = <72 months (6 years).

Adverse events

The Applicant stated that adverse events (AEs) were collected in two ways:

- Solicited AEs (i.e., local and systemic reactions) within 7 days after each vaccination;
- Unsolicited AEs from first vaccination day through 3 weeks post last vaccination, AEs necessitating a physician's consultation or physician's visit in most studies from 3 weeks post last vaccination through end of study and SAEs, throughout the entire study period.

The incidence rate of solicited local and systemic reactions, pooled from studies V70P2, V70P6, the pivotal efficacy study and V87P6, in the age group from 6 to < 36 months, is shown in the table below.

Table 2.5.5.1.1-1 Solicited Local and Systemic Reactions by Vaccination (7.5 µg) – Pooled Safety Population Ages 6 to <36 Months

V70P2, V70P6, V70P5, and V87P6	Percentages Subjects with any (with severe) Local and Systemic Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control[a]	Fluad	Flu-Control[a]
Pooled Safety Population	**N=1494**	**N=1337**	**N=1408**	**N=1248**
Ecchymosis[b]	8% (0)	7% (0)	7% (<1%)	5% (0)
Erythema[b]	23% (<1%)	19% (0)	26% (<1%)	20% (0)
Induration[b]	9% (0)	6% (0)	12% (<1%)	7% (0)
Swelling[b]	5% (0)	4% (0)	7% (<1%)	5% (0)
Tenderness[c]	21% (1%)	18% (<1%)	19% (1%)	16% (<1%) N=1247
Sleepiness[e]	20%	18%	18%	14% N=1247
Diarrhea[e]	13%	13%	11%	9% N=1247
Vomiting[e]	6%	6%	5%	5% N=1247
Irritability[e]	23%	24%	20%	19% N=1247
Change in eating habits[e]	18%	16%	15%	12% N=1247
Shivering[e]	4% N=1364	4% N=1198	3% N=1291	3% N=1120
Unusual Crying[e]	21%	20%	20%	18% N=1247
Fever[d]	20% (<1%) N=1493	18% (<1%) N=1336	22% (<1%)	17% (1%)
Stayed at home due to reaction	14% N=125	8% N=122	15% N=115	15% N=114
Analgesics/Antipyretics	19% N=1492	18%	19%	17%

Source: Section 2.7.4, Tables 2.7.4.2.1.1.1-10 and 2.7.4.2.1.1.1-16; ISS Table 2.4.1.
[a]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; [b]Severe (>50mm); [c]Severe = cried when limb was moved; [d]Any (≥38°C), severe (≥40°C); [e]Classification by severity was only evaluated in study V70P2 (no severe systemic reaction were reported in this study).

The incidence rate of solicited local and systemic reactions, pooled from studies V70P6, the pivotal efficacy study and V87P6, in the age group from 3 to < 9 years, is shown in the table below.

Table 2.5.5.1.1-2 Solicited Local and Systemic Reactions by Vaccination (15 µg) – Pooled Safety Population Ages 3 to <9 Years

V70P6[1], V70P5[1], and V87P6	Percentages Subjects with any (with severe) Local and Systemic Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control[2]	Fluad	Flu-Control[2]
Pooled Safety Population	**N=922**	**N=826**	**N=900**	**N=804**
Ecchymosis[3]	9% (0)	7% (0)	9% (0)	7% (0)
Erythema[3]	24% (<1%)	22% (<1%)	31% (2%)	26% (1%)
Induration[3]	11% (<1%)	11% (0)	16% (1%)	15% (<1%)
Swelling[3]	9% (<1%)	9% (0)	14% (1%)	13% (1%)
Pain at injection site	45% (1%) N=921	35% (<1%)	43% (1%)	32% (<1%)
Chills	10% (1%) N=921	4% (<1%)	8% (1%)	4% (<1%)
Malaise	16% (2%) N=921	11% (1%)	13% (1%)	8% (1%)
Myalgia	14% (1%) N=921	8% (<1%)	14% (1%)	8% (<1%)
Arthralgia	7% (1%) N=921	3% (<1%)	4% (<1%)	2% (0)
Headache	17% (2%) N=921	8% (1%)	13% (1%)	7% (<1%)
Sweating	6% (<1%) N=921	4% (<1%)	4% (<1%)	2% (0)
Nausea	5% (3%) N=40	0 (0)	8% (5%) N=39	0 (0)
Fatigue	29% (2%) N=921	19% (1%)	23% (2%)	17% (1%)
Fever[4]	16% (<1%)	7% (<1%) N=825	16% (<1%)	8% (<1%)
Stayed home due to reaction	6% N=88	4% N=47	10% N=86	9% N=46
Analgesics/Antipyretics	16%	7% N=825	14%	7%

Source: Section 2.7.4, Tables 2.7.4.2.1.1.1-11 and 2.7.4.2.1.1.1-17; ISS Table 2.4.2; [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; [3]Severe (>50mm); [4]Any (≥38°C), severe (≥40°C)

The incidence rate of solicited local and systemic reactions, pooled from studies and V87P6 and V7P29 in the age group from 9 to < 18 years, is shown in the table below.

Table 2.5.5.1.1-4 Solicited Local and Systemic Reactions by Vaccination (15 µg) – Pooled Safety Population Ages 9 to <18 Years

V87P6 and V7P29	Percentages Subjects with any (with severe) Local and Systemic Reactions			
	1st Vaccination		2nd Vaccination	
	Fluad	Flu-Control[1]	Fluad	Flu-Control[1]
Pooled Safety Population	**N=157**	**N=100**	**N=40**	**N=0**
Ecchymosis[2]	10% (0) N=41	0	0	0
Erythema[2]	17% (1%)	9% (0)	23% (0)	0
Induration[2]	14% (2%)	14% (3%)	3% (0)	0
Swelling[2]	17% (2%) N=41	0	18% (0)	0
Pain at injection site	80% (4%)	53% (0)	63% (0)	0
Chills	17% (0)	1% (0)	5% (0)	0
Malaise	27% (1%)	6% (0)	13% (0)	0
Myalgia	17% (0)	6% (0)	18% (0)	0
Arthralgia	4% (0)	0	5% (0)	0
Headache	35% (1%)	12% (1%)	25% (3%)	0
Sweating	15% (0) N=41	0	5% (0)	0
Nausea	14% (1%)	4% (0)	15% (3%)	0
Rash	0	1% (1%)	0	0
Fatigue	49% (0) N=41	0	25% (0)	0
Fever[3]	7% (0) N=156	3% (0)	0	0
Stayed home due to reaction	16%	8%	0	0
Analgesics/Antipyretics	33%	19%	8%	0

Source: Section 2.7.4, Tables 2.7.4.2.1.1.1-12 and 2.7.4.2.1.1.1-18; ISS Table 2.4.2; [1]Flu-Control vaccines were: None for V87P6, and Fluogen/Flushield for V7P29; [2]Severe (>50mm); [3]Any (≥38°C), severe (≥40°C).

In study V7P29, the reactogenicity of Fluad paediatric was clearly superior in the age group (9-17 y old) as compared to that of the non-adjuvanted vaccine:

Study Synopsis Table B
Numbers and percentages of subjects experiencing postimmunization reactions, days 0 through 6, in both phases of the study

Postimmunization Reaction	FLUAD n = 116	FLUOGEN/ FLUSHIELD n = 100
Local		
***Pain	96 (83%)	53 (53%)
Temperature	37 (32%)	23 (23%)
Erythema	19 (16%)	9 (9%)
Induration	19 (16%)	14 (14%)
Systemic		
**Chills	13 (11%)	1 (1%)
Nausea	12 (10%)	4 (4%)
***Malaise	28 (24%)	6 (6%)
Myalgia	11 (9%)	6 (6%)
Arthralgia	2 (2%)	0
**Headache	31 (27%)	12 (12%)
Rash	0	1 (1%)
Fever ≥ 38°C	10 (9%)	3 (3%)
Stayed Home	18 (16%)	8 (8%)
**Analgesic/Antipyretic Use	43 (37%)	19 (19%)

** $P \leq 0.01$; *** $P \leq 0.001$

Because of the high vaccine reactogenicity observed in children 9 through 12 years of age, the protocol of study V7P29 was amended to exclude children less than 9 years of age from participation to the study.

Table 12.2.1.1-1: Percentages of Subjects with Local and Systemic Reactions

	Injection 1		Injection 2		Injection 3	
	Pan IV	Seas IV	Pan IV	Seas IV	Pan IV	Seas IV
Toddlers	**N=145**	**N=56**	**N=138**	**N=56**	**N=124**	**N=0**
Any	76%	75%	68%	63%	80%	-
Local	47%	50%	46%	41%	60%	-
Systemic	59%	54%	51%	46%	54%	-
Other	17%	23%	16%	20%	19%	-
Children	**N=96**	**N=40**	**N=93**	**N=39**	**N=85**	**N=0**
Any	72%	80%	68%	56%	79%	-
Local	66%	63%	58%	49%	74%	-
Systemic	32%	58%	33%	36%	45%	-
Other	9%	15%	12%	15%	14%	-
Adolescents	**N=93**	**N=41**	**N=91**	**N=40**	**N=83**	**N=0**
Any	91%	88%	82%	78%	89%	-
Local	81%	71%	70%	65%	81%	-
Systemic	69%	80%	52%	50%	69%	-
Other	26%	34%	15%	8%	16%	-

Source: Table 14.3.1.1.1.2, Table 14.3.1.1.1.3

Table 12.2.3-2: Percentages of Subjects With Any (and Severe) Systemic Reactions

	Injection 1		Injection 2		Injection 3	
	Pan IV	Seas IV	Pan IV	Seas IV	Pan IV	Seas IV
Toddlers[a]	**N=145**	**N=56**	**N=138**	**N=56**	**N=124**	**N=0**
Sleepiness	23%	20%	21%	14%	20%	-
Diarrhea	19%	14%	15%	16%	11%	-
Vomiting	8%	5%	2%	4%	2%	-
Irritability	39%	21%	29%	20%	27%	-
Change Eating habits	19%	16%	16%	14%	19%	-
Shivering	1%	7%	1%	4%	6%	-
Unusual Sweating	6%	0%	1%	2%	4%	-
Unusual Crying	33%	30%	27%	16%	23%	-
Fever ≥ 38C (≥ 40 C)[b]	0%	0%	0%	0%	0% (N=123)	-
Analg Anti Medication	17%	23%	16% (N=137)	20%	19%	-
Children	**N=96**	**N=40**	**N=93**	**N=39**	**N=85**	**N=0**
Chills	6% (0%)	10% (3%)	5% (0%)	15% (0%)	9% (0%)	-
Malaise	6% (0%)	10% (3%)	12% (1%)	15% (0%)	13% (0%)	-
Myalgia	6% (0%)	13% (3%)	8% (0%)	21% (3%)	25% (2%)	-
Arthralgia	2% (0%)	5% (0%)	1% (0%)	0% (0%)	4%(0%)	-
Headache	17% (0%)	23% (0%)	9% (1%)	23% (0%)	16% (2%)	-
Sweating	5 %(0%)	8% (0%)	3% (1%)	10% (0%)	4% (0%)	-
Nausea	6% (0%)	5% (3%)	10% (0%)	8% (5%)	4% (0%)	-
Vomiting	2% (1%)	8% (3%)	4% (0%)	3% (3%)	1% (0%)	-
Diarrhea	10% (1%)	5% (0%)	9% (2%)	5% (0%)	7% (0%)	-
Fatigue	15% (0%)	33% (3%)	16% (0%)	21% (0%)	25% (2%)	-
Fever ≥ 38C (≥ 40 C)[b]	4% (0%)	5% (0%)	2% (0%)	5% (0%)	6% (1%)	-
Stay Home	4%	5%	4%	10%	6%	-
Analg Anti Medication	6%	13%	11%	8%	12%	-
Adolescents	**N=93**	**N=41**	**N=91**	**N=40**	**N=83**	**N=0**
Chills	11% (0%)	34% (0%)	3% (0%)	5% (0%)	14% (2%)	-
Malaise	22% (0%)	37% (2%)	14% (0%)	13% (0%)	14% (2%)	-
Myalgia	37% (2%)	37% (0%)	33% (1%)	18% (0%)	42% (2%)	-
Arthralgia	4% (0%)	10% (0%)	2% (0%)	5% (0%)	4% (0%)	-
Headache	40% (1%)	59% (2%)	22% (0%)	25% (3%)	35% (6%)	-
Sweating	13% (0%)	15% (0%)	4%(0%)	5% (0%)	5% (0%)	-
Nausea	14% (0%)	24% (2%)	9% (1%)	15% (3%)	8% (0%)	-
Vomiting	1% (0%)	5% (0%)	1% (0%)	0% (0%)	0% (0%)	-
Diarrhea	4% (0%)	10% (0%)	8% (1%)	3% (0%)	8% (0%)	-
Fatigue	32% (0%)	49% (0%)	11% (1%)	25% (0%)	20% (2%)	-
Fever ≥ 38C (≥ 40 C)	0% (0%)	2% (0%)	1% (0%)	0% (0%)	2% (0%)	-
Stay Home	5% (N=92)	17%	4%	0%	2%	-
Analg Anti Medication	22%	22%	13%	8%	16%	-

Source: Table 14.3.1.1.2, Table 14.3.1.1.2.1: [a]Systemic reactions in toddlers were not graded by severity:
[b](≥40C) indicates severe reaction: Analg Anti Medication= Analgesic Antipyretic Medication Use

Table 2.5.5.1.2-1 Overview of Unsolicited AEs in the Pooled Safety Population by Safety Monitoring Period, Age Group and Vaccine Group

	Number (%) of Subjects with Unsolicited AE					
Safety Monitoring Period	**Primary Period[1]**					
Age Group	**6 to <36 Months**		**3 to <9 Years***		**9 to <18 Years**	
Vaccine	**Fluad**	**Flu-Contr.[3]**	**Fluad**	**Flu-Contr.[3]**	**Fluad**	**Flu-Contr.[3]**
Pooled Safety Population	**N=1500**	**N=1339**	**N=918**	**N=826**	**N=157**	**N=100**
AEs: all	1009 (67%)	887 (66%)	518 (56%)	478 (58%)	44 (28%)	38 (38%)
related (poss./prob.)	182 (12%)	147 (11%)	116 (13%)	79 (10%)	21 (13%)	11 (11%)
SAEs: all	22 (2%)	21 (2%)	9 (1%)	12 (1%)	0	1 (1%)
related (poss./prob.)	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
AEs leading to premature withdrawal	6 (<1%)	10 (1%)	6 (<1%)	1 (<1%)	0	0
related (poss./prob.)	3 (<1%)	2 (<1%)	2 (<1%)	0	0	0
Death	0	0	0	0	0	0
related (poss./prob.)	0	0	0	0	0	0
Safety Monitoring Period	**Follow-up Period[2]**					
Age Group	**6 to <36 Months**		**3 to <9 Years***		**9 to <18 Years**	
Vaccine	**Fluad**	**Flu-Contr.[3]**	**Fluad**	**Flu-Contr.[3]**	**Fluad**	**Flu-Contr.[3]**
Pooled Safety Population	**N=1359**	**N=1213**	**N=879**	**N=796**	**N=156**	**N=100**
AEs: all	855 (63%)	766 (63%)	418 (48%)	417 (52%)	93 (60%)	69 (69%)
related (poss./prob.)	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	0	1 (1%)
SAEs: all	56 (4%)	78 (6%)	15 (2%)	39 (5%)	0	0
related (poss./prob.)	0	0	1 (<1%)	1 (<1%)	0	0
AEs leading to premature withdrawal	1 (<1%)	2 (<1%)	0	0	0	0
related (poss./prob.)	0	0	0	0	0	0
Death	0	1 (<1%)	0	0	0	0
related (poss./prob.)	0	0	0	0	0	0

Source: Section 2.7.4.2.1.1.2, Table 2.7.4.2.1.1.2-4;
NA= not applicable; 7.5µg for 6 to <36 month olds and 15µg for ≥36 month/3 year olds.
*: Upper age limit lower than "<9 years": in V70P6="<5 years (60 months)" and in V70P5= "<6 years (72 months)".
[1]: Primary Period: from Day 1 (1st vaccination) through 21 days post last vaccination. [2]: Follow-up Period: from >21 days post last vaccination to 6 months after last vaccination. [3]: Flu-Contr.=Flu-Control seasonal vaccine: Vaxigrip for V70P2, Fluzone for V70P6, Agrippal S1 for Part I of V70P5 and Influsplit SSW for Part II and Part III of V70P5, none for V87P6 (since PanH5N1 is not a seasonal flu vaccine), and Fluogen/Flushield for V7P29.

Serious adverse events and deaths

Death

No death was reported in studies V70P2, V70P2E1, pivotal efficacy trial, V87P6 and V7P29. One death occurred in Flu-comparator group of study V70P6 (6 to <36 months) because of multiple trauma. The AE was considered not related to study vaccine.

Serious AEs

Table 2.7.4.2.1.3-1 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 Tables 2.11.2, 2.11.6, 2.12.2 (all subjects presented as treated; Note: V70P5 does not match CSR V70P5, where presentation is as randomized).
[1]: Of the subjects from V70P2 that continued in V70P2E1 about half were ≥36 months old, see Table 2.7.4.-2. [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). [4]: For randomization ratio see Table 2.7.4.-2. [5]: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 2.7.4.2.1.3-2 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 Tables 2.11.2, 2.11.6, 2.12.2 (all subjects presented as treated; Note: V70P5 does not match CSR V70P5, where presentation is as randomized)..
*: 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, see Table 2.7.4.-2. [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). [4]: For randomization ratio see Table 2.7.4.-2. [5]: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 2.7.4.2.1.3-3 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 Tables 2.11.2, 2.11.6, 2.12.2 (all subjects presented as treated).
[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, for details see Table 2.7.4.-2.

Laboratory findings

No laboratory evaluations were performed for the evaluation of safety in the Fluad studies V70P2, the extension study, V70P6, pivotal efficacy trial, and V87P6, except for V7P29. In study V7P29 clinical laboratory data were obtained on Day 1 (pre-vaccination) and Day 28, but no clinically significant abnormalities were observed.

Safety in special populations

Intrinsic Factors

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

Extrinsic Factors

No extrinsic factors likely to influence the safety profiles of the vaccines were identified.

Immunological events

NA

Safety related to drug-drug interactions and other interactions

The Applicant stated that all the studies proposed were not designed to evaluate drug interactions.

Discontinuation due to AES

Table 2.7.4.2.1.4-1 Subjects (%) with AEs Leading to Premature Withdrawal – 6 to <36 Months

	Number (%) of Subjects with AEs Leading to Premature Withdrawal									
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 AE leading to premature withdrawal	1 (1%)	2 (1%)	0	0	0	1 (1%)	6 (1%)	9 (1%)	0	1 (1%)
related (poss./prob.)	1 (1%)	0	0	0	0	0	2 (<1%)	2 (<1%)	0	0

Source: ISS Tables 2.12.3 (all subjects presented as treated).
[1]: Of the subjects from V70P2 that continued in V70P2E1 about half were ≥36 months old, see Table 2.7.4.-2. [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). [4]: For randomization ratio see Table 2.7.4-2. [5]: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 2.7.4.2.1.4-2 Subjects (%) with AEs Leading to Premature Withdrawal – 3 to <9 Years

	Number (%) of Subjects with AEs Leading to Premature Withdrawal							
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 AE leading to premature withdrawal	0	0	1 (2%)	1 (2%)	4 (<1%)	0	1 (3%)	2 (2%)
related (poss./prob.)	0	0	0	0	1 (<1%)	0	1 (3%)	0

Source: ISS Tables 2.12.3 (all subjects presented as treated).
*: 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, see Table 2.7.4.-2. [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). [4]: For randomization ratio see Table 2.7.4-2. [5]: Control A=Agrippal S1 for Part I, Influsplit SSW for Part II and Part III.

Table 2.7.4.2.1.4-3 Subjects (%) with AEs Leading to Premature Withdrawal – 9 to <18 Years

	Number (%) of Subjects with AEs Leading to Premature Withdrawal			
Study	V87P6 [1]		V7P29 [2]	
Vaccine group	Fluad	PanH5N1 [3]	Fluad	Flushield or Fluogen
Safety Population	N=41	N=93	N=116	N=100
Any AE leading to premature withdrawal	0	0	0	0
related (poss./prob.)	0	0	0	0

Source: ISS Tables 2.12.3 (all subjects presented as treated).
[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, for details see Table 2.7.4-2.

Post marketing experience

Adults

The Applicant declared that Fluad MR has been on the market for about 13 years; hence the post-marketing experience is extensive. Since 1997 (date of first launch), an estimate of 48 million doses have been distributed (over 40 million doses distributed to subjects older than 65 years old). Whilst

the experience in healthy subjects (in particular in the elderly) is extensive (approximately 3/4 of the subjects enrolled in clinical trials), limited data are available with regard to immunocompromised subjects.

No data are available in pregnant adolescent women. Adverse reactions reported from post-marketing surveillance are the following:

Uncommon (>1/1,000, <1/100): Generalised skin reactions including pruritus, urticaria or non-specific rash.

Rare (>1/10,000, <1/1,000): Neuralgia, paraesthesia, convulsions and transient thrombocytopenia. Allergic reactions, in rare cases leading to shock, have been reported.

Very rare (<1/10,000): Vasculitis with transient renal involvement and exudative erythema multiforme. Neurological disorders such as encephalomyelitis, neuritis and Guillain Barrè syndrome. Asthenia, Influenza-Like Illness (ILI), pain in the extremity, muscular weakness and lymphadenopathy.

The pooled analysis of safety described by the Applicant was performed on all 12,889 elderly subjects aged ≥65 years who were exposed to at least one dose of Fluad paediatric. The Applicant states that Fluad paediatric was generally safe and well tolerated in elderly subjects. Most of the reactions were mild, of short duration and qualitatively similar to those induced by the non-adjuvanted comparator vaccines. In the pooled analysis, local injection-site reactions (pain and temperature on injection) were more frequent in subjects who received the adjuvanted vaccine than in those who received non adjuvanted vaccine. Pain was the most common reaction in both groups and it was usually mild and transient. The Applicant stated that systemic reactions were relatively uncommon and usually mild and transient. More clinically relevant adverse events, including those requiring a physician visit during the first week of immunization were rare and quantitatively similar to those induced by control vaccines.

Applicant declared that the incidences of individual SAEs were low, and no relevant differences in the incidences of different types of SAEs between the vaccination groups were observed.

Paediatrics
The data available in paediatric population come from six H1N1 pandemic flu vaccine studies (adjuvant MF59) performed by the Applicant in paediatric populations (ages 6 months to <18 years). These clinical trials used two vaccine doses 3 weeks apart as the priming vaccination, and in some studies a 3rd vaccination 12 months later has been administered as a booster.

Up to the Applicant, from a viewpoint of reactogenicity and safety profile of the MF59 adjuvant in the 3 age groups (6 to <36 months, 3 to <9 years, and 9 to <18 years) of the paediatric population, the results summarized in MF59-Adjuvanted H1N1 Swine Flu studies show that there was no consistent or clinically meaningful difference between MF59-adjuvanted and non-adjuvanted H1N1 swine flu vaccine groups.

Discussion on clinical safety

In the original dossier submitted all the safety data of Fluad paediatric were collected from two phase 2 clinical studies (V70P2, V70P6), one pivotal efficacy phase 3 study and one extension study, conducted in children from 6 to <72 months of age. The present assessment has taken into consideration pooled data from all these studies, not considering the issue of the acceptability of data collected in the large the pivotal efficacy study, for which suspects of incorrectness of safety data collected at one study

centre have been raised. The final decision on the safety profile very much depend on the inclusion of the pivotal efficacy study, and thus on the acceptability of data from this study.

Additionally results for Fluad paediatric in paediatric population 6 months to <18 years are available from 2 supportive studies (V87P6 and V7P29).

Subjects enrolled in these trials were analyzed accordingly to three different age categories as follow:

1. 2,839 infants and children 6 to less than 36 months of age [1,500 vaccinated with Fluad Paediatric, and 1,339 with conventional non-adjuvanted influenza vaccines]
2. 1,744 children 3 years to less than 9 years of age [918 vaccinated with Fluad Paediatric, 826 with conventional non-adjuvanted influenza vaccines
3. 257 children and adolescent 9 to <18 years of age [157 received Fluad Paediatric (116 from study V7P29 + 41 from study V87P6), 100 Flu comparator vaccine].

In the studies, 2,418 paediatric patients aged from 6 months to 9 years have received at least one dose of Fluad paediatric: this sample represents the safety database. Such figure may be crucially diminished if the the pivotal efficacy study is not taken into consideration.

As the EMEA Note for Guidance on "Clinical Evaluation of New Vaccines suggests, the safety evaluation of a new vaccine requires a database of approximately 3,000 adults aged from 18 to 60 years and, for specified age groups, approximately 300 subjects each. These requirements are not completely fulfilled in this application. However, the number of 2,418 paediatric subjects, even if not reaching the 3,000 cut off, has been considered as a minor concern.

After day 120 the Applicant has provided further data in order to address the CHMP major objection which considers the safety data provided in the initial MA dossier insufficient to fully characterise the safety profile of Fluad.

The Applicant has presented safety and immunogenicity data on children with defined risk conditions from the pivotal efficacy study (entry criteria for this study were for healthy children, but it was allowed enrollment of children with various common underlying conditions, as long as they were immunocompetent, but non immunocompromised), adjuvanted pandemic H1N1 vaccine trials, as well as other Fluad trials that are enrolled but not yet completed.

Data provided by the Applicant from the two H1N1 Paediatric studies which used Fluad as a booster (V11_03, V110_04), could be considered only supportive as both have been conducted in children receiving a different monovalent pandemic influenza vaccine for primary immunization. Moreover, the number of subjects revaccinated with Fluad has not been clearly provided.

Regarding the study not yet completed, the Company has submitted data from the pivotal trial required for US licensure, not included in the original dossier and still ongoing.

As a conclusion, the additional data presented by the Applicant are not enough to enlarge the 2,418 safety database to get the limit of 3,000 as required in the EMEA Guidance.

In the safety data base, every specific age subset should be adequately represented, especially the sub-group of children aged 6-9 years which was poorly represented in the original dossier with only 19 subjects vaccinated with Fluad evaluated for safety. The sample size of the age-cohort 6 to <9 years has been subsequently increased with additional 177 other subjects; the increased number of subjects seems to confirm a higher reactogenicity profile in the oldest children. The clinical significance of this trend has not been addressed by the Applicant. A specific analysis devoted to demonstrate a possible age dependent relationships, stratifying by different age such as 3-6 yrs and 6-9 yrs, is lacking. Such issue is relevant to identify the upper age limit of indication for vaccine use that should be set at an age point when the increased immunogenicity conferred by the adjuvanted vaccine is evident and needed and the increased related reactogenicity is acceptable compared to TIVs.

The patient population enrolled in studies are healthy children. In the great majority of EU countries, immunization against seasonal influenza for the whole paediatric population is not a common policy. In fact, the paediatric target population recommended for influenza vaccination is represented by at-risk subjects (e.g. children with underlying conditions). Fluad paediatric has not been investigated in this peculiar category of patients, thus limiting the possibility to define its comprehensive safety profile. The administration of an adjuvanted flu vaccine, like Fluad paediatric, to children with underlying conditions could lead to a deregulated immune response and, consequently, to a different safety profile in terms of frequency and severity of AEs. The safety profile of immune-competent children cannot be totally extrapolated to children with underling chronic diseases. Results in children at-risk for influenza complication are thus needed, and on this regard, the final results from ongoing studies are awaited. Moreover, immunogenicity data in immuno-compromised children should be obtained

The indication proposed by the Applicant should clearly reflect the population eligible for vaccination with Fluad paediatric; the Applicant's proposal as quoted in the SmPC section 4.1 is not agreeable as such, and should be amended as follow: "Active immunization against influenza in healthy infants and children aged from 6 months to 6 year".

Furthermore, in the SmPC section 4.4. it is stated that "Very limited data are available for FLUAD Paediatric in infants and children with underlying medical conditions." According to the data presented by the Applicant, no information is available in this category of patients. The Applicant should address this lack of information and, if no data are provided in children with underlying diseases, the wording in the SmPC section 4.4 should be amended accordingly.

Long-term safety of Fluad paediatric is another important issue not completely addressed by the Applicant. It could be expected that children receiving influenza vaccination will repeat the administration over years (chronically). Therefore, the long-term safety profile has to be adequately studied especially taking into consideration that Fluad paediatric is an adjuvanted vaccine. No data on the effect of repeated exposure to adjuvanted influenza vaccines in the paediatric population is available at present. Despite that, the Applicant has provided very limited data on the annual re-exposure to Fluad paediatric (available data come from the study V70P2E1 which only provides safety results up to day 22 following vaccination for 18 subjects aged 6 to <36 months receiving Fluad as revaccination, being just 9 primo-vaccinated with Fluad, and for 60 children aged 36 to < 96 months receiving a full dose of Fluad (only 22 of these had been primo-vaccinated with Fluad).

A higher percentage of solicited reactions, both local and systemic, were reported after the third dose vaccination of the 43 children included in V70P2E1. When comparing to Flu-control, the difference in reactogenicity was high. It was mainly observed in local reactions from the 18 children ≥ 36 months group (83% Fluad vs. 48% Flu-control), being pain at injection site the most frequently reported (67% vs. 26%). These limited data both with regards to the number of subjects as well as with regards to the number of annual re-vaccinations (data are available only for the first re-vaccination, 12 months after the priming) do not allow the assessment of the long term safety profile of Fluad paediatric. Moreover, no data from children previously vaccinated with a non-adjuvanted Flu vaccine have been reported. As recommended by the VWP, data on annual revaccination should be obtained at pre-licensure at least on a representative subset of subjects of the intended target population.

The evaluation of the co-administration of Fluad paediatric with other vaccines (especially if adjuvanted) and the risk of potential interference has not been investigated by the Applicant. The proposed SmPC section 4.5 states that "No clinical data on concomitant administration with other vaccines are available. If Fluad Paediatric needs to be used at the same time as another vaccine, immunisation should be carried out on separate limbs…". The proposed phrasing is at present agreeable. Nevertheless, considering that the target population of Fluad paediatric, children between 6 months of age to 6 years, is exposed to national immunization programmes and that flu vaccination

cannot be scheduled on an age basis, the lack of data on vaccines co-administration needs further evaluation.

The safety profile of Fluad paediatric appears comparable with influenza control non-adjuvanted vaccines in healthy children aged from 6 to 72 months of age. However, overall, a consistent increase in the number of systemic reactions in the recipients of Fluad paediatric vaccine was observed through all submitted studies compared to the comparator.

It should be explored if safety is related to the serostatus at baseline in order to clarify whether the reactogenicity (local and systemic) is higher in children seropositive at baseline compared to seronegative children due to the fact that the vaccine may act as a booster in children already primed by a natural infection. If this were the case, the adjuvanted vaccine will offer, for those previously naturally infected, no immunological benefit but a higher reactogenicity as compared to a non-adjuvanted vaccine.

No sufficient data have been provided to assess the safety profile in the older children group proposed for the labelling (6 – 9 years of age). Considering any local and systemic reactions within 7 days after each vaccination there was no statistically significant difference in the cohort aged 6-36 months (RR = 1.03 [97.66% CI of 0.98-1.09].

On the contrary a slightly higher reactogenicity in the Fluad paediatric group is reported if only the cohort 6-72 months is considered (RR = 1.08 [95% CI of 1.04-1.12].

The higher reactogenicity in the older cohort is possibly due to different dose exposure to the adjuvant (which is double) and different stages of immune system maturation. More mature immune systems in older children might be more prone to react to the adjuvant, resulting into an increased reactogenicity.

In relation to solicited adverse reactions:

- in cohort aged 6 months to 36 months, the incidence rates of overall reactogenicity were higher in the Fluad paediatric than in control group and slightly higher after the first than the second vaccination. Local reactions (ecchymosis, erythema, induration, swelling and tenderness) were reported in a higher (1-6%) percentage in Fluad paediatric recipients. Systemic reactions were reported at a higher rate than local reactions. The incidence of fever was 20% after the first and 22% after the second vaccination in the Fluad paediatric group respectively compared to 18% and 17% in the Flu vaccine comparator. Fever was reported and categorized as: no fever, > 38°C and > 40°C;
- In cohort aged from 3 to 9 years, Fluad paediatric was more reactogenic than Flu control vaccine, especially in terms of systemic reactions and severe adverse reactions (for example Fluad paediatric arm almost doubles the comparator group in terms of incidence of fever, which was 16% after the first vaccination and 16% after the second in the Fluad paediatric recipients versus respectively 7% and 8% in the comparator vaccine group).

Comparing the 3 age cohorts it seems that the difference in reactogenicity among Fluad paediatric and influenza vaccine comparator increases with age. Solicited severe adverse reactions were higher in the Fluad paediatric group. The Applicant should comment and adequately reflect the higher systemic reactogenicity shown in Fluad paediatric recipients in the SmPC section 4.8. A statistical significance testing of overall solicited adverse events rates, but not for the systemic reactogenicity, has been performed by the Applicant. At any rate, considering the low sample size, this analysis is unlikely to be helpful.

Overall when analysing the unsolicited AEs, the results from the pooled analysis showed to be consistent with those from the by-study analysis. In general, unsolicited adverse events (any and related) were balanced between Fluad paediatric and influenza control vaccine groups in both age groups, 6 to <36 months and 3 to <9 years; nevertheless, a higher percentage of unsolicited AEs were judged to be possible or probably related to the vaccine in the Fluad paediatric recipients than in the

control arm. For children 9 to <18 years incidence rates in the Flu-comparator group were higher than in the Fluad paediatric group, and for both vaccination groups incidence rates were higher during the follow-up period.

No death was reported in studies V70P2, V70P2E1, the pivotal efficacy study, V87P6 and V7P29. One death occurred in the influenza comparator group of study V70P6 (6 to <36 months). This AE was considered not related to study vaccine.

Overall, serious AEs related and unrelated to the vaccine reported in the 3 age cohorts were similar in terms of incidence between the Fluad paediatric and the flu vaccine comparators. The collection time for SAEs in the pivotal efficacy study (part II) which involved the majority of patients (n=4,051) was 1 year that seems appropriate, whereas in part I and III, which involved 846 patients, the collection time of SAEs was only 6 months.

Few serious AEs or AEs leading to withdrawal are described as possible or probably related to Fluad paediatric. Generally, it could be concluded that from the evaluation of the incidence rates of AEs leading to premature withdrawal in all the studies included in the application there is no clinically meaningful differences between Fluad and non adjuvanted-comparator vaccines.

According to the description of the subject receiving Fluad Paediatric who developed strabismus with onset on Day 2 and withdrawn from the study because of AE persisted, it is recommended the inclusion of strabism in SmPC section 4.8.

The Applicant has provided Fluad paediatric post-marketing data which mainly come from the elderly population (> 65 years old). Overall, safety profile after Fluad paediatric vaccination in children was comparable to the safety profile in the elderly population, with regard to the non-adjuvanted Flu control.

Conclusions on clinical safety

The safety database is of critical size and the decision about the acceptance of the pivotal study is crucial.

Overall, a systematic increase in the number of systemic reactions in the recipients of Fluad paediatric vaccine was observed through all submitted studies compared to the comparator. Such difference was mostly present in the recipients of Fluad paediatric in the age group 3-9.

The safety profile of Fluad paediatric appears comparable with influenza control non-adjuvanted vaccines in healthy children aged from 6 to 72 months of age.

The major concerns related to the safety assessment of Fluad paediatric, proposed for seasonal flu vaccination in children aged from 6 months to 9 years, are the following:

- the paediatric population investigated in the studies is composed by healthy children, who do not represent the target population of flu seasonal vaccination in most of the EU countries. Final results from ongoing studies are awaited
- the safety dataset of patients aged from 6 to 9 years is still far too limited in order to allow a sound conclusion on the safety profile of the vaccine in this age subgroup
- very limited data on annual vaccine re-exposure are available. Considering that Fluad paediatric is expected to be administered every single year, long-term safety data are deemed necessary in order to assess the benefit/risk balance of the vaccine.

As minor concerns:

- the overall pooled data from all clinical studies (subjects receiving at least one vaccine administration) represent 2,418 subjects who have received 2,418 doses of vaccine. After day 120, new data have been provided but not enough to contribute to adequately enlarge the safety database. The safety database is still below the limit of 3,000 subjects established in the EMEA Note for Guidance on "Clinical Evaluation of New Vaccines". Every specific age subset is not adequately represented
- neither data on vaccines co-administration, nor information on timeframe of potential subsequent vaccine administration, have been provided. Since the target population is children, who undergo other vaccinations, the lack of data on vaccines co-administration needs further evaluation
- The combination of the adjuvant with more than one antigen, increases reactogenicity and decreases tolerability of the vaccine. Whether this has any potential implication on the effect of co-administration with other vaccines, should be discussed by the Applicant.

Pharmacovigilance system

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

The Applicant has provided satisfactory responses to the deficiencies in the Pharmacovigilance system highlighted at Day 120 LoQs.

A new version (15.0) of DDPS released on 3 August 2011 has been provided. However, with regard the duplicate check for spontaneous, literature and PMS reports the procedure should consider also a matching by date of birth/age and country of origin.

Provided that the minor deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the Pharmacovigilance system is in place and functioning before the product is placed on the market.

Risk management plan

The Applicant provided an updated version of the RMP (V. 2.0) in response to Day 120 LoQ.

No clinical data on co-administration of Fluad paediatric with other vaccines are available. Given the requested therapeutic indications, it is necessary to have more information about co-administration with other vaccines (aged from 6 months old to 9 years). It should be noted that the adverse reactions may be intensified. Therefore this risk should be discussed and "interaction with regular childhood vaccines" and added as a potential risk.

There is no information on children with chronic illness, immunocompromised paediatric patients and limited information is available for immunocompromised adult subjects (58 subjects with renal transplantation, 46 subjects positive for HIV infection).

Subjects aged from 9 to 18 years old are another potential population for off-label use. This issue should also be clarified in the SmPC.

Anaphylactic and allergic reactions are now considered as identified risks; "interaction with regular childhood vaccines" has been added amongst important missing information. Cases of the potential risks have been reported in the RMP by seriousness, frequency age group.

Safety specification

Clinical

1.2.1 Limitations of the Human Safety Database

The FLUAD clinical database consists of more than 21,000 subjects, from trials conducted from 1992-93 up to now. These subjects include elderly, adults, children ≥6 months of age, and adolescents. One additional collaborative observational study has started in fall 2006 in which approximately 107,000 elderly subjects were vaccinated with Fluad or the non-adjuvanted subunit vaccine Agrippal. Fluad is currently approved for use in elderly subjects. The experience in this group is extensive and includes more than 13 thousand subjects in clinical trials, more than 100 thousand subjects in a postmarketing observational study, and more than 50 million subjects exposed post-approval.

More than 2,000 children have been vaccinated with Fluad. Limited information is available for paediatric subjects with regard to repeated annual re-vaccination, interaction with childhood vaccines, safety in immunocompromised children or children with underling diseases.

A summary of Fluad exposure in clinical studies by age groups and by number of vaccinations is included in the RMP.

Post-marketing (non study) exposure

From launch in 1997 until April 30, 2011, approximately 57 million doses of Fluad (for elderly) and copy products have been distributed.

Populations Not Studied in the Pre-Authorization Phase

Fluad has been studied in several populations including elderly (≥65 years of age), adults (18 to 64 years), adolescents (9 to 17 years), children (6 months to 8 years), and patients with underlying chronic diseases (adults and elderly subjects). Whilst the experience in elderly, adults and children is extensive (more than 13,000, 2,000 and 2,500 elderly, adult an paediatric subjects, respectively, received at least one dose of Fluad), limited data are available with regard to adolescents and patients with underlying chronic diseases or immunocompromised patients, in particular in children. In addition, limited information is available regarding annual revaccination in healthy children and no data are available regarding interactions of Fluad with regular childhood vaccines.

Populations not studied in the pre-authorization phase, and studies ongoing or planned to address missing information are described in the sections Important Missing Information) and Pharmacovigilance Plan, respectively.

Adverse Reactions

Identified and potential risks are discussed throughout this Risk Management Plan by the order in which they appear in the following subsections. Risks are not listed by order of importance or any other reason. The following sections describe frequency and seriousness of post-marketing spontaneous reports from first launch through 30 April 2011. Only Fluad-confirmed cases are mentioned for each risk. In addition, serious adverse events for Fluad paediatric and elderly from clinical trials are included. Note that because of under-reporting of spontaneous post-marketing events, the spontaneous post-marketing reporting frequency provided for the events in the following subsections most likely underestimate the actual incidence of the events.

Cumulatively through 30 April 2011, the reporting frequency for all case reports is approximately 2.7 per 100,000 doses distributed. This frequency was estimated considering the cumulative number of

spontaneous case reports received (approximately 1,556) and doses distributed (approximately 57 million). This estimation also included INN (International Non-proprietary Name) reports (accounting for about 40% of the total number).

Identified Risks
Anaphylactic Reaction

Potential Risks
As with other seasonal influenza vaccines, there are a number of adverse events of special interest, which have been rarely reported following influenza and pandemic vaccination.

These events have the potential to negatively affect the benefit/risk of Fluad paediatric and include: Neuritis, Convulsion, Encephalitis (incl. myeloencephalitis), Vasculitis, Guillan-Barré Syndrome (GBS), Demyelination disorder, Bell's Palsy, ITP, and vaccination failure.

Identified and Potential Interactions with Other Medicinal Products, Food, and Other Substances
There are no studies investigating the potential interaction between Fluad paediatric and other vaccines. Besides, there are no studies investigating the potential interaction between Fluad paediatric and regular childhood vaccines.

Important Missing Information

Paediatric Subjects (< 9 years)

SAFETY IN CHILDREN WITH UNDERLYING DISEASES AND IMMUNOCOMPROMISED CHILDREN

Limited data coming from an ancillary analysis from the pivotal efficacy study enrolling healthy children has been provided in the RMP.

SAFETY AFTER ANNUAL RE-VACCINATION

Revaccination with Fluad paediatric after priming has been well characterized over one season in four studies. There is no information regarding revaccination with Fluad paediatric over several influenza seasons.

As is generally observed at priming, the reactogenicity is increased in the groups that receive Fluad compared to those who received a non-adjuvanted vaccine.

Besides a slight increase of local reactogenicity in the 3-8 years olds in one study, the reactogenicity of the Fluad re-vaccination appears comparable to the reactogenicity of the priming regimens

VACCINATION EFFECTIVENESS

There are no data on vaccine effectiveness in the paediatric age group.

1.6.2 Adolescent Subjects (≥ 9, < 18 years)

Two studies in adolescent subjects have been completed and are described hereafter:

V7P29 Phase II study - 1996/1997 Season
This Phase II, observer-blind trial compared the safety, tolerability, and immunogenicity of Fluad paediatric (n = 101) to that of a non-adjuvanted subunit vaccine, Fluogen/Flushield (n =100), in healthy adolescents (aged 9 to 17 years). In the open-label, pilot phase of the study, 15 healthy

children received Fluad paediatric. The 2 age groups in the pilot study received the study treatment sequentially in the following order: children 13 through 17 years of age (n = 5) and children 9 through 12 years of age (n = 10).

Safety results: Both vaccines were safe and generally well tolerated. Fluad paediatric recipients reported significantly more injection site pain, chills, malaise, headache, and analgesic/antipyretic use than Fluogen/Flushield recipients. Solicited local and systemic reactions were generally mild in intensity and of short duration. No vaccine-related SAEs occurred.

V87P6 (H5N1) Phase II – 2008/2009 Season

The study started in September 2007 and LSLV was completed on 18 May, 2009. Overall, 471 children aged 6 months to 17 years have been enrolled into this trial and were randomized 3:1 to either Fluad-H5N1 or seasonal Fluad™. This trial is overseen by an Independent Data Monitoring Committee (IDMC). Interim safety analyses for the first 90 subjects enrolled have been conducted in a blinded fashion after the first and the second dose and were reviewed by this committee. The IDMC had no safety concerns, did not request the unblinding of the results, and allowed further enrolment into this trial. Booster for the Aflunov group started in September 2, 2008. 24 SAEs have been reported; no SAEs related to study vaccines have been reported. Two withdrawals occurred, one due to exanthema and the cause for the other one not yet reported. There were no deaths or possibly/probably related SAEs.

In conclusion, the MF59-PanH5N1 influenza vaccine, containing 7.5 µg of H5N1 antigen per injection, was immunogenic, met all CHMP criteria after primary and booster vaccination, and was safe and well tolerated with the overall percentages experiencing local, systemic and other adverse events in the MF59-PanH5N1 IV group being similar to that in the MF59-Seasonal IV group, in subjects aged 6 months to 17 years. Final study report was released in August 2009.

Epidemiology

A full description on Epidemiology of Influenza, burden of disease in children, as well as vaccine efficacy and effectiveness in children have been reported in the RMP.

Epidemiology of Important Risks

The following have been analysed by the applicant:

- Neuritis
- Convulsions
- Anaphylactic reactions
- Acute Disseminated Encephalomyelitis (ADEM);
- Vasculitis
- Guillain-Barrè Syndrome (GBS)
- Demyelination
- Bell's palsy
- Immune thrombocytopenia

Pharmacological Class Effects

1.8 Pharmacological Class Effects

Risk	Frequency in clinical trials of Fluad (Serious Adverse Events)	Frequency for other vaccines (scientific literature source)
Neuritis	Children: very rare Elderly: very rare	0.09% of all reactions reported to VAERS Isolated reports in the literature.
Convulsion	Children: rare event Elderly: rare event	Reporting frequency of seizures after seasonal influenza vaccine in children 6-23 months of age ranged from 17% to 34% of all serious adverse events occurring within 2 days after vaccination (McMahon et al 2005; Rosenberg et al 2009) In 2010, during the pediatric influenza vaccination program in Western Australia an estimate rate of febrile convulsions in children under 5 years related to receipt of the 2010 Fluvax TIV was 3.3 per 1,000 doses which is high when compared with the reported rate of 1.4 per 100,000 TIV doses in 2004-2005 administered in USA (Hambidge SJ et al 2006). In adults the frequency of convulsion/convulsion grand mal in adults (≥ 18 years old) after vaccination has been reported as a rate of 0.16 per million vaccinations (Vellozzi et al 2009). 4.4% of all reactions reported to VAERS
Anaphylactic reaction	Children: rare event Elderly: rare event	1–10 per 1 million doses distributed (Ruggeberg RU et al, 2007) 0.68 cases per million doses

		sold (Nakayama T et al, 2007) No cases of anaphylaxis when administering of influenza vaccine containing 0.008 mg of ovalbumin per 0.5-mL dose to 830 patients with confirmed egg allergy, and more than 3,600 with reported egg allergy without vaccine skin testing, dividing the dose (10%/90%) only in those with a history of respiratory or cardiovascular reactions after egg ingestion(Gagnon R et al 2010). 1.8% of all reactions reported to VAERS
Encephalitis (ADEM)	Children: very rare Elderly: very rare	0.1 to 0.2 per 100,000 vaccinated individuals. Post-vaccination encephalomyelitis is a rare complication associated with vaccinations and accounts for less than 5% of present cases of ADEM (Huynh W, 2008). 0.4% of all reactions reported to VAERS
Vasculitis	Children: rare Elderly: rare	Isolated reports or small series of vasculitis after flu vaccination. Relapse rate per 100 patients with history of vasculitis was 3.4 in vaccinated vs. 6.3 in unvaccinated subjects (Stassen PM et al, Nephrol Dial Transplant 2008: 654-658) 0.3% of all reactions reported to VAERS

Guillain-Barré Syndrome	Children: very rare Elderly: very rare	1 case per million above background incidence has been associated with the 1976 New Jersey swine influenza vaccination programme in the US. The absolute effect of vaccination could range from one avoided case of GBS up to three excess cases within six weeks after H1N1 vaccination in one million people in Europe. Cases in children were rare (9%) (Dieleman J et al 2011) 0.6% of all reactions reported to VAERS
Demyelination	Children: very rare Elderly: very rare	Isolated reports in the literature for optic neuritis after Influenza vaccine (Ray CL, Dreizin IJ, 1996 and Hull TP, Bates JH, 1997) Multiple sclerosis (MS): risk of relapse in a meta-analyisis with pooled odds ratio of developing MS and influenza vaccination was 0.97 with a 95% CI of 0.77-1.23 and a p value of 0.873. Pooled relative risk was 1.24 with 95% CI of 0.89-1.72 and a p value of 0.2 (Farez MF 2011).
Bell's palsy	Children: very rare Elderly: very rare	The relative risk of Bell's palsy within 1–91 days of influenza vaccination was 0.92 (95% CI, 0.78–1.08). No significant increased risk was observed when the analyses were separated into three age groups (0–44 years, 45–64 years, ≥ 65 years) (Stowe et al 2006). The relative risk of Bell's palsy in children within 1–42 days of influenza vaccination was 0.67, 1.81, and 1.27 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons,

		respectively (Greene et al 2010) In contrast to parenteral vaccines, the intranasal flu vaccine significantly increased the risk of Bell's palsy (13 excess cases per 10,000 vaccinees) 0.5% of all reactions reported to VAERS
Immune thrombocytopenia	Children: very rare Elderly: very rare	The incidence of hospitalization is 3 to 4 per 100,000/year for children immunized with MMR. Sporadic reports published for influenza vaccines. Epidemiological studies in children did not show an association with influenza vaccines (Jadavji T et al 2003, Bertuola F et al, 2010).

Very rare: (<1/10,000); rare (≥1/10,000, <1/1,000); uncommon (≥1/1,000, <1/100); common (≥1/100, <1/10); very common (≥1/10);

Potential for Off-Label Use

In case of approval for the paediatric indication, there is a potential for off-label use in older children and adolescents. As part of the risk minimization plan, appropriate measures, including risk minimization through SPC labelling changes/warning, will be implemented in agreement with the European Authority.

Medication errors

In case of approval, there is a potential for medication errors leading to the use of Fluad MR (in the elderly) in the paediatric population. This is of particular relevance when the recommended dose in children is 0.25 ml instead of the standard 0.5 ml dose used in elderly subjects.

As part of the risk minimization plan, some measures have been proposed in order to allow Healthcare professionals to distinguish respective, indications, dosages, e.g.:

- The paediatric presentations clearly read Fluad Paediatric on the labels, on the outer packages and in the package inserts.

- include warning sentences in the SmPC, section 4.4 "Warning and precautions for use" as necessary.

However, in the assessor views the target population for these presentations should be clearly reflected on the outer packages in order to avoid medication errors between paediatric patients.

Summary of Ongoing Safety Concerns

The theoretical risks and missing information is listed in the table below:

Safety concern
Important identified risks: • Anaphylaxis
Important potential risks: • Neuritis • Convulsion • Encephalitis • Vasculitis • Guillain-Barré Syndrome • Demyelination • Bell's palsy • Immune thrombocytopenia • Vaccination failure (including pneumonia as a potential tracer of vaccination failure)
Important missing information: CHILDREN • Safety in patients with underlying diseases • Safety in immunocompromised patients • Safety after annual re-vaccination • Vaccination effectiveness • Potential interactions with regular childhood vaccines
Other safety concerns • Potential for medication errors • Potential for off-label use

Pharmacovigilance plan

Routine Pharmacovigilance

Novartis Vaccines Pharmacovigilance System

Pharmacovigilance Novartis Vaccines is currently based in Cambridge, US, Siena, Italy, and Marburg, Germany. In Cambridge, US, the Global Head of Pharmacovigilance and Risk Management is responsible for overall Pharmacovigilance (PV) within Novartis Vaccines and Diagnostics, provides strategic planning, leads and manages PV activities, supervises the regional teams and provides medical support to the regional PV teams.

The EU/EEA QPPV is responsible for oversight of the Pharmacovigilance system. NV Pharmacovigilance has overall responsibility for case processing and regulatory reporting (periodic and expedited), however, the performance of some PV activities has been delegated to Novartis Pharma and third party contractors.

All safety reports spontaneously received from the worldwide market and all SAE reports from Novartis Vaccines sponsored clinical trials are transferred for processing to different NV sites depending on the source of information. Spontaneous reports are processed in Hyderabad (India) whilst SAE from clinical trials are processed in Horsham (UK). Overall, the PV activities include data processing, literature search, management of partners and third parties, reporting of ICSRs to competent authorities and other parties, writing of aggregate safety reports, signalling and signal evaluation, benefit/risk evaluation and assessment of products, training of staff within and outside Novartis Vaccines and Diagnostics, creation of Standard Operating Procedures, and escalation and communication of signals to Novartis Vaccines and Diagnostics Management in cooperation with the Global Head of Pharmacovigilance.

2.1.2 Targeted Surveillance Terms

A Key Event is defined as an important event, which has the potential to negatively affect the benefit-risk ratio of any vaccine (i.e. Key Events are not product-specific).

The list of Key Events is based on guidelines, published literature and medical experience. The QPPV is responsible for the maintenance of the Key Event List. The Key Event List should be reviewed at least annually or ad hoc in case that new events need to be added (e.g. deriving from a new or updated Risk Management Plan).

2.1.3 Signal Detection and Escalation of Safety Signals

Novartis Vaccines has implemented a signal detection/ evaluation and decision making process, to ensure timely processing of safety signals.

Routine automated signal detection to measure disproportionate reporting is performed using different methodologies such as the Empirical Bayesian method with as output the EB05 (lower 95% confidence interval limit of the Empirical Bayes Geometric Mean), with different periodicity depending on the priority level of the vaccine.

Enhanced Pharmacovigilance

The key elements of the enhanced pharmacovigilance plan for Fluad paediatric in place at Novartis VD are summarized hereafter:

1. Enhanced follow-up of key events, including the identified and potential risks, as described above.
2. Automated signal detection for Fluad Paediatric using spontaneous reports.

The analysis will be performed on a quarterly basis and will detect signals of disproportionate reporting for all Preferred Terms (PTs) and Standard MedDRA Queries (SMQs), with primary focus on the adverse events of special interest addressed in this RMP:

- Neuritis
- Convulsion
- Anaphylaxis
- Encephalitis
- Vasculitis
- Guillain-Barré Syndrome
- Demyelination
- Bell's palsy
- Immune thrombocytopenia
- Vaccination failure

1. Expected vs. Observed sensitivity analyses for AESI. Quarterly comparisons of the number of cases reported to the number of cases expected will be performed. Given some important limitations of this methods (e.g. applicable background rates frequently unavailable, absence of agreement on risk period of interest), these analyses will be considered as hypothesis generating.
2. Ongoing and planned clinical trials in paediatric subjects.

Evaluation of the need for a risk minimisation plan

The following risk minimisation measures of Fluad Paediatric are:

- Potential for off-label use
- Potential for medication errors

Risk minimisation plan

Summary of the Risk Management Plan

As a general concern, it is noted that for an important part of the targeted population, children at-risk for influenza complication, immunodeficient subjects, and immunocompetent subjects with chronic diseases, children in the age stratum 6-9 years, very little or no information is available or will become available in a short time.

4. ORPHAN MEDICINAL PRODUCTS

N/A

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

Overall, immunogenicity results show that two doses of Fluad paediatric induced higher immune response compared to non-adjuvanted seasonal vaccines. Antibody Persistency (at Day 181) was higher in subjects vaccinated with Fluad paediatric than in subjects vaccinated with non-adjuvanted vaccines.

As serologic criteria were recognized to be of unknown relevance for paediatric population, a study on vaccine efficacy has been conducted. Study results show a lower number of PCR-confirmed influenza cases among recipients of Fluad paediatric compared to recipients of the seasonal non-adjuvanted vaccine and to non vaccinated children. However, the quality of the pivotal study has been questioned by the performed GCP Inspection. The decision on whether to accept results from the pivotal study is crucial for the overall evaluation of the present MA application.

In studies presented by the Applicant, 2,418 paediatric patients aged from 6 months to 9 years have received at least one dose of Fluad paediatric: this sample represents the safety database. This number, although inferior to the requested number of 3,000 subjects might be considered sufficient, as the specified age group 6 to less than 36 months and 36 months to less than 72 months of age are adequately represented. However, the sub-group of children aged 6-9 years was poorly described.

Based on the available data (short term safety studies), the safety profile of Fluad paediatric appears comparable with flu control vaccine in healthy children aged from 6 months to 72 months, although a constant trend of a higher number of systemic reactions was observed in the recipients of Fluad paediatric.

Uncertainty in the knowledge about the beneficial effects

The safety and efficacy of any influenza vaccine intended for paediatric use has to be proven within clinical studies, as the serologic correlates for protection set up for the adult population are of unknown relevance in children.

The current MA application, although related to a product developed more than 15 years ago and authorized for use in elderly, includes only one study addressing clinical vaccine efficacy.

The quality of this study is therefore crucial to the entire product evaluation and on these grounds a GCP inspection was requested.

The GCP Inspection found not only a lack of GCP compliance in the three inspected sites but also identified a number of issues, regarding the clinical efficacy data from the pivotal trial, that were incorrectly stated in the first dossier submitted by the Applicant (see list of issues in section 2.4: "General comments on compliance with GMP, GLP, GCP" of this assessment report). Moreover concerns of inaccurate collection of safety data collected at one study centre have been raised by the inspectors. The results of the GCP inspection question the reliability of both efficacy and safety data from the pivotal study, and the corrective measures proposed by the Applicant do not solve the issues but introduce further concerns.

The patient population selected consisted mostly of healthy children who do not represent the recommended target population of flu seasonal vaccination in most EU Countries.

The patient population only partially reflect the sought indication in children aged 6 months-9 years, as children in the age group 6-9 years were not included in any of the main submitted studies. Only supportive studies included subjects older than 6 years of age. Of note, these studies showed that the adjuvanted vaccine did not perform better than the non-adjuvanted one. The claim of indication up to 8 years does not appear soundly justified.

The Applicant failed to prove that results of the three studies presented on immunogenicity consistently show the same degree of advantage of the adjuvanted vaccine compared to the TIV in subjects seronegative at baseline.

A serological correlate of protection in the childhood population has not yet been identified, and the CHMP and CBER serological criteria for the assessment of vaccine immunogenicity in adults are borrowed for the evaluation of vaccine immunogenicity in the paediatric population. The choice of serological CHMP and CBER criteria, used in the adult population, as primary endpoints of most of the submitted studies is thus appropriate in the absence of validated alternatives. However, the lack of validated serological correlates associated with clinical protection makes difficult to formulate a judgement about the clinical advantage provided by vaccination in the paediatric population.

Immunogenicity results were mainly obtained from a sample of subjects derived from the Pivotal Study. The sample was defined in the reports as a "convenience sample". In the course of the reviewing process, the Applicant has clarified that the immunogenicity analysis of the pivotal efficacy study included subjects from only one season and only from Finland (i.e., none of the children enrolled in Germany was analyzed to assess vaccine-induced immunogenicity).

The efficacy results obtained are encouraging, but vaccine efficacy was not computed per each viral strain whose antigen is contained in the vaccine, neither replicated for each study centre. Data on vaccine efficacy against B strains are lacking and should be provided before approval.

The only outcome considered in the assessment of efficacy is PCR-confirmed ILI cases. Therefore, the validation of the PCR method is crucial to allow a sound assessment of vaccine efficacy. However, the GCP inspection and further information provided by the Applicant in response to CHMP requests seriously question the validity of all PCR data as well as the reliability of ILI data. As a consequence of the deficiencies in the PCR analysis highlighted by the inspectors, the Applicant has decided to retest, using a third different PCR method, the nasal samples in a third new laboratory (D). However, the validation of the new PCR method was not correctly performed and furthermore degradation upon storage of the PCR samples and/or cross-contamination or mislabeling of the samples that underwent retesting cannot be excluded.

No measurement of either vaccine efficacy in preventing secondary household cases (although planned among the secondary objectives in the first season), or vaccine efficacy by severity of cases, has been performed.

The pivotal study was defined as "observer-blinded and not as "double-blinded". The lack of double blindness (parents and guardians were aware of the treatment received by their children) throughout the trial, may have introduced a bias related to ILI detection, as ILI and PCR-confirmed influenza cases were detected only if parents contacted the study personnel (passive surveillance). This might have resulted in incomplete detection of all ILI cases and/or different timing of ILI assessment in subjects vaccinated with Fluad paediatric.

The time of follow-up after vaccination for detection of incident influenza cases was variable across the study centres in different countries. Enrolment in Finland was completed earlier in the season compared to Germany. A not negligible proportion of children in Germany was enrolled in the latest weeks of 2008 and the beginning of 2009 when the seasonal flu and the at-risk period was likely to be

more intense. These subjects are likely to have contributed with shorter observation time to the estimate of VE as cases detected and laboratory confirmed soon after vaccination were discarded. This further substantiates the concern of an incomplete detection of ILI cases.

Seasonal influenza vaccination is routinely performed every year in the same subject. The extension Study is the only study addressing the efficacy and safety of re-vaccination with Fluad paediatric, one year after the first vaccination. However, re-vaccination was evaluated only on 41 subjects. The limited number of subjects enrolled in this study significantly hampers the correct interpretation of the results. As also recommended by the VWP, adequate data have to be provided regarding safety and immunogenicity upon repeated vaccination with Fluad paediatric before approval.

The paediatric population, in particular those in the first two years of age, is exposed to a number of recommended vaccinations. No study has been designed to address the effect of Fluad paediatric administration on other vaccinations due at the same age.

Upon request, an overall assessment of consistency across all studies has been provided by a meta-analysis resulting in a plot showing the relative ratio of GMTs, SPs and SRs of vaccinated versus unvaccinated children, taking into account the size of the study. However, the results from the meta-analysis are strongly influenced by the results of the pivotal efficacy study, the entire validity of which is questioned. Thus consistency for serological data among all studies cannot be claimed.

An increased immunogenicity (as measured by the HI assay) of Fluad paediatric as compared to non-adjuvanted vaccines was observed in most trials. However, the increase was variable depending on the trial and in fact, in one of the trials, the non-adjuvanted vaccine actually performed better than Fluad paediatric (for the H3 antigen, in the age group >36 months). A justification for the variability of the increased immunogenicity in different trials should be provided to ensure that this is not due to a lack of consistency of batches use in the clinical trial.

The present assessment of safety data has taken into consideration pooled data from all Fluad studies, not considering the issue of the acceptability of data collected in the large pivotal efficacy study, for which suspects of incorrectness of safety data collected at one study centre have been raised. The final decision on the safety profile very much depend on the inclusion of the pivotal efficacy study, and thus on the acceptability of data from this study.

No sufficient data have been provided to assess the safety profile in the older children group proposed for the labelling (6 – 9 years of age). These data do not allow a clear interpretation of Fluad paediatric safety profile in this age category, especially taking into consideration the higher reactogenicity of Fluad paediatric compared to the youngest cohort. At present, the indication in patients aged 6 – 9 years cannot be granted.

In general, unsolicited AEs (any and related) were balanced between Fluad paediatric and Flu control vaccine groups in both age groups, 6 to <36 months and 3 to <9 years; nevertheless, a higher percentage of unsolicited AEs were judged to be possible or probably related to the vaccine in the Fluad paediatric recipients than in the control arm.

The long-term safety profile has not been adequately studied especially taking into consideration that Fluad paediatric is an adjuvanted vaccine to be administered to healthy children.

No data on the effect of repeated exposure to adjuvanted influenza vaccines in the paediatric population is available at present.

Risks

Unfavourable effects

Immunogenicity versus heterologous strains was generally lower than versus homologous strains for both Fluad paediatric and non adjuvanted vaccines. In the pivotal efficacy study, irrespectively of the age group most subjects from Fluad group achieved seroprotection against the A strains. Instead CHMP/ CBER criterion for seroprotection was not met in the non adjuvanted influenza vaccine group. The response against the heterologous B strain was weak not meeting the CHMP and CBER criteria. Immunogenicity results at day 181 mirrored results at day 50 against homologous and heterologous A strains. However, seroprotection was not achieved for the B strains for both adjuvanted and non-adjuvanted vaccines.

Almost no difference has been observed in the frequency of ILI and in outcomes associated to severity of the clinical picture, as hospitalization.

The paediatric target population recommended for influenza vaccination, in most EU countries, is represented by at risk subjects (e.g. children with underlying chronic conditions). Fluad paediatric has not been investigated in this peculiar category of patients, thus limiting the possibility to define its comprehensive safety profile. The administration of an adjuvanted flu vaccine, like Fluad paediatric, to children with underlying conditions could lead to a deregulated immune response and, consequently, to a different safety profile in terms of frequency and severity of AEs.

A consistent trend towards a higher number of systemic reactions in the recipients of Fluad paediatric vaccine was observed through all submitted studies. In addition the same trend was noted when Fluad paediatric was compared to the adjuvanted H5N1 influenza vaccine, Aflunov.

A higher reactogenicity following Fluad paediatric administration was observed in older age cohorts, possibly due to different dose exposure to the adjuvant and different stages of immune system maturation. More mature immune systems in older children might be more prone to react to the adjuvant, resulting into an increased reactogenicity.

A higher percentage of unsolicited AEs were judged to be possible or probably related to the vaccine in the Fluad paediatric recipients than in the control arm.

Since the target population is children, who undergo several other vaccinations, safety problems due the interference of adjuvanted vaccine may occur.

Uncertainty in the knowledge about the unfavourable effects

Data provided by the Applicant on clinical safety appear to be still incomplete to fully understand the safety profile of a seasonal adjuvanted vaccine such as Fluad paediatric.

The safety dataset provided do not reach the requirement of 3,000 subjects. Not every specific age subset is adequately represented; in particular, the sub-group of children aged 6-9 years was poorly described.

Neither data on vaccines co-administration nor information on timeframe of potential subsequent vaccine administration has been provided.

No post-marketing data of pandemic MF59 adjuvanted flu vaccine administered to paediatric population have been provided.

The lack of long-term safety data does not allow to clarify adjuvant-mediated potential safety concern. An influenza vaccine with a similar adjuvant as the one of Fluad paediatric was recently suspected to be associated with narcolepsy.

Balance

Importance of favourable and unfavourable effects

Overall, data demonstrate that two doses of Fluad paediatric confer a higher immune response towards influenza virus strains than non-adjuvanted vaccines in a healthy population aged 6-71 months. These findings are clinically relevant as the immune system of infants and toddlers is partially developed and non-adjuvanted vaccines do not appear to induce satisfactory protective antibodies in unprimed children. This trend appears particularly evident for the B influenza homologous strain, versus which conventional non-adjuvanted vaccines constantly showed, with the exception of study V70P6, lower immunogenicity than versus A influenza antigens. Immunogenicity versus heterologous strains was generally lower than versus homologous strains for both Fluad paediatric and non-adjuvanted vaccines.

In addition, immunogenicity results were obtained mainly from a sample of subjects derived from the pivotal efficacy Study. The validity of these results relies upon the decision on the acceptability of the entire study which presented various flaws in quality. As immunogenicity is concerned for example, the lack of systematic recording of other administered vaccines to study children may represent a limit.

The entire MA Application is based on the reliability of the pivotal study results. Regrettably, besides the flaws identified in the quality of the section of the study dedicated to the assessment of vaccine immunogenicity, the GCP inspection has put in evidence many critical failures in the part of the study dedicated to the evaluation of VE, and the final inspector's report recommends not to accept the rresults of the pivotal phase III clinical trial due to a lack of compliance with GCP. The absence of the Sponsor's effective monitoring of the conduct and quality of the study does not allow to exclude that the same or different critical flaws may have happened also in other study centres not subjected to the GCP inspection. Moreover, critical findings, questioning the validity of the PCR analysis, were discovered in the central laboratory that analysed all nasal swab samples collected in all study centres. The retesting of PCR samples performed by the Applicant bears the same bias as the previous original testing. Thus, the critical findings highlighted by the inspectors cannot be solved by the exclusion of some questioned data from the final analysis. The GCP Inspection found not only lack of GCP compliance in the inspected sites but also identified a number of issues, regarding the clinical efficacy data from the pivotal trial that were incorrectly stated in the first dossier submitted by the Applicant. This greatly impacts the reliability of overall study results.

The lack of efficacy and safety data in the at-risk population for influenza complications, i.e. children with chronic morbidities, greatly limits the external validity of the study results for the clinical practice.

Data on re-vaccination (available from the extension study) are quite limited both with regards to the number of subjects (23 to 18 subjects in the two age cohorts of the Fluad paediatric recipient subjects) as well as with regards to the number of annual re-vaccinations (data are available only for the first re-vaccination (12 months after the priming), and do not help in clarifying the potential advantage of annual re-vaccination with Fluad paediatric. This is a critical issue that needs to be thoroughly addressed and clarified by the Applicant. In particular, it is not clear whether the potential benefit of a re-vaccination with an adjuvanted seasonal vaccine (Fluad paediatric) versus a non-adjuvanted seasonal vaccine is due to the priming (antibody titers were higher at baseline in Fluad paediatric recipients in the re-vaccination study) or to the subsequent new seasonal vaccination with the

adjuvanted product. What would be the results of a comparison between subjects primed with Fluad paediatric and re-vaccinated either with Fluad paediatric or with a non-adjuvanted vaccine? Is the re-vaccination with an adjuvanted vaccine necessary every year, as per the seasonal influenza vaccine schedule, or similar results would be achieved by priming with an adjuvanted vaccine and performing subsequent re-vaccinations with non-adjuvanted seasonal vaccines?

Possible interactions with concomitant or consequent immunisations with other vaccines usually recommended in the paediatric population have not been investigated. This is considered an issue due to the seasonality administration of influenza vaccines that may prevent the administration in the correct age period of other recommended vaccinations in children.

The lack of validated serological correlates associated with clinical protection makes difficult to formulate a judgment about the clinical advantage provided by vaccination in the paediatric population.

To overcome the limitations linked to lack of validated serological correlate of protection in the children population, data from a study on the clinical efficacy of the Fluad paediatric vaccination have been submitted. These data are of great clinical interest as it is the first time that a similar study is performed in children for trivalent seasonal influenza vaccines. However, besides the non GCP compliance of the study, several potential biases have been identified that may affect the correct interpretation of the results:

i. The major results of the study were obtained only from one epidemic season due to the overcome of the 2009-2010 pandemic influenza which swept out all the other circulating strains. Thus, the absolute vaccine efficacy was investigated only against one virus strain (H3N2), and no information is available for H1N1 and B strains.

ii. The only outcome considered in the assessment of efficacy is PCR-confirmed ILI cases. The validation of the PCR method was not correctly performed. Retesting of PCR samples resulted in inconsistency results and furthermore degradation upon storage of the PCR samples and/or cross-contamination or mislabeling of the samples that underwent retesting cannot be excluded.

Almost no difference has been observed in the frequency of ILI and in outcomes associated to severity of the clinical picture, as hospitalization. Thus data on ILI do not help in solving the problems associated with unreliability of PCR data.

Based on the available data, the safety profile of Fluad paediatric appears comparable with flu control vaccine in healthy children aged from 6 months to 72 months of age, although a constant trend of a higher number of systemic reactions was observed in the recipients of Fluad paediatric in the age group 3-19 years. Nonetheless, data provided by the Applicant on clinical safety appear to be still incomplete to fully understand the safety profile of a seasonal adjuvanted vaccine such as Fluad paediatric.

Benefit-risk balance

The potential benefit of eliciting a greater immune response and efficacy in a population that classically responds poorly to non-adjuvanted seasonal influenza vaccines needs to be balanced towards several factors:

- the population of the submitted studies, healthy children, does not include children with chronic co-morbidities who are the main target of influenza vaccination campaigns in most EU countries;
- the safety dataset of patients aged from 6 to 9 years presented by the Applicant is far too limited in order to be assessed. Especially, taking in consideration the higher reactogenicity associated to Fluad paediatric in the older children population, these data should be reconsidered and are not sufficient to grant the therapeutic indication in this specific age subset.

- the absolute vaccine efficacy was investigated only against one virus strain (H3N2), and no information is available for H1N1 and B strains. No estimate of the protection conferred against each of the three matched strains has been shown; this is considered of relevance for a TIV.
- no safety data are available on the yearly exposure of children to the adjuvanted vaccine, and no information is available on concomitant or consecutive administrations of Fluad paediatric with other vaccines recommended in children.
- the advantage of Fluad paediatric in terms of reduced number of influenza cases is inferred only on the basis of the number of PCR-confirmed ILI-cases, the reliability of which has been questioned, whereas no decrease was observed in the frequency of ILI and in outcomes associated to severity of the clinical picture.
- no data suggestive of a decreased transmissibility of influenza from children to the general population following Fluad paediatric administration, have been submitted.

In addition, the non compliance reported by the GCP inspection led to the recommendation not to accept the pivotal clinical trial data submitted in the dossier because of the lack of reliability for the overall efficacy and safety results.

The benefit-risk balance is considered negative until the major objections raised have been solved.

Discussion on the benefit-risk assessment

This is a potentially interesting application of an adjuvanted trivalent influenza-virus vaccine (TIV) that targets the paediatric population. For the first time a clinical study having as primary outcome influenza vaccine efficacy in children has been performed for an adjuvanted TIV. Results from this study add several important pieces of information to our knowledge of influenza vaccination outcomes in children. Overall immunological results show that two doses of Fluad paediatric elicit a greater immunological response compared to non-adjuvanted influenza vaccines, although several clarifications on potential bias that may have affected the immunological and efficacy results, as highlighted by the results of the GCP inspection, are needed and a new major objection has been raised on the basis of the inspection findings, at D150 of the review procedure.

Several issues have to be considered in the evaluation of the benefit risk of Fluad paediatric in the indication sought by the Applicant:

- The whole clinical development program of Fluad paediatric addressed efficacy and safety of the vaccine mostly in healthy children. Healthy children do not represent the recommended target population of seasonal influenza vaccines in most EU countries. The lack of the inclusion of at-risk population for influenza complications (i.e. children with chronic co-morbidities), greatly limits the external validity of the study results for the clinical practice. Efficacy and safety data in both immunocompetent chronic disease patients (e.g. asthma, rheumatologic disease) and in immunocompromised patients (e.g. HIV, bone marrow transplanted) should be provided
- Vaccine absolute efficacy has not been provided for each antigenic vaccine component. Robust data supporting the extrapolation of vaccine efficacy from A to B strains should be provided before approval.
- Seasonal influenza vaccination is administered on yearly basis to the same subject. Only very limited data from the extension Study are available on the effect (efficacy and safety) of re-vaccination with Fluad paediatric. Considering the relatively mildness of influenza in healthy children, the benefit of a yearly vaccination should be assessed against the risk of a repeated exposure to the adjuvant contained in the vaccine formulation.
- Both efficacy and safety of Fluad paediatric with concomitant or consequent administration of other vaccines usually recommended in the paediatric population were not investigated. The Applicant should investigate the potential interference of Fluad paediatric with other vaccines particularly for the adjuvant contained.
- Efficacious vaccination against influenza is expected to produce a tangible benefit in terms of the proportion of children not experiencing influenza symptoms or clinically milder influenza. Almost no difference has been observed in the frequency of ILI and in outcomes associated to severity of the clinical picture, as hospitalization.

- The transmissibility of the infection from the infected child to the community is identified as a public health problem. Reduction of secondary transmission from vaccinated subjects should contribute to the evaluation of the vaccine benefits. No measurement either of vaccine efficacy in preventing transmission in household setting (although planned among the secondary objectives of the pivotal Study), has been performed by the Applicant.

5.1. Conclusions

The overall benefit-risk balance of Fluad Paediatric is negative.