European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT

FOR

AREPANRIX

Common Name:
Pandemic Influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)
A/California/7/2009 (H1N1)v like strain (X-179A)

Procedure No. EMEA/H/C/001201

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

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant GlaxoSmithKline Biologicals S.A. submitted on 18th January 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Arepanrix, through the centralised procedure falling within the Article 3(2) a of Regulation (EC) No 726/2004 . The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 25 June 2009.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication:

Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance.

Information on Paediatric requirements

Pursuant to Article 7, the application included an EMA Decision number P/219/2009 for the following condition:

- Influenza

on the agreement of a paediatric investigation plan (PIP). The PIP is not yet completed.

Licensing status:
Arepanrix has been given a Marketing Authorisation in Canada on 21st October 2009 and in Japan on 20th January 2010. The antigen in this formulation has been approved (as part of a different formulation) in USA on 10th November 2009 and in Canada on 12th November 2009.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Ian Hudson** Co-Rapporteur: **Barbara van Zwieten-Boot**

1.2 Steps taken for the assessment of the product

- The applicant submitted several rolling review applications on the quality, non clinical and clinical data to support the marketing authorization application. The data were submitted by rolling review on 17th July 2009, 31st July 2009, 4th September 2009, 18th September 2009, 2nd October 2009, 16th October 2009, 19th October 2009, on 9th November, on 20th November and on 27th November 2009.
- On 18th August an interim Opinion on a rolling review (RR/01) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 1st September an interim Opinion on a rolling review (RR/02) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 20th October an interim Opinion on a rolling review (RR/03) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 20th October an interim Opinion on a rolling review (RR/04) was adopted by the EMEA Task Force (ETF)/CHMP.

- On 20th October an interim Opinion on a rolling review (RR/05) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 3rd November an interim Opinion on a rolling review (RR/06) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 3rd November an interim Opinion on a rolling review (RR/07) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 12th November an interim Opinion on a rolling review (RR/08) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 3rd December an interim Opinion on a rolling review (RR/09) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 11th December an interim Opinion on a rolling review (RR/10) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 11th December an interim Opinion on a rolling review (RR/11) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 15th January an interim Opinion on a rolling review (RR/12) was adopted by the EMEA Task Force (ETF)/CHMP.
- On 15th January an interim Opinion on a rolling review (RR/13) was adopted by the EMEA Task Force (ETF)/CHMP.

- The application was formally received by the EMEA on 18th January 2010 together with a request for conditional Marketing Authorisation in accordance with Articles 2(2) and 4 of Council Regulation (EC) No 507/2006.
- The procedure started on 19th January 2010.
- On 20th January 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Arepanrix on 20th January 2010. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 20th January 2010.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which a high proportion of the world's population is immunologically naïve emerges. In April 2009, a new strain of human influenza A(H1N1)v was identified and characterised. On 11 June 2009 the WHO declared Phase 6 of the influenza pandemic. The declaration reflected sustained transmission of the virus from person to person in several WHO regions. WHO and other international agencies are calling the disease **pandemic (H1N1)v 2009**. For the virus the nomenclature **influenza A(H1N1)v** (where v indicates variant) has been chosen.

Estimates for the attack rates associated with the influenza A(H1N1)v virus have varied from approximately 10-50 % in different geographical areas. The actual numbers of clinically apparent infections, cases that require hospitalisation and deaths in the pandemic period is expected to be higher than in recent years for seasonal influenza. These estimates may change (upwards or downwards) during the further course of the pandemic. Hospitalisation and deaths have occurred in previously healthy subjects as well as in those with underlying conditions or pregnancy that would predispose them to complications of influenza. For more information about the known clinical features of the disease caused by influenza A(H1N1)v virus please see the Risk Assessment report from ECDC under:
http://ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf

Specific guidance has been developed for the fast track assessment procedure for pandemic influenza vaccines[1], which can only be used once WHO/EU have officially declared a pandemic.

In 2008 GlaxoSmithKline Biologicals received a Marketing Authorisation for the mock-up vaccine of **Pandemrix**(A/VietNam/1194/2004 NIBRG-14(H5N1) strain) in line with the core dossier approach. The approval of pandemic vaccines using this mock-up/core dossier route followed by a strain change is based on a *Proof of Principle* approach by which safety and immunogenicity data are generated with mock-up vaccines containing subtypes of influenza A to which the majority of the population is naïve. These principles are based on:

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

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

The mock-up vaccine for Pandemrix is a split virion inactivated influenza vaccine containing antigen from H5N1 (NIBRG-14), which is a strain derived by reverse genetics from the influenza virus A/Vietnam/1194/2004. On 22 September 2009 GlaxoSmithKline Biologicals received a positive EC decision for a variation to change the strain used for manufacture of Pandemrix to A/California/07/2009 (H1N1)v like strain (A-179A). The strain used has been officially recommended by WHO and CHMP for the manufacture of vaccines during the current pandemic.

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

This MAA for **Arepanrix** has been filed in accordance with the Emergency Rolling Review Procedure together with a request for conditional Marketing Authorisation in accordance with Articles 2(2) and 4 of Council Regulation (EC) No 507/2006 and that is applicable to candidate pandemic vaccines for which there is no approved core dossier in place before the pandemic is declared.

Arepanrix is a split virion inactivated influenza vaccine. It is intended that the final formulation will contain antigen equivalent to A/California/7/2009 (H1N1)v-like virus 3.75 micrograms haemagglutinin per 0.5 ml dose adjuvanted by AS03. Arepanrix consists of two multidose containers, one multidose vial containing 2.5 mL of antigen suspension and one multidose vial containing 2.5 ml of adjuvant emulsion. Prior administration, the two components should be mixed.

Arepanrix and Pandemrix vaccines are manufactured at different sites by the same MAH. (i.e. Sainte-Foy, Quebec, Canada for Arepanrix and Dresden, Germany for Pandemrix).

The clinical data submitted to support this MAA included two studies that directly compared the safety and immunogenicity in adults between Pandemrix (HA manufactured in Dresden; D-Pan) and Arepanrix (HA manufactured in Quebec; Q-Pan) containing either H5N1 (study Q-Pan H5N1-001) or H1N1 (study Q-Pan H1N1-017) antigens. .

Post-Marketing data from the use of Arepanrix in Canada provided further data on safety.

Submission of further data at specific time points is included in the Specific Obligations agreed for Arepanrix containing antigen from influenza A(H1N1)v. All data will be reviewed on an ongoing basis. These ongoing and planned studies will provide safety, immunogenicity and effectiveness data for Arepanrix influenza A(H1N1)v vaccine. The Arepanrix SPO summarises the existing clinical data. The Clinical Particulars will be updated as new data are submitted and reviewed.

2.2 Quality aspects

The quality section is divided into two parts of which chapter 3.2.1 describes quality characteristics pertaining to the initial version of Arepanrix containing HA derived from A/Indonesia/5/2005 (H5N1) and chapter 3.2.2 describes quality characteristics of the new pandemic strain A/California/07/2009 (H1N1)v like strain (X-179A).

2.2.1 A/Indonesia/05/2005/PR8-IBCDC-RG2 (H5N1)

Active Substance

Arepanrix H5N1 is a split inactivated influenza vaccine. The final formulation contains 3.75 µg haemagglutinin (HA) of A/Indonesia/05/2005/PR8-IBCDC-RG2 (H5N1) per 0.5 ml dose adjuvanted by AS03.

The reference virus for Arepanrix (H5N1) used in the clinical development programme is A/Indonesia/05/2005/PR8-IBCDC-RG2 (H5N1), which was developed by the US Centre for Disease Control (CDC) using reverse genetics. The reassortment strain combines the H5 and N1 segments to the PR8 strain backbone. In addition the H5 was engineered to eliminate the polybasic stretch of amino-acids at the HA cleavage site that is responsible for high virulence of the original strains. The virus is propagated in fertilised hens'eggs.

Manufacture
The manufacturing process for the monovalent bulks is similar to the manufacturing process for the monovalent bulks of the seasonal vaccines FluLaval and Fluviral, which are licensed in USA and Canada (there is no EU licence). The manufacturing process for the monobulks is in some aspects different to the process reviewed and approved for the Pandemrix/Prepandrix licences (the

prepandemic and pandemic adjuvanted vaccines produced at the applicant's German site in Dresden). The manufacturing process can be divided into five main parts:

- Propagation of the working seed in fertilised hen's eggs, harvesting and pooling of infected allantoic fluids
- Inactivation of the monovalent virus using UV and formaldehyde/thiomersal
- Concentration and purification of the whole virus bulk
- Splitting of the monovalent with sodium deoxycholate
- Homogenisation and sterile filtration

The production process for monovalent bulks is adequately described.

Control of Materials
Control of starting materials which are of biological origin (virus seed lots, eggs and raw materials) is acceptable. The working seed release package has been provided and includes the results of pathogenicity testing in chickens and ferrets and monitoring of plaque formation on chicken embryo fibroblast cells. Data to confirm the sequence of HA and NA genome segment of the A/Indonesia strain to the CDC reference strain have been provided.

Process validation
Critical steps of the drug substance production process have been identified and are sufficiently controlled. Nine data sets from the 2006, 2007 and 2008 A/Indonesia/5/2005 drug substance production campaigns were used to illustrate the robustness and consistency of the Quebec H5N1 drug substance manufacturing process.

The capability of the UV/formaldehyde/thiomersal inactivation steps for batches of A/Indonesia/05/2005 virus has been demonstrated. Ability of the manufacturing process to inactivate avian leucosis virus and mycoplasma inactivation has been demonstrated.

Characterisation and specifications
The structure of the inactivated split monovalent bulks was studied by transmission electron microscopy and confirmed the predominance of disrupted particles after splitting.

Relevant impurities have been specified and are controlled. Release specifications for the drug substance include controls for appearance, HA content, neuraminidase identity, sterility, bacterial endotoxins, test for residual infectious viruses, residual sodium deoxycholate, residual formaldehyde and test for fragmentation (not routine) and are in line with PhEur monograph 0158. All analytical methods have been appropriately validated.

The monovalent bulks are filled and stored in 1L, 10L or 20L bags. Information on the compliance of the construction materials of two different types of bags is provided and is acceptable.

Stability
Data currently support 18 to 24 months stability at 2-8°C for bulks depending on the bag type used for storage.

Medicinal Product

The drug product is described in three parts: The drug product containing H5N1 antigen, the AS03 adjuvant and the mixed AS03 adjuvanted H5N1 influenza vaccine which is the preparation to be administered within 24 hours.

Medicinal Product (H5N1 vial)

Pharmaceutical Development

Developmental changes implemented since the first clinical studies have been stated and clinical studies have provided reassurance of product remaining comparable.

Manufacture of the Product
Manufacture for the antigen component of the drug product is relatively simple and consists of aseptic formulation of the final bulk with the excipients followed by filling into final containers.
An overage of 20% for the HA content will be applied at formulation of the commercial lots. Supporting data and satisfactory justification have been provided.

The antigen bulk is sterile. Bioburden is controlled throughout the manufacturing process.
The maximum hold time between formulation and filling is 21 days hold time at 2-8 °C for final bulks.

Product Specification
Compliance with the product specifications has been shown on a number of batches representatives of the final formulation and commercial scale manufacture. There are no final products process-related or degradation impurities.
Specifications for excipients and analytical procedures are in line with USP or NF.

Controls of final bulks (sterility, HA, total protein, residual ovalbumin, thiomersal, residual formaldehyde and residual sucrose) and final containers (sterility, bacterial endotoxins, pH, thiomersal, appearance, osmolality and HA) of the antigen vial are acceptable (in line with PhEur). Methods are either in line with PhEur or are validated.

Adequate data are provided to affirm the quality of the container/closure system. HA content, appearance, sterility, thiomersal content and pH are measured as stability-indicating parameters as part of the stability studies. Stability test methods and specifications are identical to those at release. A shelf-life of 18 months is currently acceptable until further long-term data are available.

Medicinal Product (AS03 adjuvant vial)

AS03 is an oil-in-water emulsion in 3mL multi-dose (10 dose) glass vials. It is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).

Pharmaceutical Development
Developmental changes implemented since the first clinical studies have been stated and non-clinical and clinical studies have provided reassurance of product remaining comparable.

Manufacture of the AS03 adjuvant vial
Formulation of the AS03 adjuvant consists of the preparation of the bulk followed by filling into glass vials. Process parameters are identified. No routine in-process tests are conducted. Bioburden is adequately controlled throughout the manufacturing process.

Specifications of the AS03 adjuvant
With the exception of squalene, all excipients are described and controlled in line with the Ph.Eur. Adequate quality control of squalene is performed by the supplier and by GSK (according to an internal GSK monograph which is in line with the Ph.Eur. monograph for squalane).

Emulsion bulk and AS03 final containers are tested at release for Description, Identity and Content of adjuvant components (polysorbate 80, DL-α-tocopherol and squalene), pH, Endotoxin content, Sterility, Particle size, Polydispersity index and Volume (final containers only).

Tests for sterility and bacterial endotoxins are performed in line with the Ph.Eur. and tests for polysorbate 80, α-tocopherol and squalene are validated. The method used for particle size analysis and associated system suitability measurements is acceptable.

Stability of the AS03 adjuvant

Data provided from the stability studies for the bulk emulsion support the proposed shelf life of 2 years. For final AS03 container lots a shelf-life of 36 months has been approved.

Medicinal Product (mixed H5N1 and AS03 vial)

At the time of vaccine administration, the content of the adjuvant vial is withdrawn from the vial with a syringe and is injected into the antigen vial and shaken.

Data from 'withdrawable' volume studies conducted to support the required overfill for both antigen and adjuvant vials have been provided. Results from uniformity of dose studies demonstrate that content of HA, squalene, Polysorbate 80 and tocopherol for each dose of the 10-dose vial remains equivalent.

SDS PAGE and Western blot analysis performed show that HA profiles of the adjuvanted formulation are comparable to the non-adjuvanted formulation and remain unchanged after a period of 24 hours at 25°C. Compatibility between the antigen and adjuvant after 24h at 25°C has been demonstrated by evaluation of appropriate key quality criteria. Preservative efficacy of thiomersal concentration after mixing the content of the antigen container with AS03 adjuvant has been shown in line with Ph.Eur. 5.1.3.

The applicant has shown that there is limited (less than 10%) physico-chemical interaction between the Quebec split virion antigen and the adjuvant system and thus, it is accepted that there is no need for controlling antigen/adjuvant interaction for this product as a release test. There is sufficient evidence that there is little/no effect of the reconstitution conditions on the essential characteristics of the antigen/adjuvant combination.

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

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

Active Substance

The reference virus described in the current MAA is A/California/7/2009 (H1N1)v NYMC X-179A. This strain has been developed by the NYMC using classical genetic reassortion. The reassortant strain combines the HA, NA and PB1 genes of A/California/7/2009 (H1N1)v, to the PR8 strain backbone.

Manufacture
The manufacturing process for A/California/7/2009 (H1N1)v monovalent bulks is identical to the manufacturing process for Arepanrix A/Indonesia (H5N1) monovalent bulks (see paragraph 3.2.1) with the exception of changes necessary to account for a 4-fold scale up introduced in the downstream purification, splitting and fill process. Comparability between lots produced using the old process and the new scaled-up process has been demonstrated.

Information is presented on the source and passage level history of the primary seed virus as well as on the preparation and qualification of the working seed virus lots for the strain.
Unlike for H5N1 A/Indonesia and A/Vietnam, the A(H1N1)v strain has been produced using classical reassortment on eggs rather than being attenuated by reverse genetics. HA and NA identity for the master and working seeds have been confirmed. The specifications and methods for the master and working seed are in line with that already reviewed for A/Indonesia H5N1.

Eggs used for establishing seeds are SPF. The master seed prepared by GSK corresponds to E7/E1/E1. Commercial H1N1v monobulks have been prepared with this master seed and also with

working seeds derived from the master seed with 3 additional passages (i.e. working seed E7/E1/E4). Commercial production occurs with one additional passage from the working seed. Adequate supporting data for suitability of the master and working seeds are provided.
The MAH has adequately demonstrated inactivation and data are at least as equivalent to that seen for A/Indonesia H5N1.

Characterisation and specifications
The SRD method is used to determine the HA content in the bulks and final containers. The SRD method has been satisfactorily re-qualified using intended antigen and antisera. Linearity of the dose-response has been demonstrated.
Batch analytical data are provided for the two drug substance lots to be used in clinical trials and for three process consistency lots.

Stability
Data generated on A/H5N1 strains are submitted as supportive data for the stability of the drug substance (monovalent bulks). An acceptable confirmatory stability plan for the proposed A/California (H1N1)v strain monovalent bulks has been provided.
Overall, the stability of the HA content during the period evaluated is satisfactory. The approved shelf-life for H5N1 monobulks is 18 to 24 months for bulks depending of the storage containers (two types of bags are used). The applicant commits to report any unexpected results generated during the ongoing stabilities studies, in case of a confirmed out-of-specification or unexpected trend not supporting the registered shelf-life.

Medicinal Product

After mixing with the adjuvant, 1 dose (0.5 ml) contains:

Active ingredient:
Split influenza virus, inactivated, containing antigen* equivalent to:
A/California/7/2009 (H1N1)v like strain X-179A 3.75 micrograms**

* propagated in eggs
** haemagglutinin

Adjuvant:
AS03 adjuvant composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)

The suspension and emulsion vials once mixed form a multidose container. The vaccine contains 5 micrograms of Thiomersal (see list of excipients).

List of Excipients:
Suspension vial:
Thiomersal
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for Injections

Emulsion vial:
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Water for Injections

Introduction of the pandemic strain - strain change related changes

The A/California/7/2009 (H1N1)v final bulks and final containers are respectively formulated and filled as for the H5N1 final bulks and final containers of Arepanrix H5N1.
The same control processes as for Arepanrix H5N1 are applied to the antigen component of the MAH's H1N1v A/California influenza vaccine adjuvanted with AS03.

Re-qualification data for the SRD method used for analysis of final bulks and final containers have been provided. QC release data for the H1N1v A/California final bulks and final containers presented conform to the specifications reviewed for the antigen component of Arepanrix H5N1.

The compatibility study between H1N1v antigen and adjuvant is demonstrated, throughout the vaccine's in-use shelf life of 24 hours.

No real-time real-temperature stability data are available for H1N1v final containers at the present time. Accelerated stability data for H1N1v A/California final containers stored at 30°C are available for two weeks – the specifications are met and no trend is seen. A confirmatory long-term stability program is proposed, to cover 60 months storage at 5°C ± 3°. The MAH is proposing an alignment to the shelf-life approved for the antigen component of Arepanrix H5N1 (i.e. 18 months), since the vaccine composition is unchanged apart from the vaccine strain. This is accepted until further long-term data are available for the H1N1v vaccine.
Concerning the AS03 adjuvant component the approved shelf-life, based on real-time stability data, is 36 months at 2-8°C.
After mixing, the vaccine should be used within 24 hours. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

Presence of aggregates in the antigen final containers

Presence of white aggregates have been observed in clinical and commercial lots of A/California/7/2009 antigen vials.

The reason for the occurrence of aggregation is not clear, but is known to be an inherent feature of this type of formulation. It is hypothesized that the physicochemical properties of A/H1N1 California/7/2009 strains and/or handling conditions post filling (e.g. storage and transportation) might contribute to the increased aggregate formation.

The aggregates have the same constitution as found in the antigen suspension (i.e. haemagglutinin and proteins). Different methods were used to ascertain the amount of antigen present in the aggregates. Variable values were observed depending of techniques, thus indicating that aggregates do account for a notable percentage of the final pre-mixed antigen formulation.

The level of aggregation can be considered clinically qualified. Data has been presented which provide assurance that the level of aggregation in the clinical batch at the time of the clinical studies contained similar aggregate-HA amounts as three commercial lots manufactured since.

Additional data provided support the view that when mixed with the adjuvant the aggregates present in the antigen vial are largely solubilised and therefore the presence of aggregates in the antigen drug product has only a limited impact on potency of the adjuvanted vaccine measured by SRD. The Applicant has committed to provide further data about the kinetics of resolubilisation of the aggregates.

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

2.3 Non-clinical aspects

Introduction

Preclinical development of Arepanrix was generally in agreement with current guidelines. The antigen is produced in hen's eggs using the same process as that is applied to the applicant's own FluLaval brand of seasonal influenza vaccine approved outside the EU.

The Arepanrix H5N1 (A/Indonesia/5/2005) influenza vaccine construct was tested in the ferret model to evaluate the potential of this vaccine to reduce disease symptoms (body temperature, weight loss, and histopathological changes in the respiratory tract) and viral loads in the upper (pharynx) and lower (lung) respiratory tract of ferrets challenged with homologous (A/Indonesia/5/2005) or heterologous (A/Hongkong/156/97) strains.

No new non-clinical studies with A(H1N1)v were submitted for this application.

Good Laboratory Practice (GLP)

The safety studies included in the dossier were all compliant with GLP.

Pharmacology

- Primary pharmacodynamics

Two immunogenicity studies were conducted in mice using H5N1 vaccine manufactured at the Quebec facility, adjuvanted with AS03. One study used vaccine antigens from A/Vietnam/1194/2004 and the second study used vaccine antigens from A/Indonesia/5/2005. Immunogenicity was greater in the presence of the adjuvant by both measures used (quantification of antigen-specific IgG in sera, haemagglutination inhibition tires) and a dose-response relationship was shown between antigen dose and serum IgG concentrations; however, there was no evidence of a dose-relationship using the functional antibody measure.

Vaccine efficacy studies were conducted in ferrets exposed to lethal challenge doses of homologous virus (A/Indonesia/5/2005), or heterologous virus (vaccine prepared from A/Indonesia/5/2005 H5N1 and the challenge virus was A/Hong Kong/156/97 H5N1) and a final experiment where the vaccine was based on H5N1 A/Vietnam/1194/04 and the challenge virus was A/Indonesia/05/2005. All studies indicated that adjuvanted vaccine conferred protection from lethal challenge with influenza virus, whereas without adjuvant, or with a half-dose of adjuvant, vaccine efficacy was compromised. Viral shedding, lung viral load measures and serology results were generally internally consistent, although in one experiment there was a lack of concordance between the test facility and the applicant's laboratory results for seroconversion. The adjuvant used in the study was AS03. The data also indicated cross-reactivity.

- Secondary pharmacodynamics

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

- Safety pharmacology programme

A safety pharmacology study was performed in rats treated by intravenous bolus with 1ml/kg of saline placebo (n = 4) or Quebec-sourced A/Wisconsin/67/05 influenza adjuvanted with AS03 (n = 4). The final concentration of the influenza antigen was 30µg/ml and the AS03 concentration represented the full human dose. Assuming a 250g rat, a 1ml/kg dose represents an approximately 100-fold excess over the ml/kg exposure of a 50kg human receiving a 0.5 ml intramuscular dose.

Over 120 minutes after infusion there was a tendency for minute volume to increase in all animals, and a single animal in the actively treated group showed a transient inverted P-wave on ECG. Both occurrences were considered non-specific and there was no evidence of any treatment-specific changes in cardiorespiratory performance. Overall, no concerns for human use were raised.

Pharmacodynamic drug interactions

No studies were performed

Pharmacokinetics

Experimental studies to demonstrate absorption, distribution, metabolism, and excretion of the active ingredients in Arepanrix have not been performed. This is in line with the relevant guidelines CPMP/SWP/465/95 and CPMP/VEG/4717/03.

Toxicology

- Single dose toxicity and repeat dose toxicity (with toxicokinetics)

Two single dose and two repeat dose general toxicity studies were reported. Test material was Arepanrix H5N1 vaccine, adjuvanted with AS03. Apart from pro-inflammatory changes at the injection site that are related to the primary mode of action of the AS03 adjuvant, there was no toxicity of note. These studies used the full human dose given intramuscularly to rabbits in a manner sufficient to support the intended clinical dosing.

Results of a further two general toxicity studies were ongoing at the time of the Application review. . One is a toxicity study in rabbits given three intramuscular injections of seasonal and pandemic influenza candidate vaccines with full, half and no dose of AS03 adjuvant. The other is a toxicity study in rabbits given three intramuscular injections of Arepanrix H5N1 vaccine with AS03 at the full human dose. Neither is considered critical to the approval of Arepanrix given these differences from H1N1v vaccine, however the CHMP considered that the applicant should provide the study results to rule out any unexpected toxicity.

- Genotoxicity

Genotoxicity of the adjuvant alone was assessed in two *in vitro* tests (reverse mutation test in bacteria; gene mutation in mouse cells) and one *in vivo* test (micronucleus test in the rat after intravenous administration). The vaccine was not tested. No indication of genotoxicity was evident.

- Carcinogenicity

No carcinogenicity studies were conducted which is in line with the Note for Guidance on Preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95)

- Reproduction Toxicity

In a reproductive toxicity study in rats the animals were assigned to four dose groups as in the table below which received either phosphate buffer saline (PBS), AS03 adjuvant or AS03 adjuvanted Arepanrix H5N1 (i.e. Q-H5N1) influenza vaccine.

Group	Number of rats	Test article		Dose volume
		28 days prior to mating	Gestation day 7, 9, 12, 16 and Post-natal day 7	

Group 1 (Control)	48	PBS	PBS	200µL
Group 2	48	AS03	AS03 + PBS (1:1)	200µL
Group 3	48	PBS	H5N1 (1.5µg HA) + AS03	200µL
Group 4	48	H5N1 + AS03	H5N1 (1.5µg HA) + AS03	200µL

Doses were intramuscular in the rear limbs 28 days prior to cohabitation (with an untreated male) and on gestation days (GD) 7, 9, 12, and 16 and on postnatal day (PND) 7 (littering cohort dams only). Dams were subject to section on day 21, or to deliver normally and assessments in the latter group were carried out to postnatal day 25. Serological analysis proved vaccine exposure of dams during pregnancy and exposure of foetuses and pups to anti-H5N1 antibodies. There were no effects on any of the parameters evaluated for the F_0 generation and all dams survived until their scheduled termination. There were no abnormalities on c-section data or fetal examinations and in the pups followed to postnatal day 25, no toxic effects were observed.

The reproductive toxicity study did not identify toxicity associated with vaccination in pregnancy animals when dosed from day 6 or pregnancy. This is considered satisfactory proof to support the use of the vaccine in pregnant women in the second or third trimester and to support vaccination of lactating women. However, vaccination in early pregnancy, that is, prior and up to implantation of the embryo has not been directly studied. The applicant is conducting a study with AS03-adjuvanted vaccine to address this specifically.

In addition, two supportive studies assessed the effect of both Fluarix and FluLaval influenza vaccines, and both AS03 alone and AS03 with H5N1 antigen produced with Fluarix-process on embryo-fetal and peri- and post-natal development in naïve or pre-immunised rats following intramuscular administration.

In the studies conducted with Fluarix and FluLaval seasonal vaccines, there were no findings in the F0 females or F1 offspring that were considered related to treatment. No signs of maternal toxicity were observed during the reproductive and developmental study performed in rats. Likewise, treatment of naïve or pre-immunized female rats with the AS03-adjuvanted Pandemrix H5N1 or the AS03 adjuvant alone on days 6, 8, 11 and 15 of gestation did not adversely affect the embryofoetal development or pre- and post-natal development of the offspring. Treatment with the AS03-adjuvanted Pandemrix H5N1 influenza vaccine prior to pairing did not adversely affect the mating performance or fertility of the females.

Overall, no reproductive toxicity effect was observed, neither with antigen prepared according to the FluLaval process (used for Arepanrix), nor with AS03-containing influenza vaccine candidates nor with the AS03-adjuvanted Arepanrix (A/Indonesia/5/2005) influenza vaccine.

Overall, testing suggested that the Quebec-manufactured vaccines tested did not adversely affect female fertility or pregnancy and no effect was indicated in the F1 generation.

- Local tolerance

Local tolerance assessment of AS03 alone and Quebec-manufactured H3N2 antigen (same process as Arepanrix) at a dose containing 15µg of HA (i.e., approximately 20-fold higher than the intended human dose on a body weight basis) combined with a full human dose of AS03 did not show any adverse clinical observation in rabbits. Dermal responses did not differ between controls and experimental groups. There were no adverse observations noted at necropsy. Minimal or mild subacute inflammation of the subcutaneous and/or epimysial tissue was noted in animals receiving the adjuvant, with or without influenza antigen.

There were no microscopic findings specifically associated with the presence of influenza antigen in the test article. In general, a single intramuscular injection of influenza vaccine containing 15µg of HA and a full human dose of AS03 were well tolerated by New Zealand White rabbits.

These results were confirmed in a second study where local tolerance was assessed using AS03 adjuvanted Quebec H5N1 antigen (Arepanrix H5N1). In this study rabbits received one single IM administration of either of three candidate vaccines - two manufactured with Quebec-sourced seasonal antigens (60µg HA/dose) adjuvanted or not with AS03 (human half-dose) and one manufactured with the Quebec pandemic H5N1 antigen (30µg HA/dose) adjuvanted with AS03 (human dose) or saline control.

Minor inflammation was observed in all vaccine and control groups, which is indicative of an effect of the dose method as opposed to any of the vaccine components. The adjuvanted vaccines were associated with fasciitis, cellulitis, and in males, granulomatous myositis. There was no clear difference in severity of these conditions between the two adjuvanted vaccines.

Ecotoxicity/environmental risk assessment

No environmental risk assessment was included in the application. According to the guideline EMEA/CHMP/SWP/4447/00 "*Environmental Risk Assessment of Medicinal Products for Human Use"* vaccines due to the nature of their constituents are exempted from the requirement to provide an environmental risk assessment in the application for a marketing authorisation for a medicinal product for human use.

2.4 Clinical aspects

This Emergency Rolling Review application dossier was based primarily on clinical studies that evaluated the safety and immunogenicity of AS03-adjuvanted vaccines containing antigens from A/Indonesia/5/2005 (H5N1) and some data from a version containing A/Vietnam/1194/2004 (H5N1). Before filing this MAA the applicant also reported data from a study that directly compared AS03-adjuvanted vaccine containing antigen from the H1N1 pandemic strain manufactured in Quebec (i.e. Arepanrix) or Dresden (i.e. Pandemrix).

In addition, during the emergency rolling review process the applicant provided results from several studies with Pandemrix (D-Pan) H1N1 and these data have also been taken into account.

Further clinical data on the approved formulation of Arepanrix A(H1N1)v are expected in accordance with agreed timelines as outlined in the Letter of Undertaking.

GCP

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

Pharmacokinetics

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

Pharmacodynamics

In relation to vaccines, the pharmacodynamic studies consist of assessments of the immune responses. The data on the immunological response to Arepanrix (H5N1) are described and discussed below.

Clinical efficacy

Main studies

The two studies with Arepanrix (= "Q-Pan", i.e. HA manufactured in Quebec and combined at that facility with AS03 manufactured at Rixensart) were initially submitted for review are shown in the table below. In both studies the Q-Pan formulation studied contained antigens derived from the A/Indonesia/05/2005 strain of H5N1.

Study ID	Study centres	Study groups	Entered *(Completed)*	Study design	Primary objectives	Study duration	Inclusion criteria
Q-Pan-001	10 centres US Canada	**Total** **H5N1 split Quebec** 3.8µg/AS03 **H5N1 split Quebec** 3.8µg/half AS03 **H5N1 split Quebec** 3.8µg no AS03 **H5N1 split Dresden** 3.8µg/AS03 **H5N1 split Dresden** 3.8µg/half AS03	**680** *(662)* 152 *(148)* 151 *(150)* 78 *(75)* 151 *(148)* 148 *(141)*	Observer-blind, randomized, phase I/II 2 doses at 0, 21 days	Immunogenicity and safety/reactogenicity of Q-Pan and D-Pan	Approximately 6 months for each subject	Healthy adults 18-64 years old (18-40 years, 41-64 years)
Q-Pan-002	40 centres US, Canada	**Total** **H5N1 Quebec 3.8µg/AS03** **lot A** **lot B** **lot C** **Placebo**	**4561 (4343)** **3422 (3263)** **1141** **1141** **1140** **1139 (1080)**	Observer-blind, randomized, phase III 2 doses at 0, 21 days	Immunogenicity and safety/reactogenicity of Q-Pan Immunogenicity in a subset of subjects, by age strata 18-60 y, N=1666; >60 y, N= 554)	Initially 6 months; amended to approximately 1 year for each subject	Healthy adults At least 18 years old

During the Rolling Review process additional clinical data were submitted from:

- Three studies with Q-Pan H5N1
- Data from one study comparing Arepanrix (H1N1) with Pandemrix (H1N1) (H1N1-017)
- Two extra study groups that were enrolled into Q-Pan-001 in accordance with the protocol once it was determined that the pre-defined criteria had been met to trigger initiation of these additional dose groups.

The studies varied in design and strains used as shown in the next table.

Study	Primary Objective	Population	Vaccine	Study Report availability	N safety	N immuno
Q-Pan-001 contingent arms	Safety and Immunogenicity	18-64 years	H5N1 A/Indonesia strain 1.9 µg HA/ full AS03 1.9 µg HA/ half AS03 2-dose schedule	Dec 2009	100	100
Q-Pan-009	Immunogenicity	18-64 years	H5N1 A/Indonesia strain 3.8 µg HA/ full AS03 Two doses at: - Day 0, Day 21 - Day 0, Day 14	Aug 2009	312	312

Study	Primary Objective	Population	Vaccine	Study Report availability	N safety	N immuno
			- Day 0, Day 7 - Day 0, Day 0			
Q-Pan-010	Immunogenicity	18-64 years Primed in Q-Pan-001	H5N1 A/Turkey strain 3.8 µg HA/ full AS03 One booster dose (M15)	Dec 2009	650	650
Q-Pan-011	Safety and Immunogenicity	Japanese (20-64 years)	H5N1 A/Indonesia strain 3.8 µg HA/ full AS03	April 2009	100	100

It should be noted that **Q-Pan-010** was actually the **booster phase of study Q-Pan-001**.

Data will be submitted in due course from one other study in adults with Q-Pan H5N1.

Study	Primary Objective	Population	Vaccine	Study Report availability	N safety	N immuno
Q-Pan-005	Safety and Immunogenicity	≥18 years	**Priming: 2 doses** H5N1 A/Indonesia strain 7.5 µg HA/ half or full AS03 3.8 µg HA/ half or full AS03 **Boost**: 1 dose H5N1 A/Turkey strain 7.5 µg HA/ half or full AS03 3.8 µg HA/ half or full AS03	Aug 2010	840	840

Data were also submitted from the **D-Pan H5N1 study 009/022/023** in children aged from 3-9 years. In the absence of data in children with Q-Pan H5N1 these data have been taken into account when considering the SPC for Arepanrix.

There are currently seven studies planned with Arepanrix (H1N1), most of which are expected to start within a few weeks or have already started. The general designs, including dose and age groups, of these studies are shown in the next table. Timelines can be found in the Letter of Undertaking.

Study	Dosage	Administration schedule	Age strata	Number of subjects
Q-Pan-H1N1-001	3.75 µg HA/AS03$_A$	Two doses (D0 and D21)	18 - 64 years	84
			> 64 years	126
		One dose (D0)	18 - 64 years	84
			> 64 years	126
Q-Pan-H1N1-002	3.75 µg HA/AS03$_A$	One dose (D0)	18 - 64 years	1500
			> 64 years	500
Q-Pan-H1N1-019	3.75 µg HA/AS03$_A$	Two doses (D0 and D21)	19 - 40 years	300
D-Pan-H1N1-017	3.75 µg HA/AS03$_A$	Two doses (D0 and D21)	18 - 60 years	160
Q-Pan-H1N1-003	3.75 µg HA/AS03$_A$	Two doses (D0 and D21)	6 - <36 months	100
			3 - <9 years	100
	1.9 µg HA/AS03$_B$	Two doses (D0 and D21)	6 - <36 months	100
			3 - <9 years	100
Q-Pan-H1N1-031	3.75 µg HA/AS03$_A$	Two doses (D0 and D21)	9 - <18 years	50

		One priming dose (D0) and one booster dose (M6)	9 - <18 years	50
	1.9 µg HA/AS03$_B$	Two doses (D0 and D21)	9 - <18 years	50
		One dose (D0) + one booster (M6)	9 - <18 years	50
Q-Pan-H1N1-032	1.9 µg HA/AS03$_B$	Two doses (D0 and D21)	2 - <6 months	30
		One dose (D0) + one booster (M6)	2 - <6 months	30

Assays
Sera obtained from subjects enrolled into the Q-Pan H5N1 studies were forwarded to GSK, Sächsisches Serumwerk Dresden, Zirkusstraße 40, 01069 Dresden (Germany). Validation reports were provided. In brief, the assays were as follows:

HI – The standardised and validated micromethod uses four HI units of the appropriate antigen and a 0.5% horse erythrocyte suspension. All HI assays were performed in duplicate in the same run along with control sera and each run was judged against acceptance criteria. The validation results of the assay based on the Indonesia strain have been provided.

SNA – The previously described microneutralisation assay was used. All SN assays are run in triplicate in the same run. The assay variability is controlled by the use of control sera included in each run and each run is judged against acceptance criteria. The assay cut-off is defined as 1:28, which results from pre-dilution of the sera and is the first computable ND50 value.

The specificity of the neutralisation assay has been estimated by testing a set of samples from naïve (i.e. previously unvaccinated) children (6 to 9 years) collected before vaccination with the seasonal vaccine. Out of 46 subjects, one was slightly positive. These data are described in the Validation Report. Based on this result, the specificity of the SNA can be estimated to be 98%.

Q-PAN-001

This was a randomised, observer-blind, multi-centre, active-controlled study conducted at 10 sites (7 in the US and 3 in Canada). The primary immunogenicity objective was to demonstrate the adjuvant activity of AS03 by comparing immune responses to Q-Pan H5N1 3.8 µg HA with AS03 at full [A] and half [B] strengths versus Q-Pan HA 3.8 µg alone. The primary immunogenicity endpoint was the Day 42 HI antibody response to homologous virus in subjects receiving two doses of vaccine Superiority of the adjuvanted formulation was declared if the lower bound of the 95% confidence interval (CI) on the geometric mean titre (GMT) ratio exceeded 2.0 and the lower bound of the 95% CI on the difference in seroconversion rate (SCR) exceeded 15%.

Formulations, lots and treatment group allocations were as follows:

Product	Formulation	Lot number	Group(s)
A/Indonesia/5/05 antigen (Quebec)	15 µg/mL	AFLPA009A	A, B, C
A/Indonesia/5/05 antigen (Dresden)	15 µg/mL	DFLSA006A	D, E
AS03	Full strength	DA3BA008A	B, D
AS03	Half strength	DA3AA006A	C, E
Phosphate-buffered saline	--	DD11A003A	A

The following formulations were used in the different groups:

Group A (“Q000ASO3”) – Quebec manufactured 3,8 µg HA (A/Indonesia/5/05), no Adjuvant
Group B (“Q100AS03”) – Quebec manufactured 3,8 µg HA, full dose Adjuvant
Group C (“Q50AS03”) – Quebec manufactured 3,8 µg HA, half dose Adjuvant
Group D (“D100AS03”) – Dresden manufactured 3,8 µg HA, full dose Adjuvant
Group E ("D50AS03") – Dresden manufactured 3,8 µg HA, half dose Adjuvant

Four blood samples were to be drawn at D0, D21, D42 and D182.

Subject populations were defined as in previous studies with H5N1 vaccine (i.e. total vaccinated {VC}, according to protocol {ATP} for safety and ATP for immunogenicity).

The sample size was based on the evaluation of superiority of Q-Pan plus adjuvant versus Q-Pan without adjuvant using the SCR and GMT at Day 42, both of which required a statistically significant result. Each test was to have α=0.05 (two-sided) at a power of 95%, yielding an overall power of approximately 90% for the simultaneous tests. Based on the FDA draft guidance on pandemic vaccines of March 2006 a 0.3 log10 mean difference (= a 2-fold difference in GMT ratio) for the HI antibody titres and a 15% difference in SCR were to be regarded as meaningful.

It was planned that if the first step of the analysis based on Day 42 data indicated that GMTs fulfilled the ≥2-fold criterion for adjuvant effect and Groups B and C both demonstrated a Day 42 point estimate for the rate of vaccine homologous HI reciprocal titres ≥ 40 of at least 76% then two additional groups were to be recruited as follows:
- Q-Pan A/Indonesia/5/05 containing 1.9 µg of HA with full strength ASO3 on Days 0 and 21
- Q-Pan A/Indonesia/5/05 containing 1.9 µg of HA with half strength AS03 on Days 0 and 21.

Data from these additional groups are described under study Q-Pan-010 below.

HI up to D42

All 680 subjects (68 at each of the 10 study sites) received at least one dose of study vaccine and 648 were evaluable for immunogenicity.

Quebec- versus Dresden-manufactured vaccine
For this analysis:
- Group B (Q100AS03) and Group C (Q50AS03) were pooled to form the Quebec group
- Group D (D100AS03) and Group E (D50AS03) were pooled to form the Dresden group.

For the groups to be considered equivalent the 95% confidence interval on the ratio was to be between 0.67 and 1.5. This criterion was met for A/Indonesia/5/05 and A/Vietnam/1194/04 as shown below.

Table 25 Adjusted GMT ratios for subjects receiving Quebec antigen with full or half strength adjuvant compared with subjects receiving Dresden antigen with full or half strength adjuvant at Day 42, by antibody (ATP cohort for immunogenicity)

	Treatment Group				Adjusted GMT ratio (Quebec / Dresden)		
	Quebec		Dresden			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/Indonesia/5/05	290	371.2	282	396.9	0.94	0.75	1.17
A/Vietnam/1194/04	290	36.6	282	31.6	1.16	0.92	1.46

Dresden = D100AS03 and D50AS03
Quebec = Q100AS03 and Q50AS03

Adjuvant activity

The differences between Group B (full adjuvant) and Group A (no adjuvant) in HI SCRs to A/Indonesia/5/05 and A/Vietnam/1194/04 demonstrated the superiority of adjuvanted vaccine.

Table 18 Comparison of seroconversion rates at Day 42 in subjects receiving Quebec antigen with full strength adjuvant and Quebec antigen with no adjuvant, by antibody and pre-vaccination status (ATP cohort for immunogenicity)

		Treatment Group						Difference in SCR (Q100AS03 minus Q000AS03)		
	Pre-vacc.	Q100AS03			Q000AS03				95% CI	
Antibody	status	N	n	%	N	n	%	%	LL	UL
A/Indonesia/5/05	S-	144	140	97.2	75	13	17.3	79.89	69.36	87.27
	S+	0	-	-	-	-	-	-	-	-
	Total	144	140	97.2	75	13	17.3	79.89	69.36	87.27
A/Vietnam/1194/04	S-	140	89	63.6	71	1	1.4	62.16	52.94	70.00
	S+	4	0	0.0	4	0	0.0	0	-52.33	52.33
	Total	144	89	61.8	75	1	1.3	60.47	51.45	68.30

S- = seronegative subjects (antibody titre < 10 1/DIL) prior to vaccination
S+ = seropositive subjects (antibody titre >= 10 1/DIL) prior to vaccination
N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Quebec antigen with half-strength adjuvant gave significantly higher SCRs and GMTs for antibody to both strains compared to unadjuvanted Quebec antigen.

Table 20 Comparison of seroconversion rates at Day 42 in subjects receiving Quebec antigen with half strength adjuvant and Quebec antigen with no adjuvant, by antibody and pre-vaccination status (ATP cohort for immunogenicity)

		Treatment Group						Difference in SCR (Q50AS03 minus Q000AS03)		
	Pre-vacc.	Q50AS03			Q000AS03				95% CI	
Antibody	status	N	n	%	N	n	%	%	LL	UL
A/Indonesia/5/05	S-	146	131	89.7	75	13	17.3	72.39	61.04	80.80
	S+	-	-	-	-	-	-	-	-	-
	Total	146	131	89.7	75	13	17.3	72.39	61.04	80.80
A/Vietnam/1194/04	S-	140	82	58.6	71	1	1.4	57.16	47.89	65.31
	S+	6	4	66.7	4	0	0.0	66.67	1.48	90.91
	Total	146	86	58.9	75	1	1.3	57.57	48.57	65.52

Table 21 Comparison of adjusted ratios of GMTs at Day 42 in subjects receiving Quebec antigen with half strength adjuvant and Quebec antigen with no adjuvant, by antibody (ATP cohort for immunogenicity)

	Treatment Group				Adjusted GMT ratio (Q50AS03 / Q000AS03)		
	Q50AS03		Q000AS03			95% CI	
Antibody	N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
A/Indonesia/5/05	146	311.2	75	10.4	29.96	20.68	43.41
A/Vietnam/1194/04	146	33.5	75	5.8	5.83	4.04	8.84

There were numerically higher SCRs and GMTs with full strength adjuvant but the differences were not large enough to indicate superiority of full over half strength adjuvant. The results for homologous virus are shown below.

								Difference in seroconversion rate (Q100AS03 minus Q50AS03)		
		Q100AS03			Q50AS03				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
FLU A/IND/05 AB (1/DIL)	S-	144	140	97.2	146	131	89.7	7.50	1.97	13.84
	S+									
	Total	144	140	97.2	146	131	89.7	7.50	1.97	13.84

Q100AS03 = Q100AS03: 3.8 ug Quebec A/Indo Full AS03
Q50AS03 = Q50AS03: 3.8 ug Quebec A/Indo Half AS03

				Adjusted GMT ratio (Q100AS03 / Q50AS03)		
Q100AS03		Q50AS03			95% CI	
N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
144	450.8	146	311.2	1.45	1.07	1.97

When examined by age (18 - 40 and 41 - 64 years) the criteria for adjuvant effect were fulfilled in both strata but the homologous virus SCR dropped 4% in the younger age group and 12% in the older group when the adjuvant strength was halved. Similarly, the GMT was only slightly affected in the younger age group but there was a 2-fold reduction in GMT in the older age group.

Seroconversion and seroprotection rates (SCRs and SPRs)

The lower bound of the 95% CI for SCRs exceeded 40% at Day 42 in the four groups that received adjuvanted Quebec or Dresden antigen.

Due to the low numbers who were seropositive with respect to A/Indonesia before vaccination the SPRs followed the SCRs.

Table 22 Seroconversion rates for A/Indonesia/5/05 antibody at Days 21 and 42 (ATP cohort for immunogenicity)

			Seroconversion							
			Day 21				Day 42			
					95% CI				95% CI	
Group	Pre-vacc status	N	n	%	LL	UL	n	%	LL	UL
Q000AS03	S-	75	5	6.7	2.2	14.9	13	17.3	9.6	27.8
	S+	0	0	-	-	-	0	-	-	-
	Total	75	5	6.7	2.2	14.9	13	17.3	9.6	27.8
Q100AS03	S-	144	60	41.7	33.5	50.2	140	97.2	93.0	99.2
	S+	0	0	-	-	-	0	-	-	-
	Total	144	60	41.7	33.5	50.2	140	97.2	93.0	99.2
Q50AS03	S-	146	60	41.1	33.0	49.5	131	89.7	83.6	94.1
	S+	0	0	-	-	-	0	-	-	-
	Total	146	60	41.1	33.0	49.5	131	89.7	83.6	94.1
D100AS03	S-	139	63	45.3	36.9	54.0	134	96.4	91.8	98.8
	S+	1	1	100	2.5	100	1	100	2.5	100
	Total	140	64	45.7	37.3	54.3	135	96.4	91.9	98.8
D50AS03	S-	141	53	37.6	29.6	46.1	130	92.2	86.5	96.0
	S+	1	1	100	2.5	100	1	100	2.5	100
	Total	142	54	38.0	30.0	46.5	131	92.3	86.6	96.1

Geometric mean titres (GMTs) and geometric mean fold rates GMFRs

The difference in GMTs between adjuvanted and unadjuvanted vaccines at Day 42 was very large (being 321-480 in the adjuvanted groups and 11 in the non-adjuvanted group. A similar pattern was observed for GMTs for HI antibody to A/Vietnam/1194/04 although the actual GMTs were much lower for the clade 1 Vietnam strain. The GMFRs increased markedly after the second vaccine dose in the adjuvanted antigen groups to reach 93-95 with full strength adjuvant and 64-69 for half-strength adjuvant compared to only 2.1 in the unadjuvanted antigen group.

HI at D182

At D182 only the groups that had received full-strength adjuvanted vaccine maintained SCRs (based on HI to homologous virus) with lower 95% CI that were ≥ 40%.

Table 9 Seroconversion rates for A/Indonesia/5/05 antibody at Day 182 (ATP cohort for immunogenicity)

Group	Pre-vaccination status	N	Vaccine response			
			n	%	95% CI LL	95% CI UL
Q000AS03	S-	74	2	2.7	0.3	9.4
	S+	0	0	--	--	--
	Total	74	2	2.7	0.3	9.4
Q100AS03	S-	141	77	54.6	46.0	63.0
	S+	0	0	--	--	--
	Total	141	77	54.6	46.0	63.0
Q50AS03	S-	145	66	45.5	37.2	54.0
	S+	0	0	--	--	--
	Total	145	66	45.5	37.2	54.0
D100AS03	S-	137	67	48.9	40.3	57.6
	S+	1	0	0.0	0.0	97.5
	Total	138	67	48.6	40.0	57.2
D50AS03	S-	137	62	45.3	36.7	54.0
	S+	1	0	0.0	0.0	97.5
	Total	138	62	44.9	36.5	53.6

There was little difference between D182 SCRs in groups that received full or half-dose adjuvant and these groups had SCRs that were markedly superior to that in the unadjuvanted group. SCRs based on HI antibody to A/Vietnam/1194/04 were notably lower and were from 0% - 11% and 9% at Day 182.

At D182 the lower bound of the 95% CI for the percent of subjects achieving an HI antibody reciprocal titre ≥ 40 (SPR) was < 70% in all groups. Actual SPRs were nearly identical to the SCRs. SPRs for HI to A/Vietnam/1194/04 also did not attain the 70% target in any treatment group and ranged from 1-13%.

The GMFRs were all between 4.5 and 5.6 for the adjuvanted groups compared to 1.1 in the non-adjuvanted antigen group. The difference in GMFR between adjuvanted and unadjuvanted vaccine groups at Day 182 was similar to that observed at Day 21.

NA at D42 and D182 – subset study

Up to 40% of tested subjects per group were seropositive for NA to the vaccine strain before the first dose and up to 80% were seropositive for NA against A/Vietnam/1194/04.

At baseline 12.8% to 23.4% per group had titres ≥ 1:80 for the homologous virus. Among 195 subjects across the four adjuvanted vaccine groups all but two were seropositive at Day 21 and all were seropositive at Day 42 and at D182. At D42 all 195 subjects had titres ≥ 1:80 and there was little decline in this proportion by Day 182. D42 GMTs were highest in and similar between D-Pan (1497) and Q-Pan (1567) groups with full strength AS03. GMTs were 1242 and 1353 in the half strength AS03 groups and only 184 in the unadjuvanted group. There was less difference in GMTs between the adjuvanted vaccine groups at D182 (between 414 and 456).

After two doses of vaccine all who were seronegative with respect to A/Vietnam at baseline demonstrated a response in the adjuvanted treatment groups. At Day 182 the two groups that had received full strength AS03 vaccines retained the highest response rates relative to baseline. At Day 182 the proportions with titres ≥ 1:80 were still 16 to 20 percentage points higher in the adjuvanted groups.

NA against the drifted clade 2 strains A/turkey/Turkey/1/05 (a clade 2.2 virus) and A/Anhui/1/05 (a clade 2.3 virus) was measured in sera obtained from recipients of Q-Pan vaccine containing full strength AS03. No subject was seropositive to A/Anhui/1/05 at baseline. At D42, 80.3% had NA titres against A/Anhui of ≥ 40 and 60.6% had titres ≥ 80. However, by D182 only 23.6% were still seropositive. In contrast, the baseline seropositivity rate was 35.7% for NA to A/turkey/Turkey/1/05, at which time approximately 25% had titres ≥ 40. At D42 all subjects were seropositive and 98.6% had titres ≥ 80. In addition, NA persisted such that at D182 60.7% still maintained a response.

Table 11 **A/Anhui/1/05 and A/turkey/Turkey/1/05 neutralizing antibody GMTs pre-vaccination and at Days 42 and 182 post first dose (ATP cohort for immunogenicity)**

				GMT		
					95% CI	
Antibody	Group	Timing	N	Value	LL	UL
FLU A/ANHUI/05 AB (1/DIL)	Q100AS03	PRE	143	14.0	14.0	14.0
		DAY 42	142	91.3	78.4	106.4
		DAY 182	140	16.7	15.8	17.7
FLU A/TURKEY/05 AB (1/DIL)	Q100AS03	PRE	143	25.6	21.9	29.9
		DAY 42	143	594.4	523.6	674.7
		DAY 182	140	121.6	106.3	139.2

Data from the additional contingent arms

Data were provided up to D42. Data up to Day 182 will be available in February 2010.

As shown below the HI seropositivity rates at Day 0 were 0% - 6% but significant increases occurred in both groups by Day 21 with further increases up to Day 42 to reach SPRs of 84.0% and 95.9% in $AS03_B$ and $AS03_A$ groups, respectively. In the older age stratum (41-64 years) an absolute 21% reduction in SPR was observed with half the adjuvant dose (95.8% for $AS03_A$ versus 75.0% for $AS03_B$) with a much smaller difference between adjuvant groups in the younger stratum (92.3% for $AS03_B$ versus 96.0% for $AS03_A$). At day 42, GMTs were nearly two-fold higher in the $AS03_A$ group (331.6 versus 173.9) and were higher in the younger age stratum.

Seropositivity rates and GMTs for FLU A/IND/05 antibodies (ATP cohort for immunogenicity)

				Seropositive		SPR		GMT
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**value**
FLU A/IND/05 AB	QR50AS0	PRE	50	0	0.0	0	0.0	5.0
		DAY 21	50	29	58.0	21	42.0	20.8
		DAY 42	50	43	86.0	42	84.0	173.9
	QR100AS	PRE	49	3	6.1	1	2.0	5.6
		DAY 21	49	27	55.1	23	46.9	23.0
		DAY 42	49	48	98.0	47	95.9	331.6

1. QR50AS03 = QR50AS03: 1.9 ug Quebec A/Indo Half AS03
2. QR100AS0 = QR100AS03: 1.9 ug Quebec A/Indo Full AS03

All CHMP criteria (SPR, SCR and SCF) were met at Day 42 in both adjuvanted groups and in both age strata.

These results are in line with those already described for the 3.8 µg H5N1 antigen recipients in Q-Pan-001 study report. That is, halving the adjuvant dose had a relatively small effect on immune responses in the younger subjects but there was a more marked difference in the older age stratum. The effect was even more marked when the antigen content was halved.

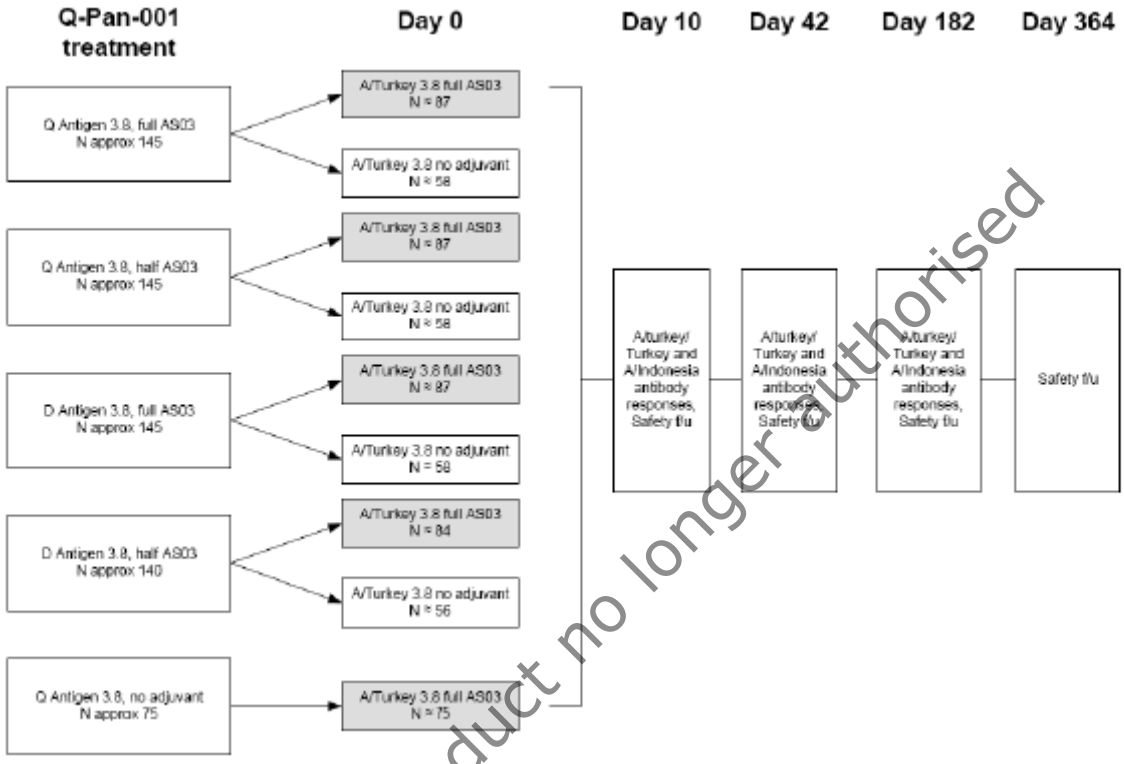
3. SCR and GMT ratios for anti-IND/05 antibodies (ATP cohort for immunogenicity)

4.

Group	**Timing**	**N**	**n**	**SCR**	**GMT ratio**
QR50AS03	DAY 21	50	21	42.0	4.2
	DAY 42	50	42	84.0	34.8
QR100AS03	DAY 21	49	23	46.9	4.1
	DAY 42	49	47	95.9	59.2

Q-Pan-010

This was the booster phase of **Q-Pan-001** in which A/turkey/Turkey vaccine was administered at about 15 months after the initial immunisation series. There were 469 subjects enrolled, representing 69% of the 680 that were randomised into Q-Pan-001. Subjects were randomised to receive adjuvanted or unadjuvanted booster doses in a ratio of 3:2. Adjuvanted vaccine was used to boost Groups A (primed with unadjuvanted vaccine; bottom in diagram), B1, C1, D1 and E1 (grey shaded boxes from top). Unadjuvanted vaccine was administered to Groups B2, C2, D2 and E2 (unshaded boxes from top).



The primary objective was to assess whether a single booster dose of H5N1 (A/turkey/Turkey/1/2005) adjuvanted with AS03A (= full approved dose) is more immunogenic in subjects primed with two doses of a heterologous H5N1 vaccine adjuvanted with AS03 (full dose [A] or half dose [B]) compared to subjects primed with unadjuvanted antigen. HI responses to the booster dose were to be compared against the FDA's Center for Biologics Evaluation & Research (CBER) criteria for HI SCRs and SPRs at 10 days post-dose.

On Day 0 of study 010 16.3% of subjects primed with unadjuvanted vaccine (Group A) were still seropositive to A/Indonesia/5/2005 H5N1 compared to 68.6% primed with AS03A (Groups B1, B2, D1 and D2) and 63.5% primed with AS03B (Groups C1, C2, E1 and E2). Seropositivity against A/turkey/Turkey/1/2005 H5N1 was observed for 10.2% in Group A, 55% primed with AS03A and 49% primed with AS03B.

At 10 days post-dose the **SCR** was 96% in Groups B1 + D1 and 91.5% in Group A, with a difference that did not meet the target of a lower bound of 95% CI ≥ 15%. Thus, an adjuvanted booster dose after priming with an AS03A adjuvanted vaccine was not significantly more immunogenic compared to an adjuvanted booster dose after unadjuvanted priming. The difference in SCR between these groups was larger for subjects who were seropositive at baseline than for those were seronegative at baseline (14.3% and 5.4%, respectively) but the lower bound of the 95% CI did not meet the target ≥ 15% in either case. In addition, the difference between groups did not meet the target of a lower bound of 95% CI ≥ 15% for either age stratum.

Table 20 Difference between adjuvanted and non-adjuvanted groups (Groups B1 + D1 versus Group A) in percentage of subjects with seroconversion to A/turkey/Turkey/1/2005 antibody at Day 10 by pre-vaccination status in subjects 18 to 64 years of age (ATP cohort for immunogenicity)

Antibody	Pre-vaccination status	B1 + D1			A			Difference in SCR (B1 + D1 minus A)		
									95% CI	
		N	n	%	N	n	%	%	LL	UL
A/turkey/Turkey/1/2005 Ab (1/DIL)	S-	56	55	98.2	42	39	92.9	5.36	-3.36	17.53
	S+	70	66	94.3	5	4	80.0	14.29	-4.01	57.34
	Total	126	121	96.0	47	43	91.5	4.54	-2.59	16.30

A = Q-Pan Indo 3.8 x 2 + Turkey 3.8, AS03A
B1 + D1 = Q-Pan and D-Pan Indo 3.8, AS03A x 2 + Turkey 3.8, AS03A

For the adjusted **GMT ratio** for Groups B1 + D1 / Group A the lower level of the 95% CI was greater than 1 signifying a superior immune but was just less than 2 and thus failed to fulfil the co-primary objective. Therefore an adjuvanted booster dose after priming with AS03A adjuvanted vaccine was not superior to adjuvanted booster dose after unadjuvanted priming.

Table 21 Adjusted ratio of adjuvanted to non-adjuvanted groups (Groups B1 + D1 versus Group A) of A/turkey/Turkey/1/2005 antibody GMTs at Day 10 in subjects 18 to 64 years of age (ATP cohort for immunogenicity)

				Adjusted GMT ratio (B1 + D1 / A)		
B1 + D1		A			95% CI	
N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
126	823.9	47	286.5	2.88	1.91	4.34

A = Q-Pan Indo 3.8 x 2 + Turkey 3.8, AS03A
B1+D1 = Q-Pan and D-Pan Indo 3.8, AS03A x 2 + Turkey 3.8, AS03A

The adjusted GMT ratio in Groups B1 + D1 (GMT 1206.6) to Group A (GMT 188.8) for subjects aged 18 to 40 years was 6.39 with a 95% CI of 3.53-11.58, which met the target of a lower limit of 95% CI greater than 2. In contrast, the adjusted GMT ratio in Groups B1 + D1 to Group A for subjects aged 41 to 64 years was 1.50 with a 95% CI of 0.85-2.63, which did not meet the target of a lower limit of 95% CI greater than 2. Therefore the lack of difference between groups in GMT ratio was driven by the results of the older age stratum.

For subjects receiving adjuvanted priming and booster doses (Groups B1 + D1) the **SCR** was 96.0% (95% CI 91.0-98.7%), which exceeded the CBER guidance target of 40%. The CBER guidance target for SCR was also exceeded both for subjects who were seronegative at baseline and those who were seropositive at baseline as well as in each age stratum. In addition, the **SPR** for Groups B1 + D1 was 99.2% (95% CI 95.7-100%), which exceeded the CBER guidance target of 70%. The SPR for each age stratum also exceeded the CBER guidance target.

For subjects who received two priming doses adjuvanted with AS03A (Groups B1 + D1) or adjuvanted with AS03B (Groups C1 + E1) the post-boost **SCRs** were high for all groups and the difference in SCR between Groups B1 + D1 and Groups C1 + E1 was only -0.43% (95% CI -5.92 to 5.28%) so it was concluded that there was no difference between responses to the booster according to the amount of adjuvant used for the priming doses.

The difference between AS03A adjuvanted and AS03B adjuvanted groups (B1+D1 versus C1+E1) in terms of **SCR** to A/turkey/Turkey/1/2005 antibody at Day 10 by pre-vaccination status also showed no difference between priming groups. Furthermore the difference in SCR between Groups B1 + D1 and Groups C1 + E1 for subjects aged 18 to 40 years was 1.67% (95% CI -4.65 to 8.90%) while that for subjects aged 41 to 64 years was -1.69% (95% CI -11.42 to 8.96).
The adjusted **GMT ratio** of Groups B1 + D1 to Groups C1 + E1 was 1.06 (95% CI 0.78 to 1.44). The GMT ratio was 1.04 (95% CI 0.68-1.59) for subjects aged 18 to 40 years and 1.13 (95% CI 0.73-1.75) for subjects aged 41 to 65 years.

For subjects in Group A, Groups C1 + E1 and Groups B1 + D1, the **SCRs at Day 10** for A/turkey/Turkey/1/2005 were 91.5%, 96.5% and 96.0%, respectively. Thus, subjects who received a booster vaccine with AS03A, regardless of whether priming was adjuvanted or unadjuvanted, had high SCRs on Day 10. In contrast, subjects who received a booster vaccine without adjuvant had lower point estimates of SCRs ranging from 64.6 to 72.9% across groups, regardless of priming condition. SCRs for A/Indonesia/5/2005 were very similar to A/turkey/Turkey/1/2005 results. With the exception of subjects in Group A, there was a trend for lower SCRs for the 41 to 64 years of age stratum. However, the SCR 95% CIs overlap for all vaccine groups given the small sample size.

Table 26 **SCR for subjects in all groups (Group A, Groups B1 + D1, Groups C1 + E1, Groups B2 + D2, Groups C2 + E2, Groups B1 + C1, Groups D1 + E1, Groups B2 + C2, Groups D2 + E2) for A/turkey/Turkey/1/2005 and A/Indonesia/5/2005 H5N1 antibody at Day 10 in subjects 18 to 64 years of age (ATP cohort for immunogenicity)**

				Seroconversion rate			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
A/turkey/Turkey/1/2005 Ab (1/DIL)	A	S-	42	39	92.9	80.5	98.5
		S+	5	4	80.0	28.4	99.5
		Total	47	43	91.5	79.6	97.6
	B1+D1	S-	56	55	98.2	90.4	100
		S+	70	66	94.3	86.0	98.4
		Total	126	121	96.0	91.0	98.7
	C1+E1	S-	55	55	100	93.5	100
		S+	58	54	93.1	83.3	98.1
		Total	113	109	96.5	91.2	99.0
	B2+D2	S-	37	30	81.1	64.8	92.0
		S+	47	27	57.4	42.2	71.7
		Total	84	57	67.9	56.8	77.6
	C2+E2	S-	44	32	72.7	57.2	85.0
		S+	36	24	66.7	49.0	81.4
		Total	80	56	70.0	58.7	79.7
	B1+C1	S-	57	57	100	93.7	100
		S+	70	65	92.9	84.1	97.6
		Total	127	122	96.1	91.1	98.7
	D1+E1	S-	54	53	98.1	90.1	100
		S+	58	55	94.8	85.6	98.9
		Total	112	108	96.4	91.1	99.0
	B2+C2	S-	41	32	78.0	62.4	89.4
		S+	38	19	50.0	33.4	66.6
		Total	79	51	64.6	53.0	75.0
	D2+E2	S-	40	30	75.0	58.8	87.3
		S+	45	32	71.1	55.7	83.6
		Total	85	62	72.9	62.2	82.0
A/Indonesia/5/2005 H5N1 Ab (1/DIL)	A	S-	39	36	92.3	79.1	98.4
		S+	8	6	75.0	34.9	96.8
		Total	47	42	89.4	76.9	96.5
	B1+D1	S-	40	39	97.5	86.8	99.9
		S+	86	83	96.5	90.1	99.3
		Total	126	122	96.8	92.1	99.1
	C1+E1	S-	38	38	100	90.7	100
		S+	75	70	93.3	85.1	97.8
		Total	113	108	95.6	90.0	98.5
	B2+D2	S-	25	21	84.0	63.9	95.5
		S+	59	29	49.2	35.9	62.5
		Total	84	50	59.5	48.3	70.1
	C2+E2	S-	32	22	68.8	50.0	83.9
		S+	48	22	45.8	31.4	60.8
		Total	80	44	55.0	43.5	66.2

				Seroconversion rate			
						95% CI	
Antibody	Group	Pre-vaccination status	N	n	%	LL	UL
	B1+C1	S-	41	41	100	91.4	100
		S+	86	81	94.2	87.0	98.1
		Total	127	122	96.1	91.1	98.7
	D1+E1	S-	37	36	97.3	85.8	99.9
		S+	75	72	96.0	88.8	99.2
		Total	112	108	96.4	91.1	99.0
	B2+C2	S-	26	18	69.2	48.2	85.7
		S+	53	23	43.4	29.8	57.7
		Total	79	41	51.9	40.4	63.3
	D2+E2	S-	31	25	80.6	62.5	92.5
		S+	54	28	51.9	37.8	65.7
		Total	85	53	62.4	51.2	72.6

A = Q-Pan Indo 3.8 x 2 + Turkey 3.8, $AS03_A$
B1+D1 = Q-Pan and D-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8, $AS03_A$
C1+E1 = Q-Pan and D-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8, $AS03_A$
B2+D2 = Q-Pan and D-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8
C2+E2 = Q-Pan and D-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8
B1+C1 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8, $AS03_A$ and Indo 3.8, $AS03_B$ x 2 + Turkey 3.8, $AS03_A$
D1+E1 = D-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8, $AS03_A$ and Indo 3.8, $AS03_B$ x 2 + Turkey 3.8, $AS03_A$
B2+C2 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8 and Indo 3.8, $AS03_B$ x 2 + Turkey 3.8
D2+E2 = D-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8 and Indo 3.8, $AS03_B$ x 2 + Turkey 3.8

For Group A, Groups C1 + E1 and Groups B1 + D1, the **SCRs at Day 42** for A/turkey/Turkey/1/2005 were 87.2%, 95.6% and 96.1%, respectively. Day 42 SCRs for subjects who received a booster dose of unadjuvanted vaccine were lower than for subjects who received a booster dose of adjuvanted vaccine. SCRs ranged from 57.0 to 96.4 for all groups. SCRs for A/Indonesia/5/2005 were similar to A/turkey/Turkey/1/2005 results. As with SCRs at Day 10, with the exception of subjects in Group A, there was a trend for lower SCRs for the 41 to 64 years of age group compared with the 18 to 40 years age stratum.

For Group A, Groups C1 + E1 and Groups B1 + D1 the **SPRs at Day 10** were 93.6% (95% CI 82.5-98.7%), 100% (95% CI 96.8-100%), and 99.2% (95% CI 95.7-100%), respectively. **The SPRs at Day 42** were similar or slightly decreased from Day 10 with values of 87.2% (95% CI 74.3-95.2%), 100% (95% CI 96.8-100%), and 98.4% (95% CI 94.5-99.8%), respectively. SPRs were very similar between the age strata.

GMTs at Day 10 for subjects in Group A, Groups C1+E1 and Groups B1+D1 were 229.6, 810.5 and 847.3, respectively, with lower values at **Day 42** of 155.4, 699.5 and 652.2. For subjects primed and boosted with adjuvanted vaccines, the GMT for subjects aged 41 to 64 years was approximately half of that seen in younger subjects. For subjects who received an unadjuvanted booster there was little difference between the age strata. Older subjects in Group A had GMTs that were nearly double those seen in the younger age stratum.

Therefore it appeared that subjects who received AS03A or AS03B adjuvanted priming doses and a booster with AS03A adjuvant (Groups B1, C1, D1, and E1) had the most robust immune response at both Days 10 and 42. Also, as expected since both A/Indonesia/5/2005 and A/turkey/Turkey/1/2005 are clade 2 viruses, the SPRs and GMTs were comparable.

The **GMT ratio** for the A/turkey/Turkey/1/2005 booster responses between subjects in Groups B1 + C1 (**Q-Pan** priming with AS03A adjuvant booster) and Groups D1 + E1 (**D-Pan** with AS03A adjuvant booster) was 0.99 (95% CI 0.73-1.34). Similar results were observed between Groups B2 + C2 (**Q-Pan** priming with unadjuvanted booster) and Groups D2 + E2 (**D-Pan** priming with unadjuvanted booster) with a GMT ratio of 0.88 (95% CI 0.61-1.27). Therefore the site of manufacture of HA did not seem to affect responses to the booster dose.

For Group A, Groups C1 + E1 and Groups B1 + D1, the **GMFRs at Day 10** were 37.4, 56.3, and 61.6 and at **Day 42** decreased to 25.3, 48.6, and 48.2, respectively. Overall, subjects who received AS03A adjuvanted booster vaccination (Groups A, B1, C1, D1, and E1) had much higher GMFRs than those who received unadjuvanted boosters (Groups B2, C2, D2, and E2). The GMFRs for unadjuvanted booster groups at Day 10 were within a range of 6.9 to 9.6 and at Day 42 were 4.9 to 7.8.

The GMFR for A/Indonesia/5/2005 for Group A was similar to the GMFRs in the other adjuvanted booster groups whereas GMFRs for A/turkey/Turkey/1/2005 for Groups B1, C1, D1 and E1 were roughly twice that of Group A. As previously seen with SCRs, with the exception of subjects in Group A, there was a trend for lower GMFRs for the 41 to 64 years age stratum compared with the 18 to 40 years age stratum.

Discussion on Q-Pan-001 and Q-Pan-010

Q-Pan-001 compared Q-Pan and D-Pan containing antigen from the same strain without adjuvant (Q-Pan only) or with full or half dose AS03. The applicant's pre-defined criteria for assessing the comparability of immune responses at D42 to Q-Pan and D-Pan when each contained A/Indonesia were met. The data for individual groups did not indicate any consistent differences between Quebec and Dresden antigen groups whether administered with full or half-strength AS03 adjuvant.

HI seropositivity rates and GMTs against A/Indonesia/05/2005 and their respective 95% confidence intervals were near-identical at all time points for Q-Pan and D-Pan with corresponding AS03 contents. Seropositivity rates, GMTs, SPRs and SCRs against heterologous virus (A/Vietnam/1194/2004) were slightly higher in the Quebec antigen group post-vaccination but in all cases the 95% CI overlapped.

At Day 42 and Day 182 in Q-Pan-001 the HI antibody to homologous virus (A/Indonesia/5/05) elicited by Q-Pan and D-Pan was reasonably similar to that observed for HI to homologous virus (but in this case A/Vietnam/1194/2004) in the previously reported studies with D-Pan.

The immunogenicity of Dresden and Quebec antigen when each was formulated with AS03 was comparable. On this basis the data generated with D-Pan H5N1 can be considered to support the data available from the Q-Pan H5N1 studies, including the data from the D-Pan H5N1 study in children.

The additional arms of the study showed that 1.9 µg H5N1 HA antigen with full dose ($AS03_A$) or half dose ($AS03_B$) adjuvant was sufficient to meet the three CHMP criteria in both age strata after two doses. However, as had been shown previously with the approved dose of HA, there were some advantages for full dose AS03 compared to half dose AS03, especially in the older subjects.

Early data on immune responses to Pandemrix (D-Pan H1N1v) suggest that a single dose of the approved amount of HA and AS03 may be sufficient in healthy adults aged 18-60 years. It cannot be surmised from these data that a single dose of a lower HA content (H1N1)v vaccine with full or half the amount of AS03 could suffice in any age group. Specific data would be needed to support any deviation from the current recommendation in the SPC for Pandemrix (H1N1)v. However, there is a possibility that a single dose of either of these formulations might be sufficient in one or both age strata from 18-40 and 41-64 years.

A single booster dose of Q-Pan A/turkey/Turkey/1/2005 adjuvanted with AS03A elicited an immune response at Day 10 that exceeded CBER guidance targets for HI SCR and SPR against the booster strain and the priming strain in subjects who had been primed with A/Indonesia/5/2005/AS03A.

Booster responses were comparable between groups that had received Q-Pan or D-Pan-manufactured HA plus AS03 during priming.

A/turkey/Turkey/1/2005/AS03A was not more immunogenic based on the protocol criteria in those who had been primed with A/Indonesia/5/2005/AS03A compared to those who had received unadjuvanted vaccine in Q-Pan-001. The immunogenicity of the adjuvanted booster dose was also very similar among recipients of adjuvanted (full or half dose) vaccine for priming. All groups that received adjuvanted booster doses had SCRs in excess of 90% but the post-boost GMTs showed a clear trend to be higher in those who had received adjuvanted vaccine for priming. In addition, those primed with full or half dose AS03 and boosted with AS03 vaccine had the most robust immune response at both Days 10 and 42 after the booster dose.

This study did not demonstrate an inhibitory effect on the booster response of unadjuvanted priming as has been noted in some other trials. This may relate to the fact that the booster viral strain used in this study is more closely related to the priming antigen (clade 2.2 vs. 2.1) than has been the case in prior datasets (clade 2.1 vs. clade 1). Additionally, because the preceding protocol included a two dose regimen only, there was no opportunity to assess whether adjuvanted or unadjuvanted formulations would be more effective if single dose priming were used.

Q-Pan-002

This randomised, observer-blinded and placebo-controlled study was conducted during 2008 at 40 centres in the US (30) and Canada (10). It included a lot to lot consistency study and an assessment of age-specific immune responses. Participants were to be aged 18 to 49 years and in good health or aged > 49 years and in stable health. Subjects in each age stratum were randomly assigned (3:1 ratio) to receive vaccine from one of three lots or placebo. The study vaccine contained 3.75 µg HA derived from A/Indonesia/5/05 H5N1 plus the same AS03 and thiomersal content as already approved for D-Pan (i.e. before the variation to approve thiomersal-free product). The assignment of treatment was as follows:

Table 2 Study Groups, by Age Strata and Study Vaccine Lot

Study Arms	Age in Years[1]	Antigen lot	Adjuvant lot	Placebo[2]	Subject (N)	Tested for Immunogenicity		
						Lot consistency	SCR/SPR 18-64 yrs	SCR/SPR >64 yrs
A	18-49	A	1		555	420	1260 (420/lot, combined)	
B	18-49	B	2		555	420		
C	18-49	C	3		555	420		
D	18-49			PBS	555		60	
E	50-64	A	1		555 (185/ lot)		420 (140/lot, combined with arms A, B, & C)	
		B	2					
		C	3					
F	50-64			PBS	185		20	
G	> 64	A	1		1110 (370/lot)			420 (140/lot, combined)
		B	2					
		C	3					
H	> 64			PBS	370			40

Subjects in Groups A-D were to be stratified by age 18-30 years and 31-49 years. Subjects in Groups G & H were to be stratified by age 64-75 years and >75 years.
Placebo consisted of 0.5 ml of sterile preserved isotonic saline for injection administered intramuscularly (IM).

The primary immunogenicity objectives were:

- To demonstrate that HI antibody responses to Q-Pan at D42 met or exceeded the CBER Guidance targets for SCRs and SPRs when tested separately for subjects aged 18 to 64 years and > 64 years.
- To demonstrate lot to lot consistency in subjects aged 18 to 49 years. Equivalence was to be tested for each of the 3 pair wise ratios of HI GMTs based on a 2-sided 95% confidence bounds for all the 3 pair wise ratios falling between the limits 0.67 to 1.5.

The target sample size was approximately 4440 healthy adults aged 18 years or older in 8 dose groups (3330 to receive Q-Pan and 1110 placebo). Subjects were sub-randomised to have samples analysed for primary immunogenicity assessments and a subset of D182 sera was to be analysed.

Of 4561 randomised in the study 3072 were aged 18 to 64 years (2304 vaccine and 768 placebo) and 1489 were aged > 64 years (1118 vaccine and 371 placebo). By D182 there had been 218 subjects withdrawn from the study, mainly due to loss to follow-up (58 Q-Pan and 24 placebo with a complete primary vaccination course; 24 and 13 with an incomplete primary vaccination course).

HI at D42 and D182

Very few subjects were seropositive based on HI before vaccination in either of the age strata. The post-vaccination D42 SCRs were higher in the younger age stratum but the lower 95% CI in subjects in the two age strata who were seronegative at baseline exceeded the CBER requirements. In the Q-Pan group, the D42 SCRs (and the lower 95% CI around these SCRs) exceeded the CHMP criteria in the 18 to 60 years and > 60 years age strata.

Table 24 A/Indonesia/5/05 seroconversion rates (SCR) at Day 42 in subjects 18 to 64 years of age and greater than 64 years of age (ATP cohort for immunogenicity)

		SCR 18-64 years					SCR >64 years				
		18-64 years			95% CI		>64 years			95% CI	
Group	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
Q-Pan	S-	1566	1422	90.8	89.3	92.2	387	287	74.2	69.5	78.5
	S+	5	5	100	47.8	100	9	6	66.7	29.9	92.5
	Total	1571	1427	90.8	89.3	92.2	396	293	74.0	69.4	78.2
Placebo	S-	76	1	1.3	0.0	7.1	40	1	2.5	0.1	13.2
	S+	0	0	.	.	.	0	0	.	.	.
	Total	76	1	1.3	0.0	7.1	40	1	2.5	0.1	13.2

Q-Pan recipients aged 18-64 years and > 64 years maintained SCRs at D182 that still reached or exceeded the CBER criteria. In each case the lower 95% CI exceeded 50%. In addition, the D182 SCRs in Q-Pan recipients still reached or exceeded the CHMP criteria.

Table 10 A/Indonesia/5/05 seroconversion rates (SCR) at Day 182 in subjects 18 to 64 years of age and greater than 64 years of age (ATP cohort for immunogenicity)

		SCR 18-64 years					SCR > 64 years				
		18-64 years			95% CI		>64 years			95% CI	
Group	Pre-vaccination status	N	n	%	LL	UL	N	n	%	LL	UL
Q-Pan	S-	365	224	61.4	56.2	66.4	90	59	65.6	54.8	75.3
	S+	1	1	100	2.5	100	1	0	0.0	0.0	97.5
	Total	366	225	61.5	56.3	66.5	91	59	64.8	54.1	74.6
Placebo	S-	37	1	2.7	0.1	14.2	19	0	0.0	0.0	17.6
	S+	0	0	.	.	.	0	0	.	.	.
	Total	37	1	2.7	0.1	14.2	19	0	0.0	0.0	17.6

The D42 the SPRs were almost the same as the SCRs and conclusions were generally the same. In contrast, at D182 the SPRs in Q-Pan subjects no longer met the CBER criteria but were > 60% for both age strata and the lower 95% CI exceeded 55%. The SPR among Q-Pan recipients aged 18-60

years had fallen to 62.0% and was comparable with the SPR for the older cohort (63.5%). Therefore the rate in the younger cohort no longer met the CHMP criterion. The D42 GMFRs in both age cohorts met the CHMP criteria after vaccination (51.4 and 17.2, compared to 1.0 in the placebo groups) and D182 GMFRs in vaccinated subjects were 7.4 and 7.8.

Despite the difference in strain, the responses in the older cohort in Q-Pan-002 were comparable with those in the D-Pan study 010. The lower immune responses in the older subjects even when baseline data suggested a higher degree of priming most likely reflects immunosenescence.

Assessment of lot to lot consistency based on HI GMTs

The 95% CI for the GMT ratios at D42 are shown in the next table. In each case these fell within the pre-specified limits and therefore the applicant concluded that lot to lot consistency was demonstrated.

Table 26 Adjusted ratios of H5N1 GMTs for Q-Pan Lot A and Q-Pan Lot B, Q-Pan Lot A and Q-Pan Lot C, and Q-Pan Lot B and Q-Pan Lot C at Day 42 in subjects 18-49 years of age (ATP cohort for immunogenicity)

	Q-Pan Lot A		Q-Pan Lot B		Q-Pan Lot C	
	N	GMT	N	GMT	N	GMT
Adjusted GMT	394	275.8	379	291.7	394	333.5
Adjusted GMT Ratio (95% CI)						
Q-Pan Lot A and Q-Pan Lot B	0.95 (0.78, 1.15)					
Q-Pan Lot A and Q-Pan Lot C	0.83 (0.68, 1.00)					
Q-Pan Lot B and Q-Pan Lot C	0.87 (0.72, 1.06)					

NA at D42

At baseline, the majority of subjects in the 18 to 64 years age group were seronegative for NA against A/Indonesia/5/05 (72%) and A/Vietnam/1194/04 (60%). At Day 42 all subjects tested in the 18 to 64 years group were seropositive against A/Indonesia/5/05 and all had titres ≥ 1:80 while the seropositivity rate against A/Vietnam/1194/04 was 96.7% and 85.1% had titres ≥ 1:80.

Table 30 Distribution of vaccine-homologous and drift variant H5N1 viruses tested by MN in subjects 18 to 64 years of age (ATP cohort for immunogenicity)

				<28 1/DIL				>=28 1/DIL				>=40 1/DIL				>=80 1/DIL			
						95% CI				95% CI				95% CI				95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
FLU A/IND/05 AB	Q-Pan	PRE	188	136	72.3	65.4	78.6	52	27.7	21.4	34.6	40	21.3	15.7	27.8	25	13.3	8.8	19.0
		DAY 42	188	0	0.0	0.0	1.9	188	100	98.1	100	188	100	98.1	100	188	100	98.1	100
FLU A/VIET/04 AB	Q-Pan	PRE	181	108	59.7	52.1	66.9	73	40.3	33.1	47.9	62	34.3	27.4	41.7	37	20.4	14.8	27.1
		DAY 42	181	6	3.3	1.2	7.1	175	96.7	92.9	98.8	174	96.1	92.2	98.4	154	85.1	79.0	89.9

The majority of subjects aged > 64 years were seropositive at baseline for the two viruses there was still a demonstrable response to vaccination with >90% reaching titres of at least 1:80 against these viruses by D42.

A 4-fold rise in NA (vaccine response) was documented against A/Indonesia/5/05 in 94% of vaccinated subjects in the 18 to 64 years group and 78% of older subjects compared to rates against A/Vietnam/1194/04 of 62% and 27%. These differences reflect the fact that response rates to Q-Pan were higher in subgroups that were seronegative before vaccination.

NA GMTs were higher in the elderly for both viruses. For A/Indonesia/5/05 the GMT for the 18 to 64 years age group had increased by 66-fold at D42 while there was a 12-fold increase in the older age group. Increments in GMTs against A/Vietnam/1194/04 were 5-fold and just over 2-fold in respective age groups after two doses of Q-Pan. Again these data reflect baseline status differences by age.

Discussion on Q-Pan-002

The study demonstrated that Q-Pan containing A/Indonesia/5/05 elicited HI responses to homologous virus at D42 that met the CBER and CHMP criteria in the respective age groups. However, the responses in the younger age stratum were significantly higher than in the older age stratum. The SCR criteria and GMFR criteria were still met at D182 in both age strata while the CBER SPR criteria were not met in either of the age strata and the CHMP criteria were met only in the older age stratum. Lot consistency was demonstrated based on the pre-defined criteria.

Pre-vaccination NA seropositivity rates were higher than pre-vaccination HI seropositivity rates and were higher for A/Vietnam than for A/Indonesia. Nevertheless, there was a clear response to vaccination in both age strata at D42 with responses documented with respect to vaccine-homologous virus and A/Vietnam.

Q-Pan-009

This was an open-label, randomised study in Canadian adults aged 18-64 years in which Q-Pan A/Indonesia/5/2005 plus AS03 adjuvant (single lots) was administered to equal groups as follows:

Group A:	One 3.8 µg dose A/Indonesia/5/2005/AS03 on Day 0 and Day 21
Group B:	One 3.8 µg dose A/Indonesia/5/2005/AS03 on Day 0 and Day 14
Group C:	One 3.8 µg A/Indonesia/5/2005/AS03 on Day 0 and Day 7
Group D:	Two 3.8 µg doses A/Indonesia/5/2005/AS03 on Day 0 (one in each arm).

The primary objective was to demonstrate that HI responses to H5N1/AS03 at Day 14 after the second dose (after D0 in Group D) met the CBER criteria for SCR and elicited seroprotective titres in at least 50%. The study was stratified by age 18-40 years and 41-64 years.

At 14 days post-dose 2 the SCRs were lower when the interval between doses was < 14 days. There was no appreciable difference between groups A and B or between groups C and D. The lower bound of the 98.75% CI for all treatment groups exceeded the CBER guidance targets for SCRs.

Table 25 SCR for A/Indonesia/5/2005 measured by HI 14 days after the second dose in subjects 18-64 years of age (ATP cohort for immunogenicity)

Group	Pre-vaccination status	N	Seroconversion rate			
			n	%	98.75% CI	
					LL	UL
Q-Pan A	S-	63	61	96.8	86.5	99.8
	S+	2	2	100	7.9	100
	Total	65	63	96.9	86.9	99.8
Q-Pan B	S-	67	62	92.5	80.7	98.3
	S+	2	2	100	7.9	100
	Total	69	64	92.8	81.2	98.3
Q-Pan C	S-	71	52	73.2	58.2	85.2
	S+	3	1	33.3	0.2	95.4
	Total	74	53	71.6	56.8	83.7
Q-Pan D	S-	70	51	72.9	57.7	85.0
	S+	5	3	60.0	9.0	97.4
	Total	75	54	72.0	57.3	83.9

SCRs did not differ greatly by age group but were slightly higher for the 18-40 years age stratum within Groups A and B and for the 41-64 age stratum within Groups C and D. SCRs for Groups C and D were lower than those for Groups A and B regardless of age.

Table 26 **SCR for A/Indonesia/5/2005 measured by HI 14 days after the second dose, by age group (ATP cohort for immunogenicity)**

Group	Seroconversion rate									
	18-40 years					41-64 years				
	N	n	%	98.75% CI		N	n	%	98.75% CI	
				LL	UL				LL	UL
Q-Pan A	30	30	100	84.4	100	35	33	94.3	76.7	99.7
Q-Pan B	31	29	93.5	74.1	99.6	38	35	92.1	74.6	99.0
Q-Pan C	36	24	66.7	44.6	84.5	38	29	76.3	55.3	90.9
Q-Pan D	35	24	68.6	46.2	86.1	40	30	75.0	54.5	89.7

At 21 days post dose 2, SCRs for Groups A, B, C, and D were 95.2%, 92.8%, 80.6% and 74.3%, respectively, and the lower bound of the 95% CI for all treatment groups exceeded CBER guidance targets.

At 14 days post dose 2 for all treatment groups the **SPRs** showed no major differences by age group. However, subjects aged 18-40 years in Groups C and D did not meet the target 98.75% CI lower limit of SPR ≥ 50% (47.4% and 49.1%, respectively) whereas the older subjects in these two groups did meet the target. Subjects aged 18-40 years in Groups A and B had slightly higher SPRs than older subjects while subjects aged 41-64 years in Groups C and D had slightly higher SPRs than younger subjects.

Table 28 **Proportion of subjects with post-immunization reciprocal HI antibody titer >/= 40 (SPR) for A/Indonesia/5/2005 antibody 14 days after the second dose, by age group (ATP cohort for immunogenicity)**

Antibody	Group	>= 40 1/DIL									
		18-40 years					41-64 years				
		N	n	%	98.75% CI		N	n	%	98.75% CI	
					LL	UL				LL	UL
A/INDONESIA/5/2005	Q-Pan A	30	30	100	84.4	100	35	33	94.3	76.7	99.7
	Q-Pan B	31	29	93.5	74.1	99.6	38	35	92.1	74.6	99.0
	Q-Pan C	36	25	69.4	47.4	86.5	38	30	78.9	58.3	92.5
	Q-Pan D	35	25	71.4	49.1	88.1	40	31	77.5	57.3	91.3

At 21 days post dose 2 the corresponding SPR values were 95.2%, 92.8%, 81.9% and 77.0% and the lower bound of the 95% CI for SPR exceeded the ≥ 50% target for all treatment groups. SPR values 21 days after the second dose did not differ greatly by age group.

At Day 14 post-dose 2 the **GMTs** were highest in Group A followed by Group B at 640 and 345, respectively. GMTs in Group C and Group D were 77.7 and 67.4, respectively. Subjects in the 18-40 age stratum in Groups A and B had higher GMTs compared to the older age stratum (1180.5 versus 378.7 for Group A and 418.5 versus 294.8 for Group B). Subjects aged 41-64 years in Groups C and D experienced slightly higher GMTs compared to the younger age stratum. Overall, GMTs for Groups C and D were lower than those for Groups A and B, regardless of age.

GMT values 21 days after the second dose differed by age group, which was especially apparent for Groups A and B. Trends between age groups were similar to those seen at Day 14 after the second dose. Overall, GMTs for Groups C and D were lower than those for Groups A and B, regardless of age.

Immune responses to drift-variant virus were lower than for vaccine-homologous virus. The **GMFR** values were much lower for the drift-variant viruses, particularly within Groups A and B. Immune responses against A/turkey/Turkey/1/2005 were generally higher than against A/Vietnam/1194/2004.

Table 34 Summary of HI response to drift-variant viruses at 7, 14, and 21 days after the second vaccination in subjects 18-64 years of age, by treatment group (ATP cohort for immunogenicity)

Antibody/Statistic	Group	7 days after second dose	14 days after second dose	21 days after second dose
A/VIETNAM/1194/2004 (1/DIL)				
SCR, % (95% CI LL)	Q-Pan A	36.9 (25.3)	76.9 (64.8)	66.1 (53.0)
	Q-Pan B	37.7 (26.3)	59.4 (46.9)	49.3 (37.0)
	Q-Pan C	26.0 (16.5)	33.8 (23.2)	26.4 (16.7)
	Q-Pan D	6.8 (2.2)	33.3 (22.9)	31.1 (20.8)
SPR, % (95% CI LL)	Q-Pan A	38.5 (26.7)	78.5 (66.5)	67.7 (54.7)
	Q-Pan B	37.7 (26.3)	59.4 (46.9)	49.3 (37.0)
	Q-Pan C	30.1 (19.9)	35.1 (24.4)	30.6 (20.2)
	Q-Pan D	10.8 (4.8)	37.3 (26.4)	36.5 (25.6)
GMFR, Value (95% CI LL)	Q-Pan A	3.9 (2.8)	11.6 (8.3)	9.1 (6.5)
	Q-Pan B	2.8 (2.1)	5.5 (4.0)	4.9 (3.7)
	Q-Pan C	2.6 (2.0)	3.0 (2.3)	2.9 (2.2)
	Q-Pan D	1.4 (1.1)	2.8 (2.2)	2.8 (2.2)
A/TURKEY/TURKEY/1/2005(1/DIL)				
SCR, % (95% CI LL)	Q-Pan A	58.5 (45.6)	83.1 (71.7)	83.9 (72.3)
	Q-Pan B	52.2 (39.8)	76.4 (63.5)	71.0 (58.8)
	Q-Pan C	47.9 (36.1)	51.4 (39.4)	51.4 (39.3)
	Q-Pan D	12.2 (5.7)	42.7 (31.3)	50.0 (38.1)
SPR, % (95% CI LL)	Q-Pan A	70.8 (58.2)	92.3 (83.0)	93.5 (84.3)
	Q-Pan B	60.9 (48.4)	82.6 (71.6)	79.7 (68.3)
	Q-Pan C	57.5 (45.4)	58.1 (46.1)	61.1 (48.9)
	Q-Pan D	25.7 (16.2)	52.0 (40.2)	58.1 (46.1)
GMFR, Value (95% CI LL)	Q-Pan A	6.1 (4.2)	23.9 (16.3)	21.7 (15.1)
	Q-Pan B	5.1 (3.6)	11.8 (8.2)	10.5 (7.4)
	Q-Pan C	3.7 (2.7)	4.6 (3.3)	4.8 (3.4)
	Q-Pan D	1.5 (1.2)	3.8 (2.8)	4.2 (3.1)

Antibody titres were also compared between baseline, the day of administering dose 2 and the post-dose data in groups A, B and C. There was an increase in antibody titres for all virus strains between the first and second vaccinations. The data suggested that a longer interval between vaccinations is associated with a larger increase in HI antibodies, with the largest increases seen for Group A. This indicates that the HI antibody response continues to increase at least 21 days after a single vaccination.

Discussion on Q-Pan -009

The data demonstrated that a dose interval of at least 14 days should be retained and that there are likely some advantages for 21 days between doses. However, these data on the effects of dose interval on responses to H5N1 vaccine may now be of low relevance to the (H1N1)v vaccine unless additional data suggest that a second dose of pandemic vaccine should be given at least in some age groups.

The additional data supported the current dose recommendations for Arepanrix H5N1 vaccine.

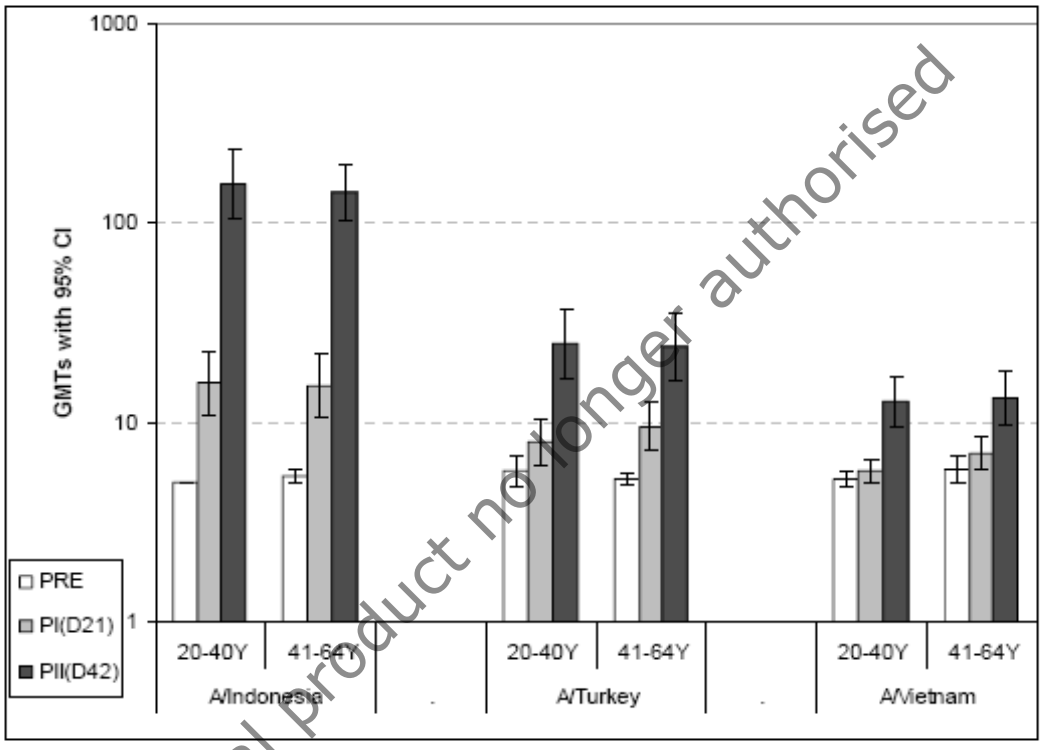
Q-Pan-011

This was an open-label non-comparative study conducted at two centres in Japan and with stratification by age (20-40 and 41-64 years; N=50 per age stratum planned and enrolled). Subjects received two doses of Q-Pan H5N1 containing antigen from A/Indonesia/5/2005 plus AS03. HI was measured against A/Indonesia/5/2005 Clade 2.1, A/turkey/Turkey/1/2005 Clade 2.2 and A/Vietnam/1194/2004 Clade 1 and NA responses were measured against A/Indonesia/5/2005 and A/Vietnam/1194/2004.

All 100 subjects enrolled were evaluable for safety and immunogenicity at D42 and only one was eliminated from the Day 182 ATP cohort for persistence. Prior to vaccination, 5/100 subjects were seropositive for HI antibody against A/Indonesia/5/2005, 4/100 for A/turkey/Turkey/1/2005 and 6/100 for A/Vietnam/1194/2004. Pre-vaccination GMTs were similar between age strata and were low (all < 6).

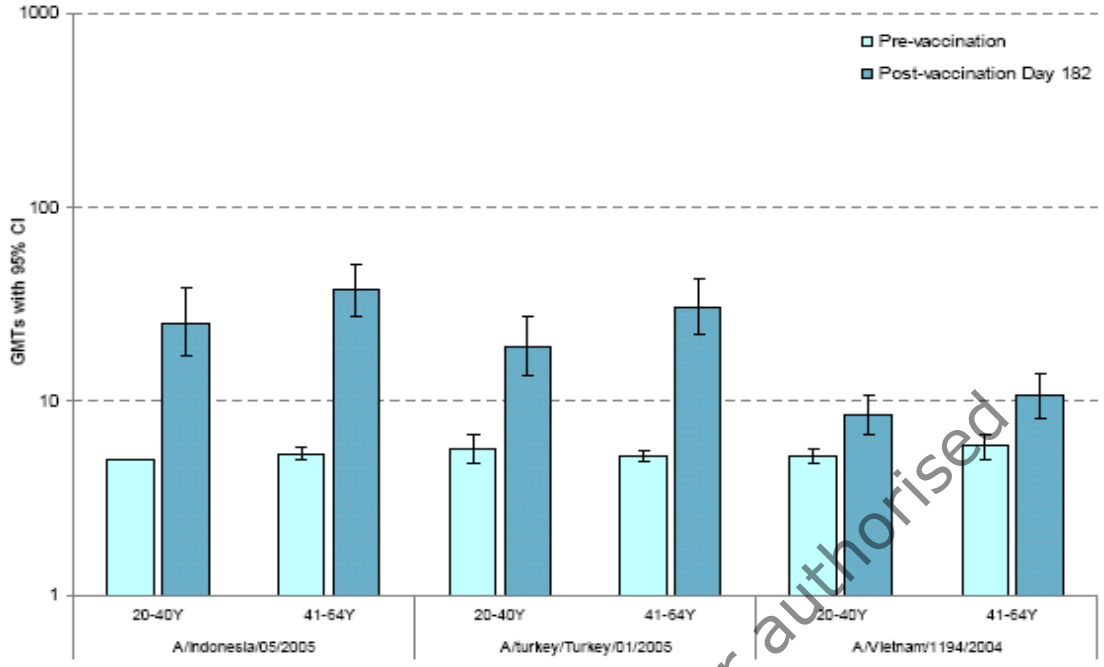
Seropositivity rates against each strain increased after the first and second doses in both age strata but were highest (with highest GMTs) for A/Indonesia and lowest for A/Vietnam at D42.

Figure 1 **GMTs of H5N1 HI antibody titers against A/Indonesia/5/2005, A/turkey/Turkey/1/2005 and A/Vietnam/1194/2004 strains with 95% confidence interval at Days 0, 21 and 42 by age strata 20-40 years and 41-64 years (ATP cohort for immunogenicity)**



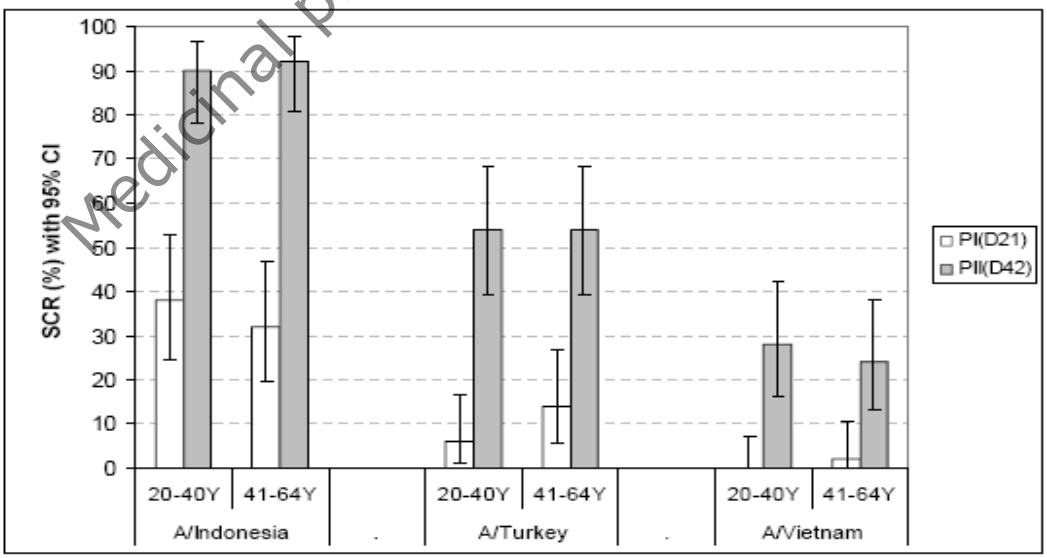
On Day 182, the GMTs against all three strains were lower versus Day 42 but higher than values observed at Day 21. In both age strata the GMTs against A/Indonesia/05/2005 were comparable to those against A/turkey/Turkey/01/2005 and higher than observed for A/Vietnam/1194/2004. The seropositivity rates and GMTs against vaccine-homologous and drifted strains tended to be higher in the older age cohort.

Figure 1 **H5N1 HI GMTs against A/Indonesia/05/2005, A/turkey/Turkey/01/2005 and A/Vietnam/1194/2004 strains with 95% CI on Days 0 and 182 by age strata (ATP cohort for persistence)**



The >40% SCR threshold was exceeded at Day 42 in both age strata for HI antibodies against A/Indonesia/5/2005 and A/turkey/Turkey/1/2005 but not for A/ Vietnam/1194/2004. The SCRs were similar between age strata for all three strains tested.

Figure 2 **Seroconversion rate (SCR) for H5N1 HI antibody titer against A/Indonesia/5/2005, A/turkey/Turkey/1/2005 and A/Vietnam/1194/2004 strains with 95% CI at Days 21 and 42 by age strata 20-40 years and 41-64 years (ATP cohort for immunogenicity)**



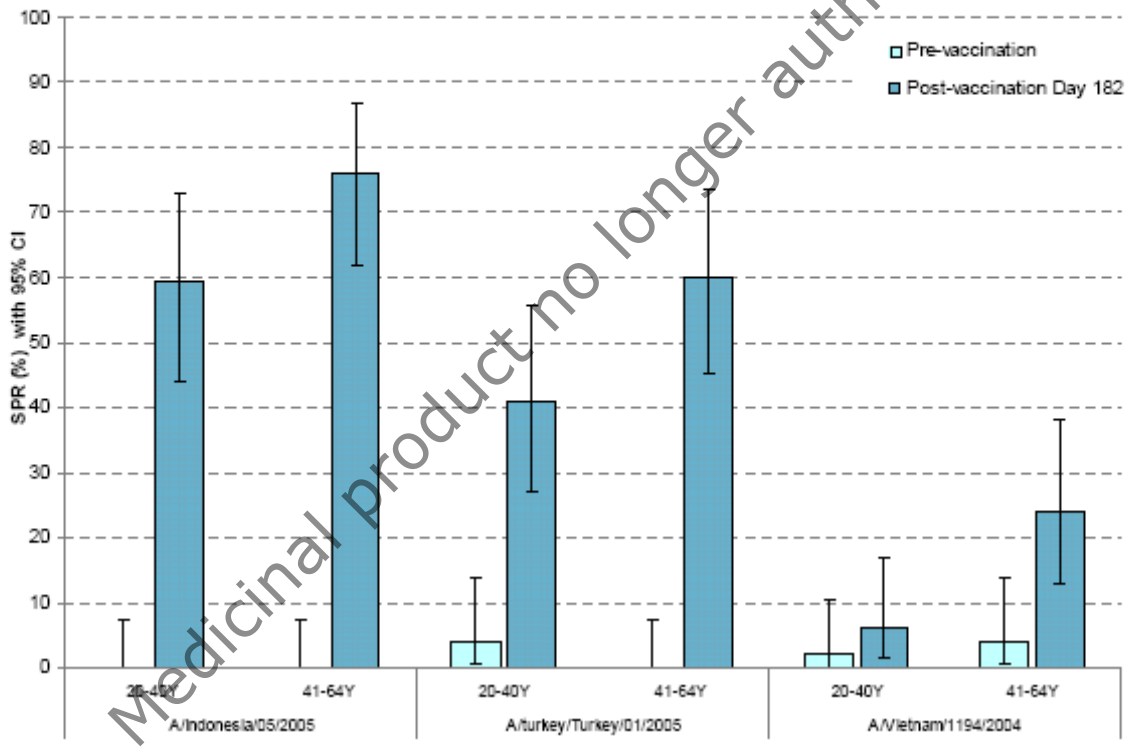
The > 40% SCR threshold was still exceeded on Day 182 for HI antibodies against A/Indonesia/05/2005 and A/turkey/Turkey/01/2005. The threshold was met in both age strata against A/Indonesia/05/2005 but was met only in the older age stratum for A/turkey/Turkey/01/2005. The ≥ 40% threshold for the lower bound of the 95% CI for seroconversion required by CBER was also still

met for HI antibodies against A/Indonesia/05/2005 in both age strata but again only the older age group still met the criterion against A/turkey/Turkey/01/2005.

The >70% SPR required by the CHMP for adults aged 18-60 years and the CBER criterion were exceeded for HI antibodies against A/Indonesia/5/2005 strain at D42 in both age cohorts but these thresholds were not met for the other two strains in either age stratum.

At D182 the > 70% SPR threshold was not met against any strain but rates still followed the same pattern by strain as observed at D42. However, the > 70% SPR threshold was still met against A/Indonesia/05/2005 strain in the 41 to 64 years stratum (76.0%) while the CBER criterion was not met.
The Day 182 SPRs were still considerably higher compared with those seen D21 but lower than observed at D42. The SPR values against A/Vietnam/1194/2004 were low on Day 182 in both age strata (6.1% for 20-40 years; 24.0% for 41-64 years).

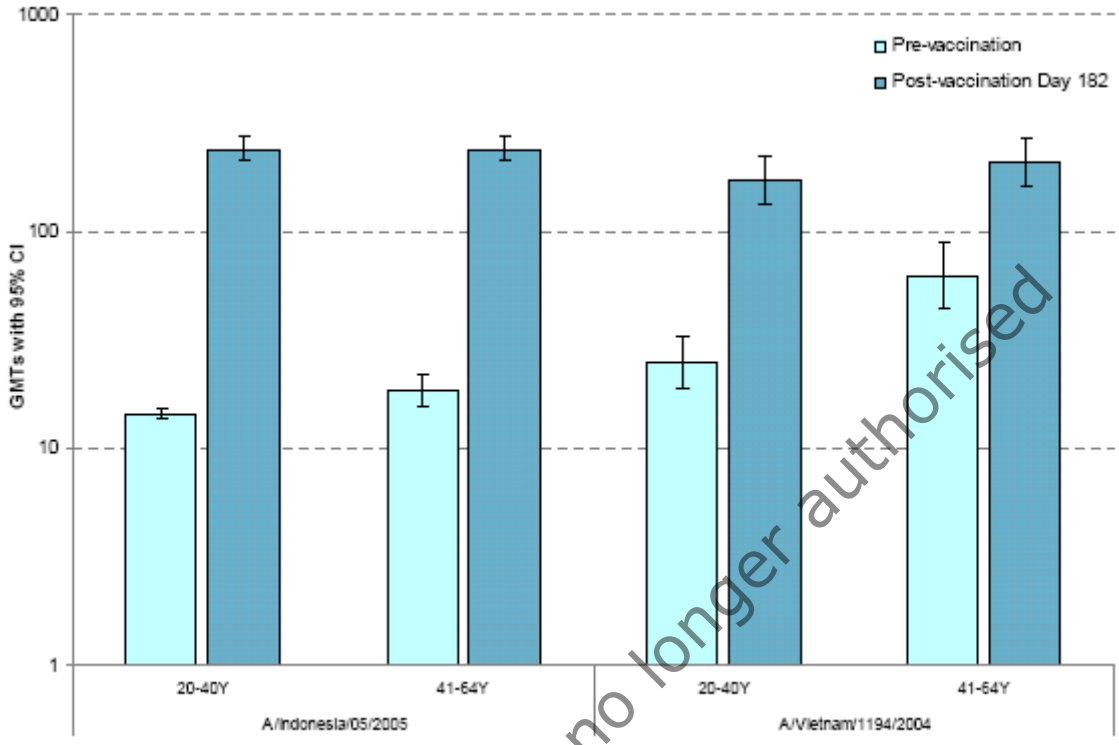
Figure 4 **Seroprotection rates (SPR) for H5N1 HI antibodies against A/Indonesia/05/2005, A/turkey/Turkey/01/2005 and A/Vietnam/1194/2004 strains with 95% CI on Days 0 and 182 by age strata (ATP cohort for persistence)**



The >2.5 SCF threshold against the A/Indonesia/5/2005 strain was exceeded at D21 (3.0) and reached 28.6 by D42. At D42 the threshold was also reached for A/turkey/Turkey/1/2005 but not for A/Vietnam/1194/2004 in either age stratum.

At D182 the > 2.5 SCF threshold was still exceeded in both age strata for A/Indonesia/05/2005 and A/turkey/Turkey/01/2005.
Neutralising antibody (NA) seropositivity rates against A/Indonesia/5/2005 at baseline were low (11/100). By D42 all subjects were seropositive in both age strata. Similarly, baseline GMTs were 14.4 in the 20-40 years and 18.3 in the 41-64 years groups but reached 579.6 and 473.8 by D42. A higher proportion of subjects were already seropositive before vaccination against A/Vietnam/1194/2004 with 70% in the older and 30% in the younger age stratum and GMTs of 61.9 and 24.8, respectively. At D42 the seropositivity rates were 92.0% and 98.0% in respective age groups with GMTs of 106.5 and 154.7.

The D182 GMTs and seropositivity rates for both strains were still high. The GMTs in each age stratum were higher for vaccine-homologous virus. GMTs against A/Indonesia/05/2005 had decreased compared to Day 42 in each age stratum (from 579.6 to 240.5 and from 473.8 to 240.1) but GMTs against A/Vietnam/1194/2004 tended to increase in both age strata (from 106.5 to 173.5 and from 154.7 to 208.0) suggesting some natural boosting effect during the 5 months between samplings.



The NA SCR against both strains increased after the second vaccination and reached 97.0% and 47.0% at Day 42, respectively. The D42 SCRs against A/Indonesia/5/2005 were comparable between age strata. The SCR against A/Vietnam/1194/2004 was higher in the younger group but this reflects the baseline differences in NA titres. On Day 182, the SCRs were 93.9% against A/Indonesia/05/2005 and 58.6% against A/Vietnam/1194/2004 and again showed an age difference.

The proportions with NA titres of at least 1:40 and 1:80 did not change substantially between D42 and D182 against A/Indonesia/05/2005 and were comparable between age groups. However, the corresponding percentages for NA against A/Vietnam/1194/2004 showed increments at the 1:80 level between D42 and d182, reflecting the observed increases in GMTs. This phenomenon applied in both age strata and the final rates were comparable between age groups.

Supplement 17 **Percentage of subjects that reached H5N1 neutralising antibodies against A/Indonesia/05/2005 and A/Vietnam/1194/2004 titre of 1:40 and 1:80 on Days 0, 42 and 182 by age strata (ATP cohort for persistence)**

				≥40 1/DIL				≥80 1/DIL			
						95% CI				95% CI	
Antibodies against	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Indonesia	20-40Y	PRE	50	1	2.0	0.1	10.6	0	0.0	0.0	7.1
		PII(D42)	50	50	100	92.9	100	50	100	92.9	100
		PII(D182)	49	49	100	92.7	100	49	100	92.7	100
	41-64Y	PRE	49	6	12.2	4.6	24.8	3	6.1	1.3	16.9
		PII(D42)	50	50	100	92.9	100	50	100	92.9	100
		PII(D182)	50	50	100	92.9	100	49	98.0	89.4	99.9
A/Vietnam	20-40Y	PRE	50	13	26.0	14.6	40.3	9	18.0	8.6	31.4
		PII(D42)	50	44	88.0	75.7	95.5	33	66.0	51.2	78.8
		PII(D182)	49	44	89.8	77.8	96.6	44	89.8	77.8	96.6
	41-64Y	PRE	50	31	62.0	47.2	75.3	21	42.0	28.2	56.8
		PII(D42)	50	46	92.0	80.8	97.8	39	78.0	64.0	88.5
		PII(D182)	50	45	90.0	78.2	96.7	45	90.0	78.2	96.7

20-40Y = Subjects aged 20-40 years; 41-64Y = Subjects aged 41-64 years; N = number of subjects with available results; n/% = number/percentage of subjects with titre within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination on Day 0; PII (D42) = Post-vaccination two on Day 42; PII D182) = Post-vaccination two on Day 182

Discussion on Q-Pan-011

Overall it appears that this study in Japanese subjects gave comparable immunogenicity and safety results to those obtained in non-Japanese populations with Q-Pan/AS03 vaccine containing antigen from A/Indonesia/5/2005.

Study D-Pan H5N1-009, -022, -023

This open label study in three phases (009, 022 and 023) carried out with Pandemrix ("D-Pan") was divided into three parts as shown below:

Figure 1 **Sequential staggered study design of study H5N1-009**

	Phase A H5N1-009	**Phase B H5N1-022**	**Phase C H5N1-023**
Half Adult Dose HA antigen **Half** Adult Dose AS03	•6-9 yr olds •3-5 yr olds		
Full Adult Dose HA antigen **Half** Adult Dose AS03		•6-9 yr olds •3-5 yr olds	
Full Adult Dose HA antigen **Full** Adult Dose AS03			•6-9 yr olds •3-5 yr olds

1. Full adult dose HA = 3.8 µg, Half adult dose HA = 1.9 µg HA

In Phase A randomisation was to half the adult dose (1.9 µg of HA) + half the AS03 or to *Fluarix*
In Phase B and Phase C randomisation was to (allocation ratio 3:1) full HA/half AS03 (**Phase B**) or to the adult dose (**Phase C**) with a *Fluarix* control group.

Immunogenicity up to D42

Phase A

The pre-vaccination HI GMTs for A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 and so seropositivity rates were zero. On Day 21, the GMTs against A/Vietnam/1194/2004 strain were slightly increased in the Half HA/Half AS03 group in both age strata and then increased markedly after the second dose (540.3 for 6-9 years; 392.7 for 3-5 years). A similar pattern but lower response was seen against A/Indonesia/05/2005 (60.8 for 6-9 years; 53.5 for 3-5 years).

Table 1 Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
1.9 µg HA / Half AS03 - 3-5 years													
PRE	49	5.0	5.0	5.0	0.0	0.0	7.3						
PI(D21)	49	8.7	6.2	12.3	12.2	4.6	24.8	12.2	4.6	24.8	1.7	1.2	2.5
PII(D42)	49	392.7	280.4	550.2	95.9	86.0	99.5	95.9	86.0	99.5	78.5	56.1	110.0
1.9 µg HA / Half AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2						
PI(D21)	43	12.1	8.4	17.5	30.2	17.2	46.1	30.2	17.2	46.1	2.4	1.7	3.5
PII(D42)	43	540.3	424.5	687.7	100	91.8	100	100	91.8	100	108.1	84.9	137.5
H5N1 HI Antibodies against A/Indonesia/05/2005													
1.9 µg HA / Half AS03 - 3-5 years													
PRE	49	5.0	5.0	5.0	0.0	0.0	7.3						
PI(D21)	49	5.2	4.9	5.6	0.0	0.0	7.3	0.0	0.0	7.3	1.0	1.0	1.1
PII(D42)	49	53.5	35.0	81.7	71.4	56.7	83.4	71.4	56.7	83.4	10.7	7.0	16.3
1.9 µg HA / Half AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2						
PI(D21)	43	5.2	4.8	5.8	2.3	0.1	12.3	2.3	0.1	12.3	1.0	1.0	1.2
PII(D42)	43	60.8	38.7	95.5	74.4	58.8	86.5	74.4	58.8	86.5	12.2	7.7	19.1

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03-adjuvanted vaccine group

- By Day 42 the SCRs and the SPRs against the vaccine strain were 95.9% to 100% while SCRs against A/Indonesia/05/2005 were 71.4% to 74.4 %. The ≥ 70% threshold for the lower bound of the 95% CI for seroprotection as defined in the CBER Guidance was only met for HI against A/Vietnam/1194/2004.
- On Day 42 the SCFs against A/Vietnam/1194/2004 were 78.5 and 108.1 while SCFs against A/Indonesia/05/2005 strain were 10.7 and 12.2.

In the Fluarix group no subject seroconverted for HI antibody to A/Vietnam/1194/2004 or A/Indonesia/05/2005 and no subject was seroprotected.

On Day 42 the NA GMTs against the A/Vietnam/1194/2004 in the AS03 group had reached 1155.1 in the 6-9 years age stratum and 1044.4 in the 3-5 years age stratum, whereas the increase from baseline in the control group was very small (104.5 for 6-9 years; 158.4 for 3-5 years). The NA seropositivity rates against A/Vietnam/1194/2004 in the AS03 group increased to 90.7% in the 6-9 years age stratum

and to 91.7% in the 3-5 years age stratum on Day 21, with non-overlapping CIs (when compared with Day 0). All subjects in the AS03 group were seropositive for NA at D42 while the seropositivity rates in controls for NA against the vaccine strain on Days 21 and 42 were within the same range (78.6% - 80.0%).

On Day 42 the NA SCR against the vaccine strain in the Half HA/Half AS03 group had reached 100% in the 6-9 years age stratum and 95.6% in the 3-5 years age stratum. In contrast there was no further increment in SCRs in the control group after a second dose of Fluarix.

Phase B

The pre-vaccination HI GMTs for antibody against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 in all vaccine groups and age strata except for one subject in the 3-5 years cohort. By Day 42 GMTs for HI against A/Vietnam/1194/2004 in the AS03 vaccine group were 615.8 for 6-9 years and 678.1 for 3-5 years age groups and reached 64.9 to 73.7 against A/Indonesia but were still below the cut-off value in the control group. Seropositivity rates followed the same pattern as the GMTs.

Table 3 Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
3.8 µg HA / Half AS03 - 3-5 years													
PRE	42	5.1	4.9	5.4	0.0	0.0	8.4	-	-	-	-	-	-
PI(D21)	41	22.7	14.6	35.3	48.8	32.9	64.9	48.8	32.9	64.9	4.4	2.9	6.8
PII(D42)	42	678.1	475.7	966.6	97.6	87.4	99.9	97.6	87.4	99.9	132.3	91.8	190.7
3.8 µg HA / Half AS03 - 6-9 years													
PRE	45	5.1	4.9	5.4	0.0	0.0	7.9	-	-	-	-	-	-
PI(D21)	45	22.7	14.6	35.3	42.2	27.7	57.8	42.2	27.7	57.8	4.7	2.9	7.8
PII(D42)	45	678.1	475.7	966.6	97.8	88.2	99.9	97.8	88.2	99.9	123.2	85.8	176.8
H5N1 HI Antibodies against A/Indonesia/05/2005													
3.8 µg HA / Half AS03 - 3-5 years													
PRE	42	5.0	5.0	5.0	0.0	0.0	8.4	-	-	-	-	-	-
PI(D21)	41	5.5	4.9	6.2	0.0	0.0	8.6	0.0	0.0	8.6	1.1	1.0	1.2
PII(D42)	42	73.7	45.2	120.3	76.2	60.5	87.9	76.2	60.5	87.9	14.7	9.0	24.1
3.8 µg HA / Half AS03 - 6-9 years													
PRE	45	5.0	5.0	5.0	0.0	0.0	7.9	-	-	-	-	-	-
PI(D21)	45	5.3	4.9	5.8	0.0	0.0	7.9	0.0	0.0	7.9	1.1	1.0	1.2
PII(D42)	45	64.9	38.7	108.9	68.9	53.4	81.8	68.9	53.4	81.8	13.0	7.7	21.8

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03-adjuvanted vaccine group the Day 42 SCRs and SPRs against the vaccine strain reached 97.8% for subjects aged 6-9 years and 97.6% for subjects aged 3-5 years. SCRs and SPRs against A/Indonesia/05/2005 increased to 68.9% and 76.2% in respective age groups. The ≥70% threshold for the lower bound of the 95% CI as defined in the CBER Guidance was met for HI against A/Vietnam/1194/2004. At Day 42 the SCFs against A/Vietnam/1194/2004 were 123.2 for 6-9 years and 132.3 for 3-5 years. The increments in SCFs against A/Indonesia/05/2005 strain were relatively modest (13.0 and 14.7).

In the Fluarix group no subject seroconverted for HI antibody to A/Vietnam/1194/2004 or A/Indonesia/05/2005 and no subject was seroprotected.

Pre-vaccination NA GMTs were ≥1:28 and were 25.6 to 65.5 while baseline seropositivity rates ranged from 47.1% to 78.6%. On Day 42 GMTs exceeded 1500 in the AS03 group but there was a negligible increase in the control group. The seropositivity rates and seroconversion rates followed the same pattern as the GMTs.

Phase C

Pre-vaccination GMTs for HI antibody against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were <1:10 regardless of age stratum or vaccine group and so seropositivity rates were zero. Day 21 HI GMTs against A/Vietnam/1194/2004 were slightly increased in the AS03 vaccine group in both age strata and by Day 42 they had reached 883.5 for 6-9 years and 956.4 for 3-5 years. HI GMTs against A/Indonesia/05/2005 in the AS03 group were also much higher at D42 (92.5 for 6-9 years; 167.9 for 3-5 years) compared with D21. Corresponding seropositivity rates followed a similar pattern and by D42 all subjects in both age strata were seropositive against A/Vietnam while rates against A/Indonesia/05/2005 had reached 83.7% in the 6-9 years age stratum and 95.5% in the 3-5 years age stratum.

Table 5 Humoral immune response - H5N1 HI antibodies

H5N1 HI Antibodies against A/Vietnam/1194/2004													
		GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI	
Timing	N	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
3.8 µg HA / Full AS03 - 3-5 years													
PRE	44	5.0	5.0	5.0	0.0	0.0	8.0	-	-	-	-	-	-
PI(D21)	43	25.0	16.0	39.3	46.5	31.2	62.3	46.5	31.2	62.3	5.0	3.2	7.9
PII(D42)	44	956.4	769.2	1189.3	100	92.0	100	100	92.0	100	191.3	153.8	237.9
3.8 µg HA / Full AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2	-	-	-	-	-	-
PI(D21)	30	27.3	16.2	46.0	56.7	37.4	74.5	56.7	37.4	74.5	5.5	3.2	9.2
PII(D42)	43	883.5	737.3	1058.6	100	91.8	100	100	91.8	100	176.7	147.5	211.7
H5N1 HI Antibodies against A/Indonesia/05/2005													
3.8 µg HA / Full AS03 - 3-5 years													
PRE	44	5.0	5.0	5.0	0.0	0.0	8.0	-	-	-	-	-	-
PI(D21)	43	7.7	6.0	9.8	7.0	1.5	19.1	7.0	1.5	19.1	1.5	1.2	2.0
PII(D42)	44	167.9	121.7	231.5	95.5	84.5	99.4	95.5	84.5	99.4	33.6	24.3	46.3
3.8 µg HA / Full AS03 - 6-9 years													
PRE	43	5.0	5.0	5.0	0.0	0.0	8.2	-	-	-	-	-	-
PI(D21)	30	6.0	5.0	7.2	3.3	0.1	17.2	3.3	0.1	17.2	1.2	1.0	1.4
PII(D42)	43	92.5	59.3	144.2	79.1	64.0	90.0	79.1	64.0	90.0	18.5	11.9	28.8

1. 3-5y = 3-5 years; 6-9y = 6-9 years
2. GMT = geometric mean antibody titre calculated on all subjects; Seroconversion defined as: For initially seronegative subjects, antibody titre ≥ 40 1/DIL after vaccination; For initially seropositive subjects, antibody titre after vaccination ≥4 fold the pre-vaccination antibody titre, SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]
3. N = number of subjects with available results, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = pre-vaccination; PI(D21) = post-vaccination at Day 21; PII(D42) = post-vaccination at Day 42

In the AS03 vaccine group the Day 42 SCRs and SPRs were 100% for both age strata against A/Vietnam and 79.1% to 95.5% against A/Indonesia. The ≥ 70% threshold for the lower bound of the 95% CI for seroprotection as defined in the CBER Guidance was met for HI antibody against A/Vietnam/1194/2004 in both age strata and was met against A/Indonesia/05/2005 in the 3-5 year age stratum. On Day 42 the SCFs against A/Vietnam/1194/2004 were 176.7 and 191.3 compared to 18.5 and 33.6 against A/Indonesia/05/2005.

In the control group no subject seroconverted for HI against either strain and none was seroprotected with the exception of one subject with a response to A/Vietnam/1194/2004 on Day 21 only.

Pre-vaccination NA GMTs were ≥1:28 and were generally comparable between the age strata (range 25.6 to 37.3). Despite the low GMTs, the baseline seropositivity rates ranged from 30.8% to 46.7%.

By Day 42 NA GMTs against A/Vietnam/1194/2004 increased about 10-fold in the AS03 group in both age strata and all children were seropositive whereas there was no further increase in GMTs in the control group and the seropositivity rates ranged from 61.5% to 87.5%. The seroconversion rates also showed the marked differences between AS03 and control for both age strata.

Comparison between Phases at D42

There was a trend for higher HI GMTs and SCFs against both strains and a higher NA GMT against the vaccine strain with the formulations tested in Phases C and B compared to Phase A. The immune response tended to be higher in Phase C when compared with Phase B. When comparing the formulation used in Phase C or in Phase B with that used in Phase A the difference between A and C was marked whereas the difference between A and B was much less apparent. There were advantages for C over B for HI and NA GMTs and for HI responses to A/Indonesia.

Immunogenicity at Month 6

By Month 6 the HI GMTS had fallen but were still at least 6-fold higher than the pre-vaccination GMTs in the groups that had received AS03 vaccines. Against A/Vietnam the seroprotection rates at Month 6 in children who received the adult dose vaccine in Part C of the study were 82.8% for 3-5 year-olds and 78% for 6-9 year-olds. These rates compare with 56% and 63.6% in respective age groups who received the half/half vaccine in Part A and with 70.2% and 68.9% who received full dose HA and half AS03 in Part B. The 95% CI overlap between Parts A, B and C within each age stratum. The results for the other parameters shown follow a similar pattern.

Vaccine strain homologous (against H5N1 A/Vietnam) immune response persistence in terms of HI antibodies at month 6

		≥ 10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H5N1 HI Antibodies against A/Vietnam/1194/2004																
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	50	0.0	0.0	7.1	5.0	5.0	5.0	0.0	0.0	7.1						
PII(M6)	50	64.0	49.2	77.1	29.3	19.2	44.6	56.0	41.3	70.0	56.0	41.3	70.0	5.9	3.8	8.9
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	42	0.0	0.0	8.4	5.0	5.0	5.0	0.0	0.0	8.4						
PII(M6)	44	65.9	50.1	79.5	33.4	21.2	52.7	63.6	47.8	77.6	61.0	44.5	75.8	6.1	3.8	9.7
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	47	2.1	0.1	11.3	5.1	4.9	5.3	0.0	0.0	7.5						
PII(M6)	47	72.3	57.4	84.4	46.3	29.8	72.0	70.2	55.1	82.7	68.1	52.9	80.9	9.1	5.8	14.1
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	45	73.3	58.1	85.4	43.2	27.9	66.8	68.9	53.4	81.8	68.9	53.4	81.8	8.6	5.6	13.4
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	32	0.0	0.0	10.9	5.0	5.0	5.0	0.0	0.0	10.9						
PII(M6)	29	82.8	64.2	94.2	80.0	47.0	136.4	82.8	64.2	94.2	82.8	64.2	94.2	16.0	9.4	27.3
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	43	0.0	0.0	8.2	5.0	5.0	5.0	0.0	0.0	8.2						
PII(M6)	41	78.0	62.4	89.4	61.5	38.9	97.3	78.0	62.4	89.4	78.0	62.4	89.4	12.3	7.8	19.5

SPR = percentage with antibody titre ≥ 40 1/DIL; SCR = percentage with antibody titre ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥ 4-fold the pre-vaccination antibody titre for initially seropositive subjects; SCF = fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PII(M6) = post-vaccination at Month 6

In the Fluarix groups in each Part of the study there was no difference between the D0 and the Month 6 HI seropositivity rates and GMTs against either A/Vietnam or A/Indonesia in 3-5 year-olds or 6-9 year-olds. Therefore there was no evidence of any augmentation of the HI immune response as a result of intervening natural exposure to cross-reacting antigens between D42 and Month 6.

Against the heterologous A/Indonesia strain 69% of children aged 3 to 5 years who had received the adult dose were seroprotected at Month 6 compared to 6.0% from Part A and 48.9% from Part B of the study. Corresponding rates in children aged 6 to 9 years were 61% versus 4.5% and 26.7%.

Vaccine strain heterologous (against H5N1 A/Indonesia) immune response persistence in terms of HI antibodies at month 6

		≥ 10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
H5N1 HI Antibodies against A/Indonesia/05/2005																
Half HA/Half AS03 - 3-5 years (Phase A)																
PRE	50	0.0	0.0	7.1	5.0	5.0	5.0	0.0	0.0	7.1						
PII(M6)	50	20.0	10.0	33.7	6.9	5.6	8.4	6.0	1.3	16.5	6.0	1.3	16.5	1.4	1.1	1.7
Half HA/Half AS03 - 6-9 years (Phase A)																
PRE	42	0.0	0.0	8.4	5.0	5.0	5.0	0.0	0.0	8.4						
PII(M6)	44	18.2	8.2	32.7	6.6	5.2	8.4	4.5	0.6	15.5	2.4	0.1	12.9	1.2	1.0	1.5
Full HA/Half AS03 - 3-5 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	47	55.3	40.1	69.8	21.7	14.3	33.0	48.9	34.1	63.9	48.9	34.1	63.9	4.3	2.9	6.6
Full HA/Half AS03 - 6-9 years (Phase B)																
PRE	47	0.0	0.0	7.5	5.0	5.0	5.0	0.0	0.0	7.5						
PII(M6)	45	40.0	25.7	55.7	11.9	8.4	16.9	26.7	14.6	41.9	26.7	14.6	41.9	2.4	1.7	3.4
Full HA/Full AS03 - 3-5 years (Phase C)																
PRE	32	0.0	0.0	10.9	5.0	5.0	5.0	0.0	0.0	10.9						
PII(M6)	29	69.0	49.2	84.7	42.5	23.7	76.3	69.0	49.2	84.7	69.0	49.2	84.7	8.5	4.7	15.3
Full HA/Full AS03 - 6-9 years (Phase C)																
PRE	43	0.0	0.0	8.2	5.0	5.0	5.0	0.0	0.0	8.2						
PII(M6)	41	65.9	49.4	79.9	36.8	22.3	60.6	61.0	44.5	75.8	61.0	44.5	75.8	7.4	4.5	12.1

SPR = percentage with antibody titre ≥ 40 1/DIL; SCR = percentage with antibody titre ≥ 40 1/DIL after vaccination for initially seronegative subjects, or ≥ 4-fold the pre-vaccination antibody titre for initially seropositive subjects; SCF = fold increase in GMTs post-vaccination compared with pre-vaccination; PRE = pre-vaccination; PII(M6) = post-vaccination at Month 6

NA against A/Vietnam at Month 6 was reported from Part A of the study (i.e. half adult dose versus Fluarix) and showed that in the AS03 vaccine group the GMTs had dropped to a similar degree in both age strata. As at D42 (GMTs 1026 and 1111) the actual GMTs at D180 were comparable for children aged 3-5 years and 6-9 years (776 and 759). At Month 6 all children who had received the AS03 vaccine had NA titres of at least 1:80.

However, in the Fluarix group the GMTs increased between D42 and D180. In the younger age group (3-5 years) the increment was small (from 166 to 200) but is none the less remarkable since a drop in GMT would usually have been expected. In the older age group (6-9 years) the increase was by 6-fold (from 75 at D42 to 482 at D180). These results suggest that natural exposure to cross-reacting antigens had occurred in the interim period.

As a result the seroconversion rates in the 6-9 year-olds at Month 6 were 95% for the AS03 group and 93% for the Fluarix group. Also, all children aged 6-9 years who received Fluarix had NA titres of at least 1:80 at Month 6, while the corresponding rate in the 3-5 year-olds was 80%.

Percentage with NA titres 1:40 and 1:80 against A/Vietnam/1194/2004 on Day 180 (ATP)

					≥1:40 1/DIL				≥1:80 1/DIL			
							95% CI				95% CI	
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Vietnam	H5N1/2+AS03/2	3-5y	PRE	48	16	33.3	20.4	48.4	13	27.1	15.3	41.8
			PI(D21)	49	43	87.8	75.2	95.4	37	75.5	61.1	86.7
			PII(D42)	48	48	100	92.6	100	48	100	92.6	100

					≥1:40 1/DIL				≥1:80 1/DIL			
							95% CI				95% CI	
Antibodies against	Group	Sub-group	Timing	N	n	%	LL	UL	n	%	LL	UL
			PII(M6)	50	50	100	92.9	100	50	100	92.9	100
		6-9y	PRE	43	17	39.5	25.0	55.6	11	25.6	13.5	41.2
			PI(D21)	42	38	90.5	77.4	97.3	33	78.6	63.2	89.7
			PII(D42)	41	41	100	91.4	100	41	100	91.4	100
			PII(M6)	42	42	100	91.6	100	42	100	91.6	100
	Fluarix™	3-5y	PRE	14	2	14.3	1.8	42.8	2	14.3	1.8	42.8
			PI(D21)	15	12	80.0	51.9	95.7	10	66.7	38.4	88.2
			PII(D42)	15	12	80.0	51.9	95.7	12	80.0	51.9	95.7
			PII(M6)	15	12	80.0	51.9	95.7	12	80.0	51.9	95.7
		6-9y	PRE	14	2	14.3	1.8	42.8	1	7.1	0.2	33.9
			PI(D21)	13	9	69.2	38.6	90.9	8	61.5	31.6	86.1
			PII(D42)	14	9	64.3	35.1	87.2	8	57.1	28.9	82.3
			PII(M6)	14	14	100	76.8	100	14	100	76.8	100

NA was measured against A/Indonesia/05/2005 at Day 42, Month 6 and Month 12 in children who received half dose HA + half ASO3 (Phase A subjects) or Fluarix (control group). The Day 0 samples were erroneously not tested. These samples will be tested and the results will be submitted as they become available.

There was a significant heterologous immune response at each time point and the comparison with the control group indicates that D-Pan H5N1 elicited cross-reactive immunity. There were decreases in GMTs from D42 to Month 6 and Month 12 but the proportions with NA titres of at least 1/80 remained high in both age groups (89.6% at Month 6 and 87.2% at Month 12 in the 3-6 years group and 90.2% at Month 6 and 82.9% at Month 12 in the 6-9 years group. There was a stark contrast between NA titres in the D-Pan H5N1 group and the Fluarix control group.

Discussion on D-Pan H5N1-009

The CHMP considered that the D42 HI data did not fully discriminate between dose groups, but the Month 6 data indicated a strong advantage for using the full adult dose especially in terms of antibody against the drifted strain. Nevertheless all children in the half adult dose group were later shown to have NA titres of at least 1:80 against A/Vietnam.

The NA titres at Month 6 and Month 12 against A/Indonesia were reported later and gave a markedly different picture to that provided by the HI data against this strain up to Month 6. On the basis of these additional NA data, as well as the previous observation that all children who received the half adult dose still had NA titres against A/Vietnam at Month 6, the SPC for Pandemrix (H1N1)v suggests that half the adult dose (i.e. 0.25 ml vaccine) may be sufficient for children aged < 10 years.

There are no data on the use of Q-Pan H5N1 or Arepanrix in children. Study Q-Pan-001 in adults supports a conclusion that the data obtained from D-Pan H5N1-009 in children may provide an indication of how Q-Pan H5N1 would perform in the same age group. On this basis it is proposed that the Arepanrix SPC carries the same dose recommendations as the Pandemrix SPC for children. Emerging data with Pandemrix in children, which are expected before data with Arepanrix, should be reflected in both SPCs until such time as Arepanrix-specific data become available from various age groups.

Study H1N1-017

This is a Phase III, multi-centre, observer-blind, randomised (1:1) study with two parallel groups in approximately 320 healthy subjects aged 18-60 years. Each group received either Arepanrix or Pandemrix at Day 0 and Day 21.

The primary objective of the study is to assess immunological equivalence (in terms of vaccine-homologous virus H1N1 HI antibody GMTs) between Arepanrix and Pandemrix at D21 based on limits of two-sided 95% CI for the GMT ratio within the 0.5 - 2.0 interval.

One of the secondary objectives was to assess immunological equivalence in terms of seroconversion rates at D21 based on two-sided 95% CIs for the difference in SCRs falling within the -10% to +10% interval.

The study actually enrolled 167 subjects into each group of which one subject in the Pandemrix group had withdrawn consent up to D21. The mean age of subjects was 40 years and there was an equal split between genders. The history of prior seasonal influenza vaccinations was as follows:

Supplement 12 History of influenza vaccination in the last 3 seasons (Total vaccinated cohort)

		Q-PAN N = 167		D-PAN N = 167		Total N = 334	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
One season at least	Yes	81	48.5	77	46.1	158	47.3
	No	86	51.5	90	53.9	176	52.7
Season 1= 2007-2008	Yes	63	37.7	57	34.1	120	35.9
	N	104	62.3	110	65.9	214	64.1
Season 2= 2008-2009	Yes	55	32.9	54	32.3	109	32.6
	N	112	67.1	113	67.7	225	67.4
Season 3= 2009-2010	Yes	18	10.8	18	10.8	36	10.8
	N	149	89.2	149	89.2	298	89.2

Prior to vaccination 43% in the Arepanrix group and 38% in the Pandemrix group were HI seropositive with respect to the vaccine strain with GMTs around 10. However, only 11% and 13% per group were already seroprotected. At D21 all subjects were seropositive with overall GMTs of 334 and 386 in respective groups. The second table below shows that the comparison of overall GMTs met the pre-defined criterion for immunological equivalence.

Supplement 13 Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09.HA1 Ab (ATP cohort for immunogenicity)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09 .HA1 Ab	Q-PAN	PRE	164	71	43.3	35.6	51.2	10.4	8.9	12.2	<10.0	453.0
		PI(D21)	164	164	100	97.8	100	333.8	282.5	394.4	10.0	2560.0
	D-PAN	PRE	164	63	38.4	30.9	46.3	9.3	8.0	10.8	<10.0	226.0
		PI(D21)	164	164	100	97.8	100	386.3	330.0	452.2	40.0	3620.0

Table 1 Adjusted GMT ratios for HI antibodies against A/California/7/2009(H1N1)v-like strain, 21 days after the first vaccine dose, between D-PAN and Q-PAN groups (D-PAN / Q-PAN) with their 95% CIs (ATP cohort for immunogenicity)

						Adjusted GMT ratio			
								95% CI	
Group description	N	Adjusted GMT	Group description	N	Adjusted GMT	Ratio order	Value	LL	UL
D-PAN	164	393.1	Q-PAN	164	328.0	D-PAN /Q-PAN	1.20	0.96	1.49

The overall study results also showed that all CHMP criteria were met in both vaccine groups after the first dose with comparable SCRs, SPRs and SCFs although there was a trend to slightly lower rates in the Arepanrix group and the SCFs reflected the slightly lower GMT in the Arepanrix group.

Table 2 H1N1 HI Antibodies against A/California/7/2009 (H1N1) (ATP cohort for immunogenicity)

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
D-PAN group																
PRE	164	38.4	30.9	46.3	9.3	8.0	10.8	11.6	7.1	17.5	-	-	-	-	-	-
PI(D21)	164	100	97.8	100	386.3	330.0	452.2	100	97.8	100	97.6	93.9	99.3	41.5	34.3	50.2
Q-PAN group																
PRE	164	43.3	35.6	51.2	10.4	8.9	12.2	13.4	8.6	19.6	-	-	-	-	-	-
PI(D21)	164	100	97.8	100	333.8	282.5	394.4	97.6	93.9	99.3	93.9	89.1	97.0	32.0	26.5	38.6

The comparison of SCRs also met the pre-defined criterion for immunological equivalence since the 95% CI fell within (-0.82 and 8.74).

Supplement 17 Difference between groups in terms of seroconversion rates, 21 days after the first vaccine dose (ATP cohort for immunogenicity)

								Difference in vaccine response rate (D-PAN minus Q-PAN)		
		D-PAN			Q-PAN				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	Total	164	160	97.6	164	154	93.9	3.66	-0.82	8.74

The D21 GMTs in each group were higher in the subsets already seropositive at baseline (485 Arepanrix and 448 Pandemrix in the two vaccine groups) compared to those previously seronegative (251 Arepanrix and 352 Pandemrix). In each case the 95% CI overlapped despite the numerically lower GMT for Arepanrix in the seronegative subset.

Supplement 19 Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09.HA1 Ab by serostatus at prevaccination (ATP cohort for immunogenicity)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09.HA1 Ab	Q-PAN	seroneg	PRE	93	0	0.0	0.0	3.9	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	93	93	100	96.1	100	251.1	202.5	311.4	10.0	2560.0
		seropos	PRE	71	71	100	94.9	100	27.4	22.2	33.8	10.0	453.0
			PI(D21)	71	71	100	94.9	100	484.5	380.5	617.0	28.0	2560.0
	D-PAN	seroneg	PRE	101	0	0.0	0.0	3.6	5.0	5.0	5.0	<10.0	<10.0
			PI(D21)	101	101	100	96.4	100	352.3	291.8	425.3	40.0	2560.0
		seropos	PRE	63	63	100	94.3	100	25.2	19.8	32.0	10.0	226.0
			PI(D21)	63	63	100	94.3	100	447.7	338.2	592.5	40.0	3620.0

Comparisons of GMTs in each subgroup according to baseline serostatus met the pre-defined criterion for equivalence in each case.

Supplement 23 Adjusted GMT ratios for HI antibodies against A/California/7/2009(H1N1)v-like strain, 21 days after the first vaccine dose, between D-PAN and Q-PAN groups by serostatus (D-PAN / Q-PAN) with their 95% CIs (ATP cohort for immunogenicity)

						Adjusted GMT ratio			
								95% CI	
Group description	N	Adjusted GMT	Group description	N	Adjusted GMT	Ratio order	Value	LL	UL
D-PAN/seroneg	101	448.3	Q-PAN/seroneg	93	319.5	D-PAN/seroneg / Q-PAN/seroneg	1.40	1.06	1.86
D-PAN/seropos	63	321.0	Q-PAN/seropos	71	337.0	D-PAN/seropos / Q-PAN/seropos	0.95	0.68	1.34

All subjects in the Pandemrix group were seroprotected at D21. The SPRs were over 96% in the Arepanrix group regardless of baseline HI status.

Supplement 20 Seroprotection rates (SPR) for HI antibodies against Flu A/CAL/7/09.HA1 Ab at visit 1 Day 0 and visit 2 Day 21 by serostatus at prevaccination (ATP cohort for immunogenicity)

					SPR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09.HA1 Ab	Q-PAN	seroneg	PRE	93	0	0.0	0.0	3.9
			PI(D21)	93	90	96.8	90.9	99.3
		seropos	PRE	71	22	31.0	20.5	43.1
			PI(D21)	71	70	98.6	92.4	100
	D-PAN	seroneg	PRE	101	0	0.0	0.0	3.6
			PI(D21)	101	101	100	96.4	100
		seropos	PRE	63	19	30.2	19.2	43.0
			PI(D21)	63	63	100	94.3	100

The SCRs in those who were already seropositive at baseline were comparable between groups and in each case exceeded 90%.

Supplement 21 Seroconversion rate (SCR) for HI antibodies against Flu A/CAL/7/09.HA1 Ab at visit 2 Day 21 serostatus at prevaccination (ATP cohort for immunogenicity)

					SCR			
							95% CI	
Strain	Group	Sub-group	Timing	N	n	%	LL	UL
Flu A/CAL/7/09.HA1 Ab	Q-PAN	seroneg	PI(D21)	93	90	96.8	90.9	99.3
		seropos	PI(D21)	71	64	90.1	80.7	95.9
	D-PAN	seroneg	PI(D21)	101	101	100	96.4	100
		seropos	PI(D21)	63	59	93.7	84.5	98.2

Comparisons of SCRs in each subgroup according to baseline serostatus met the pre-defined criterion for equivalence in the seronegative subset but not in the seropositive subset (UL > 10%).

Supplement 24 Difference between groups in terms of seroconversion rates, 21 days after the first vaccine dose by serostatus (ATP cohort for immunogenicity)

								Difference in vaccine response rate (D-PAN minus Q-PAN)		
		D-PAN			Q-PAN				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	S-	101	101	100	93	90	96.8	3.23	-0.52	9.08
	S+	63	59	93.7	71	64	90.1	3.51	-6.70	13.66

The SCFs were 18 in each vaccine group for subjects already seropositive at baseline. SCFs in the previously seronegative subset were 50 for Arepanrix and 70 for Pandemrix.

Supplement 22 Seroconversion factor (SCF) for HI antibody titer at each post-vaccination time point by serostatus at prevaccination (ATP cohort for immunogenicity)

					SCF		
						95% CI	
Vaccine strain	Group	Sub-group	Timing	N	Value	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	Q-PAN	seroneg	PI(D21)	93	50.2	40.5	62.3
		seropos	PI(D21)	71	17.7	13.3	23.4
	D-PAN	seroneg	PI(D21)	101	70.5	58.4	85.1
		seropos	PI(D21)	63	17.8	13.3	23.8

Tables were also provided that compared responses by prior vaccination history. As shown below, the rates of pre-vaccination HI seropositivity were higher in each vaccine group in those with a history (> 50% vs. >25%) but GMTs were in the range 7-14. The D21 GMTs were from 303 to 456 but all 95% overlapped and GMTs were lower in those with a vaccine history in each group.

Other features in these tables were SPR of 100% in Arepanrix subjects with no history vs. 95% in those with a history and slightly lower SCRs in those with a history. The SCFs were much lower for those with vs. those without a history (95% do not overlap) within each vaccine group but the comparisons between corresponding subsets in the Arepanrix and Pandemrix groups all gave overlapping 95% CI.

Supplement 26 Seropositivity rates and GMTs for HI antibodies against Flu A/CAL/7/09.HA1 Ab by history of flu vaccination (ATP cohort for immunogenicity)

					>= 10 1/DIL				GMT				
							95% CI			95% CI			
Antibody	Group	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Flu A/CAL/7/09.HA1 Ab	Q-PAN	Yes	PRE	80	47	58.8	47.2	69.6	13.9	10.9	17.8	<10.0	226.0
			PI(D21)	80	80	100	95.5	100	303.7	233.4	395.2	10.0	2560.0
		No	PRE	84	24	28.6	19.2	39.5	7.9	6.5	9.6	<10.0	453.0
			PI(D21)	84	84	100	95.7	100	365.2	295.6	451.1	40.0	2560.0
	D-PAN	Yes	PRE	76	41	53.9	42.1	65.5	12.1	9.5	15.4	<10.0	226.0
			PI(D21)	76	76	100	95.3	100	318.6	250.7	404.9	40.0	2560.0
		No	PRE	88	22	25.0	16.4	35.4	7.4	6.2	8.9	<10.0	226.0
			PI(D21)	88	88	100	95.9	100	456.2	371.2	560.6	40.0	3620.0

Comparisons of GMTs and SCRs by history of seasonal vaccination showed that the pre-defined criteria were met except for SCRs in those with a vaccination history (UL > 10%).

Supplement 30 Adjusted GMT ratios for HI antibodies against A/California/7/2009(H1N1)v-like strain, 21 days after the first vaccine dose, between D-PAN and Q-PAN groups by history of flu vaccination (D-PAN / Q-PAN) with their 95% CIs (ATP cohort for immunogenicity)

						Adjusted GMT ratio			
								95% CI	
Group description	N	Adjusted GMT	Group description	N	Adjusted GMT	Ratio order	Value	LL	UL
D-PAN/No	88	505.9	Q-PAN/No	84	395.1	D-PAN/No /Q-PAN/No	1.28	0.95	1.72
D-PAN/Yes	76	295.8	Q-PAN/Yes	80	267.8	D-PAN/Yes /Q-PAN/Yes	1.10	0.81	1.51

Supplement 31 Difference between groups in terms of seroconversion rates, 21 days after the first vaccine dose by history of flu vaccination (ATP cohort for immunogenicity)

								Difference in vaccine response rate (D-PAN minus Q-PAN)		
		D-PAN			Q-PAN				95% CI	
Antibody	Pre-vaccination status	N	n	%	N	n	%	%	LL	UL
Flu A/CAL/7/09.HA1 Ab (1/DIL)	Yes	76	73	96.1	80	72	90.0	6.05	-2.33	15.17
	No	88	87	98.9	84	82	97.6	1.24	-4.04	7.29

Data generated with Pandemrix (D-Pan, H1N1) in infants, children, adolescents and elderly:

Infants and children aged 6-35 months of age:

In variation II/025 the MAH of Pandemrix provided an abridged study report describing safety and immunogenicity data following vaccination with one half of the adult dose of Pandemrix (i.e. 1.9 µg HA +$AS03_B$) in 51 children aged 6-35 months. The safety and HI immune response data were reported according to the three pre-defined age strata with 17 subjects per stratum. These data raised no particular concerns and have already been summarised in the SPC. The CHMP did not feel able ath the time of this variation to recommend the option of a single half adult dose in this age group based only on the HI data available.

Variation Pandemrix II-28 was based on further information sent from the MAH to the Rapporteur between November 20th and December 2nd, including the data filed in the variation received 27th November 2009.

In a study H1N1-009 in healthy children 6 months to 35 months of age (stratified in ranges from 6 to 11, 12 to 23 and 24-35 months of age) the anti-HA antibody responses 21 days after a first and a second half adult dose (i.e. 0.25 ml) of Pandemrix were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like						
	6-11 months			12-23 months[4]		24-35 months[4]	
	Post dose 1	Post dose 2	Post dose 1	Post dose 1	Post dose 2	Post dose 1	Post dose 2
	Total enrolled subjects [95% CI]		Seronegative subjects prior to vaccination [95% CI]	Total enrolled subjects [95% CI]		Total enrolled subjects [95% CI]	
	N=17	N = 17	N=14	N=17	N= 16	N=16	N= 17
Seroprotection rate[1]	100% [80.5; 100]	100% [80.5; 100]	100% [76.8;100]	100% [80.5; 100]	100% [79.4; 100]	100% [79.4; 100]	100% [80.5; 100]
Seroconversion rate[2]	94.1% [71.3; 99.9]	100% [80.5; 100]	100% [76.8;100]	100% [80.5; 100]	100% [79.4; 100]	100% [79.4; 100]	100% [80.5; 100]
Seroconversion factor[3]	44.4 [24.1; 81.5]	221.9 [102.6; 480.2]	70.67 [51.91; 96.20]	76.9 [55.7; 106.1]	378.0 [282.0; 506.7]	53.8 [40.7; 71.1]	409.1 [320.7; 521.9]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.
[4]all subjects seronegative prior to vaccination

The clinical relevance of the haemagglutination inhibition (HI) titre ≥1:40 in children is unknown.

Analysis of a subset of 36 subjects aged 6 months to 35 months old showed that 80.6 % had a 4 fold increase in serum neutralising antibodies 21 days after the first dose (66.7 % in 12 subjects aged 6 to 11 months old, 91.7 % in 12 subjects aged 12 to 23 months old and 83.3 % in 12 subjects aged 24 to 35 months old).

The HI data after each half adult dose demonstrated a marked immune response to the second dose in terms of increments in GMTs in each of the three age strata. The limited post-dose 1 NA data from CDC support a conclusion that there is a good response to a first half adult dose but likely leave room for a marked increment in NA also to occur after a second dose. The available data are insufficient to indicate whether a single half adult dose in this age group would be sufficient but this hypothesis cannot be ruled out.

Children aged 3 to 9 years
In study H1N1-023 in which children aged 3 to 9 years old received a half adult dose (0.25 ml) of Pandemrix derived from A/California/7/2009 (H1N1)v-like the anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	3-5 years		6-9 years	
	Total enrolled subjects N=30 [95% CI]	Seronegative subjects prior to vaccination N=27 [95% CI]	Total enrolled subjects N=30 [95% CI]	Seronegative subjects prior to vaccination N=29 [95% CI]
Seroprotection rate[1]	100% [88.4;100]	100% [87.2;100]	100% [88.4;100]	100% [88.1;100]
Seroconversion rate[2]	100% [88.4;100]	100% [87.2;100]	100% [88.4;100]	100% [88.1;100]
Seroconversion factor[3]	32.4 [25.4;41.2]	36.4 [29.1;45.4]	36.3 [28.0;47.2]	37.4 [28.7;48.7]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Children aged 10-17 years

Two clinical studies (H1N1-017 and H1N1-023, assessed within Pandemrix variations II-032 and II-033) evaluated the immunogenicity of a half (0.25 ml) dose and a full (0.5 ml) adult dose of Pandemrix in healthy children 10 to 17 years of age. The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like			
	Half dose		Full dose	
	Total enrolled subjects N=58 [95% CI]	Seronegative subjects prior to vaccination N=38 [95% CI]	Total enrolled subjects N=97 [95% CI]	Seronegative subjects prior to vaccination N=61 [95% CI]
Seroprotection rate[1]	98.3% [90.8;100]	97.4% [86.2;99.9]	100% [96.3;100]	100% [94.1;100]
Seroconversion rate[2]	96.6% [88.1;99.6]	97.4% [86.2;99.9]	96.9% [91.2;99.4]	100% [94.1;100]
Seroconversion factor[3]	46.7 [34.8;62.5]	67.0 [49.1;91.3]	69.0 [52.9;68.4]	95.8 [78.0;117.7]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Elderly (>60 years)

Another clinical study (H1N1-008) assessed for Pandemrix variation II-23, evaluated immunogenicity in healthy subjects (N=120) aged >60 years (stratified in ranges from 61 to 70, 71 to 80 and > 80 years of age). The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	Immune response to A/California/7/2009 (H1N1)v-like					
	61-70 years		71-80 years		>80 years	
	Total enrolled subjects N=75 [95% CI]	Seronegative subjects prior to vaccination N=43 [95% CI]	Total enrolled subjects N=40 [95% CI]	Seronegative subjects prior to vaccination N=23 [95% CI]	Total enrolled subjects N=5 [95% CI]	Seronegative subjects prior to vaccination N=3 [95% CI]
Seroprotection rate[1]	88.0% [78.4;94.4]	81.4% [66.6;91.6]	87.5% [73.2;95.8]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion rate[2]	80.0% [69.2;88.4]	81.4% [66.6;91.6]	77.5% [61.5;89.2]	82.6% [61.2;95.0]	80.0% [28.4;99.5]	66.7% [9.4;99.2]
Seroconversion factor[3]	13.5 [10.3;17.7]	20.3 [13.94;28.78]	13.5 [8.6;21.1]	20.67 [11.58;36.88]	18.4 [4.3;78.1]	17.95 [0.55;582.25]

[1] seroprotection rate: proportion of subjects with haemagglutination inhibition (HI) titre ≥1:40;
[2]seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre;
[3]seroconversion factor: ratio of the post-vaccination geometric mean titre (GMT) and the pre-vaccination GMT.

Overall discussion on immunogenicity

The applicant has conducted a full clinical development programme with Q-Pan/AS03 vaccine containing H5N1 antigens. There are sufficient data in adults that sections 4.8 and 5.1 of the SPC can reflect the Q-Pan H5N1 data. While the data from D-Pan H5N1-009 were considered supportive to include dose recommendations for children, the CHMP considered that the available data generated so far with D-Pan H1N1 (Pandemrix) in infants, children, adolescents and elderly should be included in the PI.

The CHMP further considered that the dose recommendations for Arepanrix should match those for Pandemrix except that the introductory sentence in 4.2 and the relevant sections in 5.1 should clarify which data were obtained with Pandemrix , Q-Pan H5N1 or with Arepanrix (H1N1).

In addition, the CHMP highlighted that the baseline serostatus of subjects in study H1N1-017 was comparable with that reported in the Pandemrix H1N1 studies thus far in subjects aged 18-60 years.

The HI data at D21 showed that both vaccines elicited immune responses that met the CHMP criteria regardless of baseline serostatus and prior vaccination history. There was a trend to lower HI responses in the Arepanrix group but the pre-defined equivalence criteria for GMT and SCR comparisons were met overall and in each subgroup by baseline serostatus. These comparisons also met the pre-defined criteria according to seasonal influenza vaccination history with the exception of SCRs in the subjects with such a history.

Clinical safety

Due to the variability in study designs and populations the safety data are described by study.

Q-Pan-001 and Q-Pan -002

Overall 2369 subjects aged 18-64 years and another 1087 subjects aged > 64 years received at least one dose of Q-Pan and were eligible for the ATP safety cohort. The numbers of doses evaluated for reactogenicity were 7048 for Q-Pan and 298 for D-Pan in these two studies.

In Q-Pan-001 pain was the most commonly reported solicited local symptom. There was no evidence of increasing local reactogenicity as a function of the second dose. Incidences of solicited local symptoms following vaccination with Q-Pan or D-Pan vaccines with full dose AS03 were comparable.

Solicited local symptoms (per dose) in study Q-Pan-001 (Total vaccinated cohort)

Study (schedule)	N	Intensity	Pain			Redness			Swelling		
			%	95%CI		%	95%CI		%	95%CI	
Group				LL	UL		LL	UL		LL	UL
H5N1 split **Quebec**	301	Total	81.7	76.9	85.9	2.3	0.9	4.7	6.0	3.6	9.3
(HA 3.8µg) **AS03 full**	301	Grade 3	4.0	2.1	6.9	0.0	0.0	1.2	0.0	0.0	1.2
H5N1 split **Dresden**	298	Total	85.2	80.7	89.1	4.0	2.1	6.9	9.1	6.1	12.9
(HA 3.8µg) **AS03 full**	298	Grade 3	3.7	1.9	6.5	0.0	0.0	1.2	0.0	0.0	1.2

In Q-Pan-002 pain was the most commonly reported solicited local symptom in subjects aged < 65 years both the Q-Pan group and the placebo group while redness and swelling were much less common. Local reactogenicity did not worsen after the second dose relative to the first dose. In those aged >64 years pain was again the most commonly reported solicited local symptom in both the Q-Pan group and the placebo group but was reported at slightly lower rates than in younger subjects in this same study. Rates for grade 3 pain were 0.8% with Q-Pan versus 0.3% in the placebo group and were lower than in the younger age group. Redness and swelling were much less common than pain in both treatment groups and only one Q-Pan vaccine dose was followed by swelling >100 mm with no medical attention required for any solicited local adverse event.

In Q-Pan-001 muscle ache was the most commonly reported solicited general symptom and was reported at much higher rates in the groups receiving adjuvanted vaccine (30.9%-41.6%) but rates of grade 3 muscle aches were 1-4%. Incidences of solicited general symptoms following vaccination with Q-Pan or D-Pan vaccines were similar when formulated with the same adjuvant content.

In Q-Pan-002 subjects aged 18-64 years muscle ache was the most commonly reported solicited general symptom and was reported at a higher rate for the Q-Pan group (39.3% of doses) than the placebo group (13% of doses). The incidence of grade 3 muscle aches was 2.3% of doses in the Q-Pan group and 1.1% in the placebo group. In those aged > 64 years incidences of general symptoms were lower than in the younger age group. Muscle ache was again the most common although grade 3 muscle ache was reported by 0.6-0.7%.

In Q-Pan-001 at least one unsolicited AE was reported following 24.5% of doses in the group receiving non-adjuvanted Q-Pan vaccine, 27.2% and 25.1% in the groups receiving Q-Pan vaccine with full and half dose AS03, respectively, and 30.2% and 36.3% in the group receiving D-Pan vaccine with full and half dose AS03 No adverse event was reported following more than 5% of doses in a treatment group.

Vaccine-related unsolicited AEs were reported following 7.1% of doses of non-adjuvanted Q-Pan vaccine, 12.6% and 10.0% of doses of Q-Pan vaccine with full and half dose AS03, respectively, and 14.4% and 13.7% of doses of D-Pan vaccine full and half dose AS03, respectively. The only vaccine-related unsolicited AE reported with an incidence greater than 2.5% in a treatment group was nausea, which was reported following 0.6% to 3.0% per group. The other most commonly reported vaccine-

related AEs (reported following more than 1% of doses in a treatment group) were lymphadenopathy and headache.

In the younger age cohort of Q-Pan-002 at least one unsolicited AE was reported following 24.5% of doses in the Q-Pan group and 23.4% in the placebo group. No single adverse event was reported with more than 2.5% of doses. Lymphadenopathy occurred following 0.5% of Q-Pan doses and 0.9% of placebo doses. Vaccine-related unsolicited AEs were reported following 10% of Q-Pan vaccine doses and 6.2% of placebo doses. The only vaccine-related unsolicited AEs reported following more than 0.5% of doses in either treatment group were nausea (1.1% Q-Pan and 0.9% placebo), injection site pruritus (0.9% and 0.2%), injection site warmth (0.9% and 0.1% of doses) and lymphadenopathy (0.5% and 0.7%).

In the older cohort at least one unsolicited (AE) was reported following 21.8% of Q-Pan doses and 18.1% of placebo doses. No adverse event was reported with more than 1.7% of doses in either treatment group. Vaccine-related unsolicited AEs were reported following 6.9% of doses in the Q-Pan group and 4.5% of doses in the placebo group. Grade 3 unsolicited AEs were reported following 2.2% of Q-Pan vaccine doses and 2.6% placebo doses. The most commonly reported were back pain (0.2% versus 0.1%), diarrhoea, nausea and vomiting (each 0.1% per group).

There were no reports of NOCD up to D42 in Q-Pan-001. One subject up to D182 had a breast mass (Q-Pan with full dose AS03) that met the criteria for a NOCD but was not considered treatment-related. Screening of the database for AEs with potential immune-mediated causation up to Day 182 identified reports in <3% of subjects overall, including 2.6% in the non-adjuvanted HA group, 2.0%, and 2.6% in the Q-Pan groups and 2.6% and 1.4% in the D-Pan groups. Many of these events seemed to be due to concurrent conditions or other environmental exposures, and essentially all proved to be transient and did not establish chronicity.

In Q-Pan-002 reports of preferred terms listed as AESI/IMDs included 7 events in the Q-Pan group (facial palsy, fourth cranial nerve palsy, erythema nodosum, psoriasis [2 subjects] and polymyalgia rheumatica [2 subjects] and one in the placebo group (ocular myasthenia). None of these symptoms was considered vaccine-related by the investigators and none was an SAE. The 3:1 randomisation must be taken into account when considering potential associations with this relatively uncommon set of conditions.

Six subjects died in study Q-Pan-002 including one death within D42 from myocardial infarction in a 59-year-old male at 17 days following one dose of Q-Pan. The other five deaths (3 in the Q-Pan group) occurred between Day 42 and Day 182 of which three had received Q-Pan. All events were considered by the investigator to be not related to vaccination.

No vaccine-related SAEs were reported up to Day 182 in Q-Pan-001. Up to D182 there were 15 SAEs reported in six subjects of which four in two subjects occurred before D42. As shown in the table 3/302 (1%) subjects in the Q-Pan group reported a total of 4 SAEs of which two received the full dose vaccine. In addition, 3/299 (1%) vaccinated with one of the AS03-adjuvanted D-Pan vaccine formulations reported 11 SAEs including two subjects with 3 SAEs in the full dose D-Pan group.

In Q-Pan-002 up to D42 in the age stratum 18-64 years, 8 subjects (0.3%) who received Q-Pan and one subject (0.1%) in the placebo group reported one SAE each. In the age stratum >64 years, 10 SAEs were reported by 8 subjects (0.7%) in the Q-Pan group and 2 subjects (0.5%) reported each one SAE in the placebo group. Up to D182 67/88 subjects that reported at least one SAE received Q-Pan (24 subjects aged 18-64 years and 43 subjects aged >64 years). None of the SAEs was assessed as related to vaccination by the investigator.

No subjects dropped out due to a serious or a non-serious AE through Day 182 in Q-Pan-001. In Q-Pan-002 up to D182 there were 14 subjects with serious (9; 4 Q-Pan and 5 placebo group) or non-serious AEs that led to premature discontinuation. One additional subject recorded as lost to follow-up in the Q-Pan group experienced a fatal SAE that was reported at later stage. None of the SAEs leading to discontinuation were considered by the investigator to be related to vaccination. Five subjects experienced non-serious AEs leading to discontinuation through D182 (3 subjects [0.1%] in the Q-Pan vaccine group and 2 subjects [0.2%] in the placebo group).

Q-Pan 010

In the booster phase of Q-Pan-001 the percentage of subjects reporting any symptom (solicited or unsolicited, local or general) was approximately twice as high in the treatment groups receiving adjuvanted booster vaccine (Groups A, B1, C1, D1 and E1) in comparison to groups receiving unadjuvanted booster vaccine (Groups B2, C2, D2 and E2). In particular, the incidence of local symptoms reported was much higher for adjuvanted booster vaccine recipients.

The overall incidence of Grade 3 symptoms ranged from 0 to 13.6%. A larger percentage of subjects in the adjuvanted booster groups experienced Grade 3 general and local symptoms compared with the unadjuvanted booster groups but only in the isolated case of group E1 was this difference substantial. Grade 3 local symptoms occurred in three subjects, all of whom received adjuvanted booster vaccine. In Group E1 there was a variety of Grade 3 solicited general symptoms, none of which required medical attention.

Table 30 Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following the booster dose (Total vaccinated cohort)

Group	Any symptom					General symptoms					Local Symptoms				
				95% CI					95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
A	49	45	91.8	80.4	97.7	49	22	44.9	30.7	59.8	49	42	85.7	72.8	94.1
B1	72	60	83.3	72.7	91.1	72	40	55.6	43.4	67.3	72	59	81.9	71.1	90.0
B2	41	17	41.5	26.3	57.9	41	11	26.8	14.2	42.9	41	10	24.4	12.4	40.3
C1	60	55	91.7	81.6	97.2	60	37	61.7	48.2	73.9	60	53	88.3	77.4	95.2
C2	40	16	40.0	24.9	56.7	40	12	30.0	16.6	46.5	40	10	25.0	12.7	41.2
D1	61	52	85.2	73.8	93.0	61	36	59.0	45.7	71.4	61	48	78.7	66.3	88.1
D2	46	17	37.0	23.2	52.5	46	12	26.1	14.3	41.1	46	13	28.3	16.0	43.5
E1	59	51	86.4	75.0	94.0	59	39	66.1	52.6	77.9	59	46	78.0	65.3	87.7
E2	41	20	48.8	32.9	64.9	41	17	41.5	26.3	57.9	41	6	14.6	5.6	29.2

A = Q-Pan Indo 3.8 x 2 + Turkey 3.8, $AS03_A$
B1 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8, $AS03_A$
B2 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8
C1 = Q-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8, $AS03_A$
C2 = Q-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8
D1 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8, $AS03_A$
D2 = Q-Pan Indo 3.8, $AS03_A$ x 2 + Turkey 3.8
E1 = Q-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8, $AS03_A$
E2 = Q-Pan Indo 3.8, $AS03_B$ x 2 + Turkey 3.8

Pain at the injection site was reported by 79-88% in the adjuvanted booster vaccine groups and 14-28% in the unadjuvanted booster vaccine groups. Only three subjects reported Grade 3 pain while Grade 2 pain was reported by 104 subjects, most of whom had received adjuvanted booster vaccination. Redness and swelling were much less common than pain in all treatment groups. One subject in Group D2, who received an unadjuvanted booster, reported swelling. No other cases of swelling and no cases of redness were reported in the unadjuvanted booster vaccine groups. Large areas of redness or swelling (> 100 mm) were not reported by any subject and no subject sought medical attention for any solicited local AE.

There was a slightly higher frequency of solicited general symptoms and Grade 3 symptoms for all groups with adjuvanted booster vaccine but there was no marked difference by age stratum. Muscle ache was the most commonly reported solicited general symptom overall and was reported at a higher rate for recipients of adjuvanted booster vaccine. The overall incidence of muscle ache was from 7-35% per group but only 0-7% per group reported severe muscle ache (Grade 3). Headache, fatigue and joint pain were very common with 15.5-25.3% of all subjects reporting these events and with generally greater incidence rates reported among the adjuvanted booster vaccine groups. Grade 3 fatigue, headache or joint pain was reported by 0-8.6% per group with highest rates among the adjuvanted booster vaccine recipients.

Shivering, sweating and temperature elevation were reported by < 10% across all treatment groups. The incidence of temperature elevation was low, with 0-7% per group reporting this symptom. Severe shivering, sweating and elevated temperature were reported by 0-3.4% per group. Oral temperature ≥ 38.5º C occurred in one subject in Group D1.

There was a specific physical examination to assess the bilateral axillary and supraclavicular lymph nodes at all study visits. Lymph node pain was reported in one subject in Group D1 and lymphadenopathy was reported by four subjects (two in Group D1 and one in each of Groups B1 and E2). These AEs were deemed to be treatment-related by the investigators. None was severe (Grade 3) and none resulted in medically-attended visits.

At least one unsolicited AE was reported by 150 subjects with a higher rate in those who received adjuvant vaccine for priming and boosting. The most commonly reported events for subjects in all treatment groups were headache, nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, nausea, cough, diarrhoea and bronchitis, none of which showed a clear trend between groups or association with adjuvant. Grade 3 unsolicited AEs were reported by 2.4 - 7.3% per group. Vaccine-related unsolicited AEs were reported by 2.5 - 13.3% per group. Of these, diarrhoea, lymphadenopathy, injection site warmth, pain in extremity and headache were reported by a slightly higher proportion who received an adjuvanted booster.

Two SAEs of acute appendicitis and thyroid cancer were reported but both events were considered by the investigators to be unrelated to study vaccine. No subjects died during the study through Day 42 and no subjects experienced an AE or SAE that led to premature discontinuation.

Q-Pan 009

The percentage of subjects reporting any symptom (solicited or unsolicited, local or general) was similar among all treatment groups in this study. The overall incidence of symptoms was similar among all groups for both doses, although the proportion of subjects reporting either local or general symptoms declined modestly after the second dose relative to the first in all treatment groups.

The overall per subject incidence of Grade 3 symptoms in Groups A, B, C, and D was 9.0%, 17.9%, 16.7% and 6.4% of subjects, respectively. A larger percentage of subjects in Groups A and B experienced Grade 3 symptoms (any symptom) after dose 2 than after dose 1. This trend was also seen for general symptoms.

Pain was the most commonly reported solicited local symptom in all treatment groups and was reported at similar rates for all groups (around 80%). Redness and swelling were much less common than pain in all treatment groups and large areas of redness or swelling were very infrequent. No subjects reported redness or swelling > 100 mm in any treatment group while five reported redness > 50 mm and eight reported swelling > 50 mm.

Table 36 Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

	Group	Any symptom					General symptoms					Local symptoms				
		N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Dose 1	Q-Pan A	78	63	80.8	70.3	88.8	78	51	65.4	53.8	75.8	78	54	69.2	57.8	79.2
	Q-Pan B	78	67	85.9	76.2	92.7	78	51	65.4	53.8	75.8	78	62	79.5	68.8	87.8
	Q-Pan C	78	62	79.5	68.8	87.8	78	48	61.5	49.8	72.3	78	60	76.9	66.0	85.7
	Q-Pan D	78	67	85.9	76.2	92.7	78	50	64.1	52.4	74.7	78	65	83.3	73.2	90.8
Dose 2	Q-Pan A	72	59	81.9	71.1	90.0	72	47	65.3	53.1	76.1	72	47	65.3	53.1	76.1
	Q-Pan B	76	60	78.9	68.1	87.5	76	45	59.2	47.3	70.4	76	56	73.7	62.3	83.1
	Q-Pan C	77	58	75.3	64.2	84.4	77	43	55.8	44.1	67.2	77	49	63.6	51.9	74.3
Overall/dose	Q-Pan A	150	122	81.3	74.2	87.2	150	98	65.3	57.1	72.9	150	101	67.3	59.2	74.8
	Q-Pan B	154	127	82.5	75.5	88.1	154	96	62.3	54.2	70.0	154	118	76.6	69.1	83.1
	Q-Pan C	155	120	77.4	70.0	83.7	155	91	58.7	50.5	66.5	155	109	70.3	62.5	77.4
	Q-Pan D	78	67	85.9	76.2	92.7	78	50	64.1	52.4	74.7	78	65	83.3	73.2	90.8
Overall/subject	Q-Pan A	78	67	85.9	76.2	92.7	78	59	75.6	64.6	84.7	78	60	76.9	66.0	85.7
	Q-Pan B	78	68	87.2	77.7	93.7	78	57	73.1	61.8	82.5	78	64	82.1	71.7	89.8
	Q-Pan C	78	67	85.9	76.2	92.7	78	56	71.8	60.5	81.4	78	65	83.3	73.2	90.8
	Q-Pan D	78	67	85.9	76.2	92.7	78	50	64.1	52.4	74.7	78	65	83.3	73.2	90.8

Muscle ache was the most commonly reported solicited general symptom overall (51-64.5%) while severe muscle ache (Grade 3) occurred in < 8% per group. Fatigue, headache and joint pain were fairly common, with rates of 14.3-39.0% per subject and with similar incidences reported among the different treatment groups but Grade 3 events were reported in 1.3-5.3%. The remaining solicited general symptoms (shivering, sweating, and temperature elevation) were reported by < 20% of subjects overall across all treatment groups. Temperatures ≥ 39º C were reported by 2.6% of subjects in Group B and by no subjects in all other treatment groups.

At least one unsolicited AE was reported by 139 subjects overall but no AE was reported by more than 6.4% of subjects in a treatment group. The most commonly reported events for subjects in all treatment groups were lymphadenopathy, nasopharyngitis, oropharyngeal pain, nausea, diarrhoea, injection site warmth and oedema peripheral, none of which showed a clear trend between groups or association with the duration between vaccinations.

No subject experienced an AE that led to premature discontinuation from the study. There were six SAEs reported by three subjects up to Day 51 but all were considered by the investigators to be unrelated to study vaccine and were non-fatal.

Q-Pan-011

In these Japanese subjects the overall incidence of symptoms was high and comparable between age strata and all subjects reported at least one symptom. Grade 3 local and general symptoms were reported with low frequencies (≤16%). Subjects from the 20-40 years age stratum reported more Grade 3 general symptoms (10%, 5 subjects) compared to the older stratum but there was no clear difference between age strata in terms of Grade 3 local symptoms including those considered to be related to vaccination.

Table 14 **Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) follow-up period after each dose and overall by age strata 20-40 years and 41-64 years (Total vaccinated cohort)**

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Sub-Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	20-40Y	50	50	100	92.9	100	50	41	82.0	68.6	91.4	50	49	98.0	89.4	99.9
	41-64Y	50	50	100	92.9	100	50	40	80.0	66.3	90.0	50	50	100	92.9	100
Dose 2	20-40Y	50	46	92.0	80.8	97.8	50	44	88.0	75.7	95.5	50	46	92.0	80.8	97.8
	41-64Y	50	48	96.0	86.3	99.5	50	37	74.0	59.7	85.4	50	48	96.0	86.3	99.5
Overall/dose	20-40Y	100	96	96.0	90.1	98.9	100	85	85.0	76.5	91.4	100	95	95.0	88.7	98.4
	41-64Y	100	98	98.0	93.0	99.8	100	77	77.0	67.5	84.8	100	98	98.0	93.0	99.8
Overall/subject	20-40Y	50	50	100	92.9	100	50	47	94.0	83.5	98.7	50	49	98.0	89.4	99.9
	41-64Y	50	50	100	92.9	100	50	47	94.0	83.5	98.7	50	50	100	92.9	100

20-40Y = Subjects aged 20-40 years; 41-64Y = Subjects aged 41-64 years; For each dose and overall/subject: N= number of subjects with at least one documented dose; n/%= number/percentage of subjects presenting at least one type of symptom; For overall/dose: N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit; Grading for quantifiable symptoms: Fever: ≥ 38.0°C, Ecchymosis, Redness, Swelling: >20mm

Local symptoms, predominantly driven by the incidence of injection site pain, were reported with high and similar frequencies in both age strata. Grade 3 local solicited symptoms were reported with low frequencies with Grade 3 pain at injection site reported in only one subject in the 20-40 years stratum. The overall per dose frequencies in both age strata ranged from 2% to 3% in the 20-40 years stratum and the 41-64 years stratum for redness and swelling/induration, respectively. In general, there was no increase in the incidence of local solicited symptoms of any type or grade between Dose 1 and Dose 2.

There were no differences were observed in terms of reported frequency of joint pain and shivering between the age strata. In contrast, trends for higher frequencies were observed for the following solicited general symptoms in the 20-40 years stratum: fatigue, headache, muscle aches, shivering, increased sweating and fever. The reported frequencies of Grade 3 general symptoms were very low.

Fatigue was the most frequently reported general symptom at 71% overall, 78% in the 20-40 years and 64% in the 41-64 years groups. Grade 3 and grade 3-related fatigue was reported only in the 20-40 years stratum (3 subjects, 6%). Muscle aches was the second most frequently reported general symptom at 70% overall, 72% in the 20-40 years stratum and 68% in the 41-64 years stratum. Grade 3 muscle aches were reported only by one subject in the 20-40 years stratum.

Headache was reported by 51.0% overall, 60% in the 20-40 years stratum and 42% in the 41-64 years stratum. There were no Grade 3 reports. Joint pain was reported by 32% and 36% per stratum with one Grade 3 report from a subject in the 20-40 years stratum. Fever of any grade (≥38°C) was reported by 12% in the 20-40 years stratum compared to 10% of subjects in the 41-64 years stratum. Grade 3 and Grade 3-related fever was reported by one subject in the 20-40 years stratum with no reports of Grade 4 fever.

Unsolicited adverse events were reported by 51 subjects, including injection site pruritus, injection site warmth and nasopharyngitis. Three subjects in the younger cohort reported at least one Grade 3 unsolicited adverse event (joint sprain, urticaria and asthma) and 28 reported at least one unsolicited adverse event which was causally related to vaccination (including the case of urticaria).

AEs prompting medically-attended visits were reported by 16 subjects. Of these, 13 subjects were in the 20-40 years stratum. However, no specific clinical pattern could be identified.
One female subject (aged 31 years) reported Grade 3 urticaria (worsening) one day after the second vaccination. Urticaria was part of the medical history of the subject but the AE was deemed to be causally related to vaccination and occurred after a first episode of urticaria worsening (Grade 1) that appeared two days after the first injection. The first episode was also considered to be related,

although it did not result in a visit to a healthcare provider. Treatment after the first episode consisted of oral antihistamines. Oral betamethasone and intravenous Neo-Minophagen C and hydrocortisone were used for the second episode. Both episodes fully resolved after 8 days (first episode) and 9 days (second episode).

There were no SAEs, discontinuations due to AEs or pregnancies reported up to D182. The additional unsolicited AEs in the Annex report did not change the safety profile demonstrated up to D42.

D-Pan-H5N1-009/-022/-023

Phase A

In the **6-9 years** age stratum, the overall incidence of AEs by subject was 96.1% in the AS03 group and 88.9% in the control group. The incidences of general symptoms were comparable between vaccine groups but local symptoms occurred more often in the AS03 group. There was no increased reactogenicity in either vaccine group after the second dose compared with the first dose.

In the **3-5 years** age stratum, AE rates were generally lower than in older children. Incidences of general symptoms per subject were comparable between vaccine groups but rates of local symptoms per subject were higher in the AS03 group. There was no increased reactogenicity in either vaccine group after the second dose compared with the first dose.

Table 14 Incidence and nature of adverse events (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort)

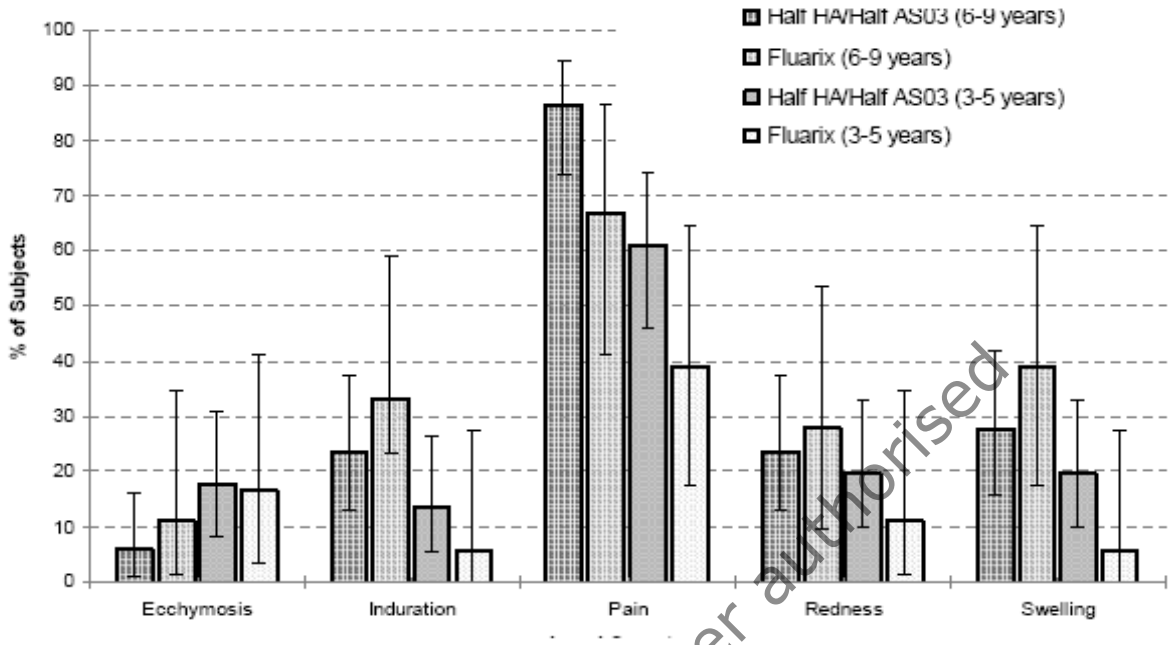
			Any symptom					General symptoms					Local symptoms				
	Group	Sub-group				95% CI					95% CI					95% CI	
			N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	18	11	61.1	35.7	82.7	18	7	38.9	17.3	64.3	18	8	44.4	21.5	69.2
		6-9y	18	13	72.2	46.5	90.3	18	6	33.3	13.3	59.0	18	12	66.7	41.0	86.7
	H5N1/2	3-5y	51	29	56.9	42.2	70.7	51	19	37.3	24.1	51.9	51	27	52.9	38.5	67.1
	+AS03/2	6-9y	51	47	92.2	81.1	97.8	51	29	56.9	42.2	70.7	51	41	80.4	66.9	90.2
Dose 2	*Fluarix*™	3-5y	17	8	47.1	23.0	72.2	17	3	17.6	3.8	43.4	17	6	35.3	14.2	61.7
		6-9y	18	14	77.8	52.4	93.6	18	10	55.6	30.8	78.5	18	10	55.6	30.8	78.5
	H5N1/2	3-5y	50	33	66.0	51.2	78.8	50	18	36.0	22.9	50.8	50	27	54.0	39.3	68.2
	+AS03/2	6-9y	49	35	71.4	56.7	83.4	49	20	40.8	27.0	55.8	49	30	61.2	46.2	74.8
Overall/dose	*Fluarix*™	3-5y	35	19	54.3	36.6	71.2	35	10	28.6	14.6	46.3	35	14	40.0	23.9	57.9
		6-9y	36	27	75.0	57.8	87.9	36	16	44.4	27.9	61.9	36	22	61.1	43.5	76.9
	H5N1/2	3-5y	101	62	61.4	51.2	70.9	101	37	36.6	27.3	46.8	101	54	53.5	43.3	63.5
	+AS03/2	6-9y	100	82	82.0	73.1	89.0	100	49	49.0	38.9	59.2	100	71	71.0	61.1	79.6
Overall/subject	*Fluarix*™	3-5y	18	13	72.2	46.5	90.3	18	9	50.0	26.0	74.0	18	10	55.6	30.8	78.5
		6-9y	18	16	88.9	65.3	98.6	18	11	61.1	35.7	82.7	18	13	72.2	46.5	90.3
	H5N1/2	3-5y	51	38	74.5	60.4	85.7	51	24	47.1	32.9	61.5	51	34	66.7	52.1	79.2
	+AS03/2	6-9y	51	49	96.1	86.5	99.5	51	33	64.7	50.1	77.6	51	46	90.2	78.6	96.7

H5N1/2 + AS03/2 = Half HA / Half AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

The incidence of grade 3 AEs was generally low with no difference between the vaccine groups in older children but with rates of 13.7% versus zero in children aged 3-5 years.

In the 6-9 year-olds the rates of pain were 61% for Fluarix and 76.5% for AS03 vaccine after the first dose (none and 5.9% with Grade 3) but were comparable after the second dose (none and 4% with Grade 3). In the 3-5 year-olds the rates of pain were higher with AS03 vaccine after both doses.

Figure 8 **Overall incidence per subject of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort)**



Rates of solicited general symptoms per subject were not markedly different between vaccine groups in the **6-9 years** age stratum. The rate of any fever (> 37.5°C) after dose 1 of AS03 vaccine was 5.9% but no subject had Grade 3 fever (> 39°C) and no subject in the Fluarix group had any fever. The rates for any fever after the second dose were 16.7% for Fluarix and 10.2% for AS03 vaccine while rates for Grade 3 fever were 5.6% and zero. The per-dose rates for any antipyretic use were 8% in both vaccine groups with per subject rates of 17% and 14% in respective groups.

In the **3-5 years** age stratum rates of solicited general symptoms per subject were higher than in the control group. The rate of any fever after dose 1 of AS03 vaccine was 9.8% but 3.9% had Grade 3 fever (> 39°C). The corresponding rates after the second dose were 6% and zero. No subjects in the Fluarix group had fever after either dose. The per-dose rates of taking any antipyretic were 9% for Fluarix and 19% for AS03 vaccine, with per subject rates of 17% and 35%.

Unsolicited AEs reported up to 51 days after the first vaccination showed no particular signal or clinical pattern in any vaccine group.

No deaths or other SAEs were reported and there were no AEs leading to withdrawal during this study phase.

Phase B

In both age strata the overall incidence incidences of AEs and rates of local and general AEs by subject were higher in the AS03 vaccine group than in the control group. There was no increased reactogenicity in either vaccine group after the second vaccination when compared with the first vaccination. There were more Grade 3 AEs in subjects aged 6-9 years in the AS03 group (8.2%) when compared with the control group (0.0%). Similarly, the incidence of Grade 3 AEs in subjects aged 3-5 years was higher in the AS03 group (11.8%) when compared with the control group (5.9%), mainly driven by a higher incidence of Grade 3 local symptoms.

The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 75.5% in the AS03 vaccine group compared with 58.8% in the control subjects. Also, among subjects aged 3-5 years the incidence of AEs assessed as causally related to the vaccination was 70.6% in the AS03 vaccine group and 35.3% in the control group.

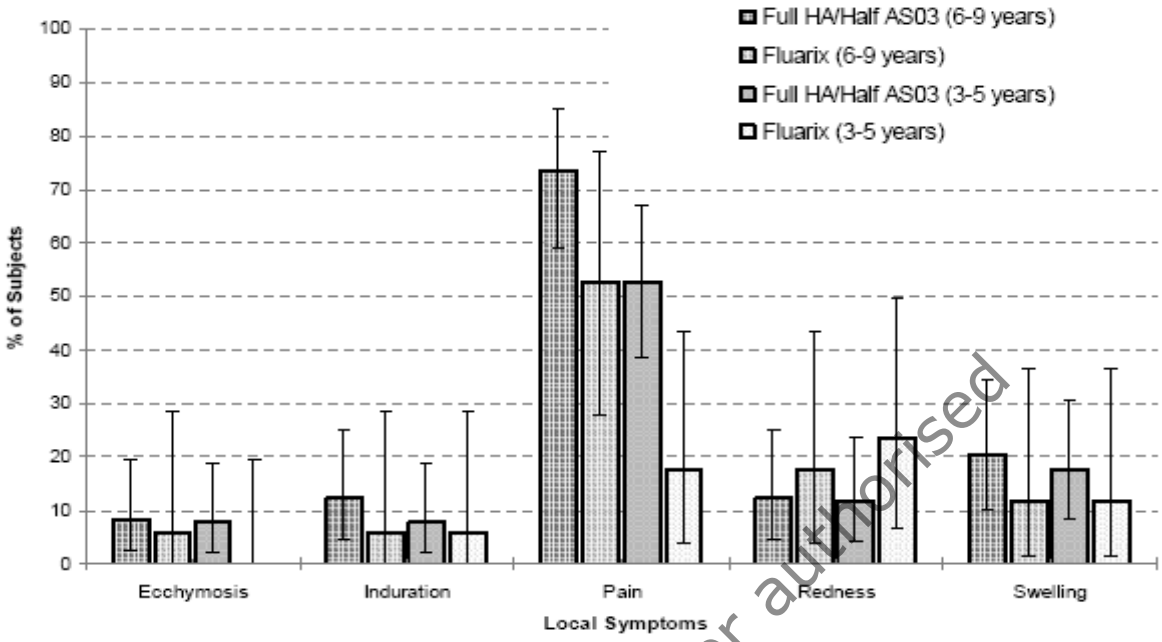
Table 19 Incidence and nature of AEs (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase B)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	17	6	35.3	14.2	61.7	17	3	17.6	3.8	43.4	17	4	23.5	6.8	49.9
		6-9y	17	9	52.9	27.8	77.0	17	5	29.4	10.3	56.0	17	8	47.1	23.0	72.2
	H5N1 +AS03/2	3-5y	51	32	62.7	48.1	75.9	51	23	45.1	31.1	59.7	51	22	43.1	29.3	57.8
		6-9y	49	35	71.4	56.7	83.4	49	17	34.7	21.7	49.6	49	33	67.3	52.5	80.1
Dose 2	*Fluarix*™	3-5y	17	3	17.6	3.8	43.4	17	2	11.8	1.5	36.4	17	2	11.8	1.5	36.4
		6-9y	17	8	47.1	23.0	72.2	17	3	17.6	3.8	43.4	17	8	47.1	23.0	72.2
	H5N1 +AS03/2	3-5y	49	34	69.4	54.6	81.7	49	21	42.9	28.8	57.8	49	22	44.9	30.7	59.8
		6-9y	47	32	68.1	52.9	80.9	47	17	36.2	22.7	51.5	47	29	61.7	46.4	75.5
Overall/dose	*Fluarix*™	3-5y	34	9	26.5	12.9	44.4	34	5	14.7	5.0	31.1	34	6	17.6	6.8	34.5
		6-9y	34	17	50.0	32.4	67.6	34	8	23.5	10.7	41.2	34	16	47.1	29.8	64.9
	H5N1 +AS03/2	3-5y	100	66	66.0	55.8	75.2	100	44	44.0	34.1	54.3	100	44	44.0	34.1	54.3
		6-9y	96	67	69.8	59.6	78.7	96	34	35.4	25.9	45.8	96	62	64.6	54.2	74.1
Overall/subject	*Fluarix*™	3-5y	17	7	41.2	18.4	67.1	17	4	23.5	6.8	49.9	17	5	29.4	10.3	56.0
		6-9y	17	10	58.8	32.9	81.6	17	6	35.3	14.2	61.7	17	10	58.8	32.9	81.6
	H5N1 +AS03/2	3-5y	51	42	82.4	69.1	91.6	51	32	62.7	48.1	75.9	51	29	56.9	42.2	70.7
		6-9y	49	38	77.6	63.4	88.2	49	24	49.0	34.4	63.7	49	37	75.5	61.1	86.7

H5N1 + AS03/2 = Full HA / Half AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited local symptoms per subject did not show marked differences between AS03 and control except for pain at the injection site.

Figure 14 **Overall incidence per subject of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort; Phase B)**



In the **6-9** years age stratum the incidences per subject of solicited general symptoms were generally higher in the AS03 vaccine group but rates for Grade 3 symptoms were low. The rates of any fever (> 37.5°C) after dose 1 were zero for Fluarix and 2% for AS03 vaccine and no subject had Grade 3 fever (> 39°C). The corresponding rates after the second dose were zero and 6.4% for any fever in respective vaccine groups and zero and 2.1% had Grade 3 fever. The per dose rates for any antipyretic use were 9% and 12% in respective vaccine groups with per subject rates of 18% and 22% in respective groups.

In the **3-5 years** age stratum, solicited general symptoms occurred more often in the AS03 vaccine group than in the control group. The rates of any fever (> 37.5°C) after dose 1 were 11.8% for Fluarix and 7.8% for AS03 vaccine and no subject had Grade 3 fever (> 39°C). The corresponding rates after the second dose were 5.9% and 14.3% for any fever and 5.9% and zero had Grade 3 fever. Within this period the per dose rates of taking any antipyretic (regardless of the reason for use) were 18% for Fluarix and 17% for AS03 vaccine, with per subject rates of 29% and 30%.

In both age strata the incidences of unsolicited AEs were comparable but higher in the younger subjects. Grade 3 AEs and AEs assessed as causally related to the vaccination were infrequent. One subject in the Full HA/ ½ AS03 group experienced an AE leading to premature discontinuation. Please see the separate AR on possible auto-immune diseases in vaccinees. There were no SAEs in Phase B during the study conduct up to Day 51.

Phase C

In the both age strata the incidences of local and general AEs were higher in the AS03 group. The incidence of Grade 3 AEs in subjects aged 6-9 years was higher in the AS03 group (18.4%) when compared with the control group (5.6%). The incidence of Grade 3 AEs in subjects aged 3-5 years was also higher in the AS03 group (22.4%) when compared with the control group (0.0%) but did not seem to be driven by the incidence of local Grade 3 symptoms.

The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 93.9% in the AS03 vaccine group and 94.4% in the control group compared to 79.6% and 41.2% in respective groups in the younger age cohort.

Table 20 Incidence and nature of AEs (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase C)

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	*Fluarix*™	3-5y	17	7	41.2	18.4	67.1	17	1	5.9	0.1	28.7	17	6	35.3	14.2	61.7
		6-9y	18	14	77.8	52.4	93.6	18	7	38.9	17.3	64.3	18	13	72.2	46.5	90.3
	H5N1 +AS03	3-5y	49	37	75.5	61.1	86.7	49	19	38.8	25.2	53.8	49	35	71.4	56.7	83.4
		6-9y	49	43	87.8	75.2	95.4	49	25	51.0	36.3	65.6	49	39	79.6	65.7	89.8
Dose 2	*Fluarix*™	3-5y	17	6	35.3	14.2	61.7	17	4	23.5	6.8	49.9	17	3	17.6	3.8	43.4
		6-9y	18	11	61.1	35.7	82.7	18	7	38.9	17.3	64.3	18	10	55.6	30.8	78.5
	H5N1 +AS03	3-5y	48	30	62.5	47.4	76.0	48	23	47.9	33.3	62.8	48	27	56.3	41.2	70.5
		6-9y	49	41	83.7	70.3	92.7	49	30	61.2	46.2	74.8	49	35	71.4	56.7	83.4
Overall/dose	*Fluarix*™	3-5y	34	13	38.2	22.2	56.4	34	5	14.7	5.0	31.1	34	9	26.5	12.9	44.4
		6-9y	36	25	69.4	51.9	83.7	36	14	38.9	23.1	56.5	36	23	63.9	46.2	79.2
	H5N1 +AS03	3-5y	97	67	69.1	58.9	78.1	97	42	43.3	33.3	53.7	97	62	63.9	53.5	73.4
		6-9y	98	84	85.7	77.2	92.0	98	55	56.1	45.7	66.1	98	74	75.5	65.8	83.6
Overall/subject	*Fluarix*™	3-5y	17	10	58.8	32.9	81.6	17	5	29.4	10.3	56.0	17	7	41.2	18.4	67.1
		6-9y	18	17	94.4	72.7	99.9	18	10	55.6	30.8	78.5	18	15	83.3	58.6	96.4
	H5N1 +AS03	3-5y	49	41	83.7	70.3	92.7	49	29	59.2	44.2	73.0	49	37	75.5	61.1	86.7
		6-9y	49	46	93.9	83.1	98.7	49	35	71.4	56.7	83.4	49	45	91.8	80.4	97.7

H5N1 + AS03 = Full HA / Full AS03; *Fluarix*™ = control; 3-5y = 3-5 years; 6-9y = 6-9 years; For each dose and overall/subject: N = number of subjects with at least one administered dose; n/% = number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; For overall/dose: N = number of administered doses; n/% = number/percentage of doses followed by at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Pain was the predominant solicited local symptom in both age strata and vaccine groups. Rates of pain were not higher after the second dose in either age stratum.

Redness and swelling were also reported with a higher incidence in the AS03 group irrespective of age stratum. In the 3-5 years age stratum there was a trend for a higher incidence of induration, redness and pain upon re-vaccination but this was not observed in the 6-9 years age stratum and was not observed in either stratum with the control vaccine. The majority of these events were Grade 1 in intensity, and there were few isolated Grade 3 cases in the AS03 group (none in the control group).

Among **6-9** year-olds rates of general solicited symptoms were higher with AS03 vaccine and the incidence of fever, headache, myalgia, shivering and sweating tended to be higher after Dose 2. Rates of fever after dose 1 were zero in the Fluarix group and 12.2% in the AS03 group (1/6 of these subjects [2% overall] had Grade 3 fever). After the second dose rates for any fever were zero and 32.7% in respective vaccine groups (6/16 of these subjects [12% overall] had Grade 3 fever). These numbers give rates for fever overall/dose of zero for Fluarix and 22.4% for AS03 vaccine (7/22 of these doses [7% overall] being associated with Grade 3 fever). The per dose rates for any antipyretic use were 14% and 43% in respective vaccine groups with per subject rates of 22% and 65% in respective groups.

Figure 15 **Overall incidence per subject of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort; Phase C)**

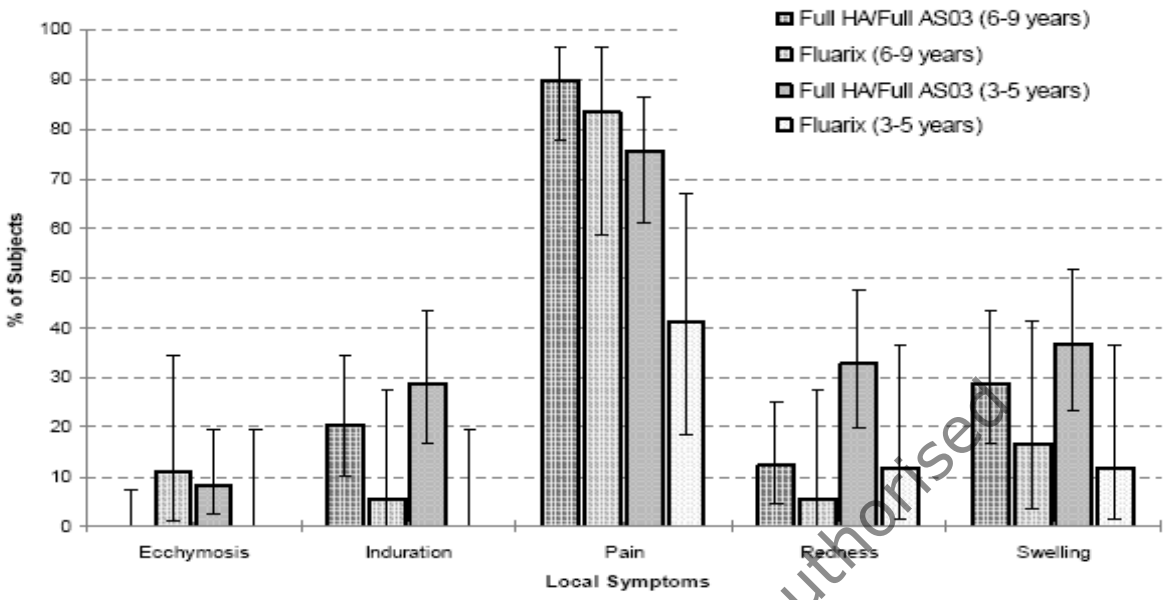
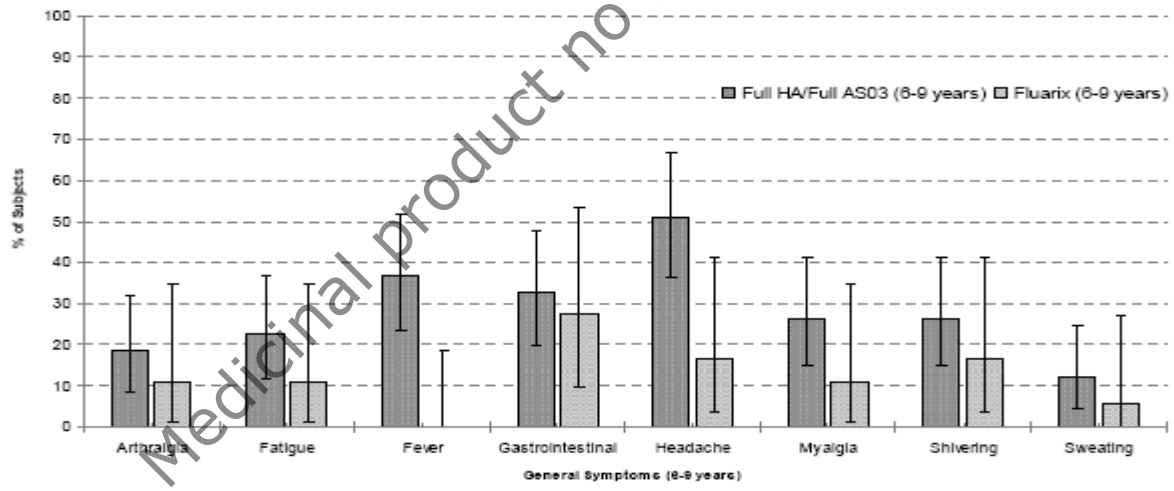
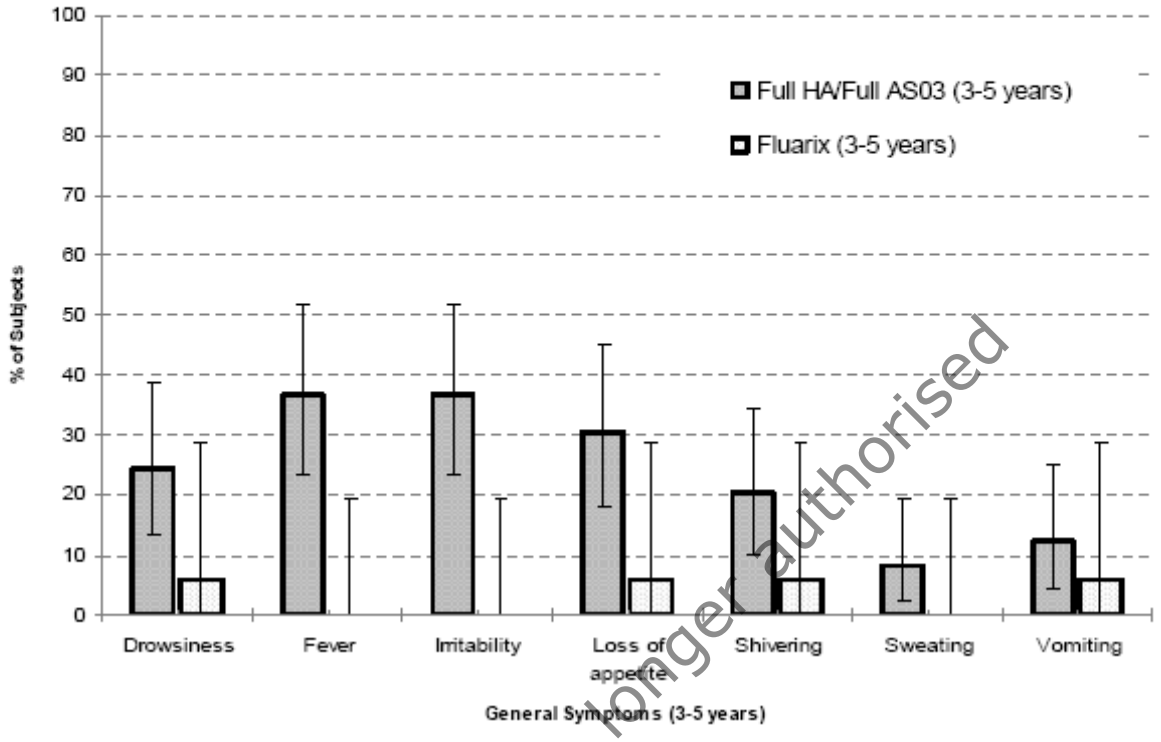


Figure 18 **Overall incidence per subject of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase C) – for children aged 6-9 years**



In the **3-5** years age stratum solicited general symptoms predominated in the AS03 group (range 8.2% - 36.7%) when compared with the control group (range 0.0% - 5.9%). After dose 1 the rates for any fever were zero in the Fluarix group and 8.2% in the AS03 group (3/4 of these subjects [6% overall] had Grade 3 fever). After dose 2 the fever rates were zero and 31.3% (2/15 [4% overall] of these subjects had Grade 3 fever) in respective vaccine groups. These numbers give overall/dose rates for fever of zero for Fluarix and 19.6% for AS03 vaccine (5/19 of these doses [5% overall] being associated with Grade 3 fever). Within this period the per dose rates of taking any antipyretic (regardless of the reason for use) in the 3-5 year-olds were 15% for Fluarix and 31% for AS03 vaccine, with per subject rates of 24% and 51%.

Figure 19 Overall incidence per subject of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total Vaccinated cohort; Phase C) – for children aged 3-5 years



The incidence of unsolicited AEs was 55.1% in the AS03 group and 33.3% in the control group in the 6-9 years age stratum. Grade 3 unsolicited AEs and unsolicited AEs were infrequently assessed as causally related to the vaccination. In the 3-5 years stratum the incidence of unsolicited AEs was 53.1% in the AS03 group and 47.1% in the control group. Few subjects reported Grade 3 unsolicited AEs in the AS03 group (6.1%) and there were none in the control group. The incidence of unsolicited AEs assessed as causally related to the vaccination was 18.4% in the AS03 group compared to zero in the control group.

One subject in the AS03 group developed an AE of uveitis for which subsequent details specified a unilateral anterior chamber uveitis at 8 days after the second dose of the H5N1 vaccine, which was considered to have a potential causal relationship to vaccination. One subject in the AS03 group was hospitalised for gastroenteritis but the event was considered not related to vaccination and resolved after two days. There were no AEs leading to premature discontinuation in Phase C and no deaths were reported.

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The overall reporting rates for general and local symptoms were comparable between vaccines and most of these were considered to be vaccine-related. Very few symptoms were of Grade 3 and the rates were again comparable between the vaccine groups.

Supplement 37 Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day (Days 0-6) post-vaccination period in following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Q-PAN	167	155	92.8	87.8	96.2	167	111	66.5	58.8	73.6	167	147	88.0	82.1	92.5
	D-PAN	167	154	92.2	87.1	95.8	167	106	63.5	55.7	70.8	167	148	88.6	82.8	93.0

Supplement 36 Incidence and nature of grade 3 symptoms (solicited and unsolicited) reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Any symptom					General symptoms					Local symptoms				
					95% CI					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Q-PAN	167	9	5.4	2.5	10.0	167	8	4.8	2.1	9.2	167	4	2.4	0.7	6.0
	D-PAN	167	11	6.6	3.3	11.5	167	7	4.2	1.7	8.4	167	7	4.2	1.7	8.4

Pain at the injection site was the most frequently reported solicited local symptom with much lower rates for redness and swelling. Frequencies were comparable between vaccines.

Supplement 39 Incidence of solicited local symptoms by maximum grading reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Q-PAN					D-PAN					Total				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Pain	All	167	144	86.2	80.1	91.1	167	148	88.6	82.8	93.0	334	292	87.4	83.4	90.8
	Grade 1	167	81	48.5	40.7	56.3	167	92	55.1	47.2	62.8	334	173	51.8	46.3	57.3
	Grade 2	167	59	35.3	28.1	43.1	167	50	29.9	23.1	37.5	334	109	32.6	27.6	38.0
	Grade 3	167	4	2.4	0.7	6.0	167	6	3.6	1.3	7.7	334	10	3.0	1.4	5.4
Redness (mm)	All	167	19	11.4	7.0	17.2	167	25	15.0	9.9	21.3	334	44	13.2	9.7	17.3
	[20.1 - 50.1[	167	13	7.8	4.2	12.9	167	15	9.0	5.1	14.4	334	28	8.4	5.6	11.9
	[50.1 - 100.1[	167	6	3.6	1.3	7.7	167	10	6.0	2.9	10.7	334	16	4.8	2.8	7.7
	[100.1 - ...	167	0	0.0	0.0	2.2	167	0	0.0	0.0	2.2	334	0	0.0	0.0	1.1
Swelling (mm)	All	167	29	17.4	11.9	24.0	167	32	19.2	13.5	26.0	334	61	18.3	14.3	22.8
	[20.1 - 50.1[	167	20	12.0	7.5	17.9	167	21	12.6	8.0	18.6	334	41	12.3	9.0	16.3
	[50.1 - 100.1[	167	9	5.4	2.5	10.0	167	9	5.4	2.5	10.0	334	18	5.4	3.2	8.4
	[100.1 - ...	167	0	0.0	0.0	2.2	167	2	1.2	0.1	4.3	334	2	0.6	0.1	2.1

The most frequently reported solicited general symptoms were muscle aches (48.5% Arepanrix, 34% Pandemrix), fatigue (32.9% with both) and headache (28.7% and 32.9%).

Supplement 40 Incidence of solicited general symptoms by maximum grading reported during the 7-day (Days 0-6) post-vaccination period following each dose and overall (Total vaccinated cohort)

		Q-PAN					D-PAN					Total				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1																
Fatigue	All	167	55	32.9	25.9	40.6	167	60	35.9	28.7	43.7	334	115	34.4	29.3	39.8
	Grade 1	167	38	22.8	16.6	29.9	167	41	24.6	18.2	31.8	334	79	23.7	19.2	28.6
	Grade 2	167	15	9.0	5.1	14.4	167	16	9.6	5.6	15.1	334	31	9.3	6.4	12.9
	Grade 3	167	2	1.2	0.1	4.3	167	3	1.8	0.4	5.2	334	5	1.5	0.5	3.5
	Rel	167	54	32.3	25.3	40.0	167	54	32.3	25.3	40.0	334	108	32.3	27.3	37.6
	Grade 1*Rel	167	37	22.2	16.1	29.2	167	36	21.6	15.6	28.6	334	73	21.9	17.5	26.7
	Grade 2*Rel	167	15	9.0	5.1	14.4	167	15	9.0	5.1	14.4	334	30	9.0	6.1	12.6
	Grade 3*Rel	167	2	1.2	0.1	4.3	167	3	1.8	0.4	5.2	334	5	1.5	0.5	3.5
Headache	All	167	48	28.7	22.0	36.2	167	55	32.9	25.9	40.6	334	103	30.8	25.9	36.1
	Grade 1	167	34	20.4	14.5	27.3	167	36	21.6	15.6	28.6	334	70	21.0	16.7	25.7
	Grade 2	167	12	7.2	3.8	12.2	167	15	9.0	5.1	14.4	334	27	8.1	5.4	11.5
	Grade 3	167	2	1.2	0.1	4.3	167	4	2.4	0.7	6.0	334	6	1.8	0.7	3.9
	Rel	167	44	26.3	19.8	33.7	167	46	27.5	20.9	35.0	334	90	26.9	22.3	32.0
	Grade 1*Rel	167	30	18.0	12.5	24.6	167	28	16.8	11.4	23.3	334	58	17.4	13.5	21.9
	Grade 2*Rel	167	12	7.2	3.8	12.2	167	14	8.4	4.7	13.7	334	26	7.8	5.1	11.2
	Grade 3*Rel	167	2	1.2	0.1	4.3	167	4	2.4	0.7	6.0	334	6	1.8	0.7	3.9
Joint pain at other location	All	167	38	22.8	16.6	29.9	167	37	22.2	16.1	29.2	334	75	22.5	18.1	27.3
	Grade 1	167	29	17.4	11.9	24.0	167	28	16.8	11.4	23.3	334	57	17.1	13.2	21.5
	Grade 2	167	7	4.2	1.7	8.4	167	8	4.8	2.1	9.2	334	15	4.5	2.5	7.3
	Grade 3	167	2	1.2	0.1	4.3	167	1	0.6	0.0	3.3	334	3	0.9	0.2	2.6
	Rel	167	37	22.2	16.1	29.2	167	33	19.8	14.0	26.6	334	70	21.0	16.7	25.7
	Grade 1*Rel	167	29	17.4	11.9	24.0	167	25	15.0	9.9	21.3	334	54	16.2	12.4	20.6
	Grade 2*Rel	167	6	3.6	1.3	7.7	167	7	4.2	1.7	8.4	334	13	3.9	2.1	6.6
	Grade 3*Rel	167	2	1.2	0.1	4.3	167	1	0.6	0.0	3.3	334	3	0.9	0.2	2.6
Muscle aches	All	167	81	48.5	40.7	56.3	167	57	34.1	27.0	41.9	334	138	41.3	36.0	46.8
	Grade 1	167	66	39.5	32.1	47.4	167	39	23.4	17.2	30.5	334	105	31.4	26.5	36.7
	Grade 2	167	11	6.6	3.3	11.5	167	15	9.0	5.1	14.4	334	26	7.8	5.1	11.2
	Grade 3	167	4	2.4	0.7	6.0	167	3	1.8	0.4	5.2	334	7	2.1	0.8	4.3
	Rel	167	79	47.3	39.5	55.2	167	55	32.9	25.9	40.6	334	134	40.1	34.8	45.6
	Grade 1*Rel	167	64	38.3	30.9	46.2	167	38	22.8	16.6	29.9	334	102	30.5	25.6	35.8
	Grade 2*Rel	167	11	6.6	3.3	11.5	167	14	8.4	4.7	13.7	334	25	7.5	4.9	10.9
	Grade 3*Rel	167	4	2.4	0.7	6.0	167	3	1.8	0.4	5.2	334	7	2.1	0.8	4.3
Shivering	All	167	24	14.4	9.4	20.6	167	34	20.4	14.5	27.3	334	58	17.4	13.5	21.9
	Grade 1	167	16	9.6	5.6	15.1	167	25	15.0	9.9	21.3	334	41	12.3	9.0	16.3
	Grade 2	167	6	3.6	1.3	7.7	167	9	5.4	2.5	10.0	334	15	4.5	2.5	7.3
	Grade 3	167	2	1.2	0.1	4.3	167	0	0.0	0.0	2.2	334	2	0.6	0.1	2.1
	Rel	167	24	14.4	9.4	20.6	167	32	19.2	13.5	26.0	334	56	16.8	12.9	21.2
	Grade 1*Rel	167	16	9.6	5.6	15.1	167	23	13.8	8.9	19.9	334	39	11.7	8.4	15.6
	Grade 2*Rel	167	6	3.6	1.3	7.7	167	9	5.4	2.5	10.0	334	15	4.5	2.5	7.3
	Grade 3*Rel	167	2	1.2	0.1	4.3	167	0	0.0	0.0	2.2	334	2	0.6	0.1	2.1
Sweating	All	167	14	8.4	4.7	13.7	167	13	7.8	4.2	12.9	334	27	8.1	5.4	11.5
	Grade 1	167	10	6.0	2.9	10.7	167	8	4.8	2.1	9.2	334	18	5.4	3.2	8.4
	Grade 2	167	3	1.8	0.4	5.2	167	4	2.4	0.7	6.0	334	7	2.1	0.8	4.3
	Grade 3	167	1	0.6	0.0	3.3	167	1	0.6	0.0	3.3	334	2	0.6	0.1	2.1
	Rel	167	14	8.4	4.7	13.7	167	12	7.2	3.8	12.2	334	26	7.8	5.1	11.2
	Grade 1*Rel	167	10	6.0	2.9	10.7	167	7	4.2	1.7	8.4	334	17	5.1	3.0	8.0
	Grade 2*Rel	167	3	1.8	0.4	5.2	167	4	2.4	0.7	6.0	334	7	2.1	0.8	4.3
	Grade 3*Rel	167	1	0.6	0.0	3.3	167	1	0.6	0.0	3.3	334	2	0.6	0.1	2.1

Rates of fever were low in both groups and no subjects took prophylactic antipyretic medications.

		Q-PAN					D-PAN					Total				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Temperature/(Axillary) (°C)	All	167	5	3.0	1.0	6.8	167	2	1.2	0.1	4.3	334	7	2.1	0.8	4.3
	[38 - 38.5[	167	3	1.8	0.4	5.2	167	0	0.0	0.0	2.2	334	3	0.9	0.2	2.6
	[38.5 - 39[	167	0	0.0	0.0	2.2	167	1	0.6	0.0	3.3	334	1	0.3	0.0	1.7
	[39 - 40.1[	167	2	1.2	0.1	4.3	167	1	0.6	0.0	3.3	334	3	0.9	0.2	2.6
	[40.1 - ...	167	0	0.0	0.0	2.2	167	0	0.0	0.0	2.2	334	0	0.0	0.0	1.1
	Rel	167	5	3.0	1.0	6.8	167	2	1.2	0.1	4.3	334	7	2.1	0.8	4.3
	[38 - 38.5[*Rel	167	3	1.8	0.4	5.2	167	0	0.0	0.0	2.2	334	3	0.9	0.2	2.6
	[38.5 - 39[*Rel	167	0	0.0	0.0	2.2	167	1	0.6	0.0	3.3	334	1	0.3	0.0	1.7
	[39 - 40.1[*Rel	167	2	1.2	0.1	4.3	167	1	0.6	0.0	3.3	334	3	0.9	0.2	2.6
	[40.1 - ...*Rel	167	0	0.0	0.0	2.2	167	0	0.0	0.0	2.2	334	0	0.0	0.0	1.1

Unsolicited AEs considered as related to vaccination were reported by 6.6% of Arepanrix subjects and 10.2% of Pandemrix subjects. Four unsolicited AEs were Grade 3, comprising one case of back pain in the Arepanrix group and two cases of influenza-like illness plus a case of nasopharyngitis in the Pandemrix group.

Supplement 50 Global Summary of unsolicited adverse events reported within the 21-day (Days 0-20) post-vaccination period (Total vaccinated cohort)

	Group		
	Q-PAN	D-PAN	Total
Number of subjects with at least one unsolicited symptom reported	31	37	68
Number of unsolicited symptoms classified by MedDRA Preferred Term*	44	43	87
Number of unsolicited symptoms reported	44	43	87

There were no AEs of Specific Interest (AESI) reported up to D21. The only SAE was the case of back pain in the Arepanrix group but this was not considered as causally related to the vaccine by the investigator.

Post marketing experience

As Arepanrix is authorised outside the EU, the applicant provided two simplified periodic safety update reports (sPSURs), which have been assessed within the rolling reviews. These reports follow the abbreviated format as agreed as part of the assessment process for pandemic vaccine sPSURs.

1st sPSUR

The reporting period for this report is 21 October 2009 to 17 November 2009. According to the applicant 9,435,000 doses were distributed to Canada during the reporting period, however the number of doses actually vaccinated was not available.

During the reporting period, the applicant received 315 reports of which 37 were serious and including 3 cases with a fatal outcome. Canada is the only country to which Arepanrix has been supplied.

The vast majority of events reported related either to the signs and symptoms of flu-like illness (including events specifically listed such as headache, nausea, vomiting, dizziness, fever, myalgia/arthralgia, fatigue, malaise, asthenia, chills, sweating), allergic ADRs (including dyspnoea

and generalised rashes), lymphadenopathy, injection site reactions (including pain, swelling and localised paraesthesia or numbness) or 'psychogenic' events (i.e. events related to fear or anticipation of the injection process including syncope and related symptoms).

Cases of fever and febrile convulsion have been reported in children following Arepanrix, however, no details of these cases were provided and no comment on level of fever and dose relationship can be made. The CHMP considered that data on rates of fever in children with Pandemrix should be considered as part of the safety evaluation of Arepanrix. The corresponding wording should therefore be included in the Product Information.

Fatal events

An 81-year-old male subject died due to anaphylaxis after vaccination with Arepanrix batch number A80CA009A. Concurrent medical conditions included chronic obstructive pulmonary disease, recurrent lung neoplasm and venous insufficiency. Around eighty five minutes after vaccination with Arepanrix the subject experienced rapid increasing dyspnoea with wheezing. The subject experienced respiratory difficulty with bronchospasm, mouth oedema and throat oedema. He was admitted to the Intensive Care Unit for intubation, at the time of the intubation there was a mild throat oedema and also pharyngeal and laryngeal oedema were noted, during the intubation the subject vomited which caused an aspiration pneumonia. The subject remained intubated because of the aspiration pneumonia but his condition was stable. On 31 October 2009 am the subject condition was stable, it was also mentioned that the subject condition of COPD was controlled at the time of vaccination. The patient subsequently died. Cause of death was severe renal failure possibly related to the allergic reaction to the vaccine (an autopsy report not available).

A 39-year-old female experienced an unspecified bacterial infection 2 days after vaccination with Arepanrix H1N1. The subject was also receiving Tamiflu. She died 5 days later. It was reported that the physician told the subject's family that the subject died of 'blood infection'.

A subject of unspecified age and gender died due to an unknown cause, 7 days after vaccination. It was unknown whether an autopsy was performed.

Two cases contain insufficient detail to allow any causality assessment. The applicant is requested to follow these reports up for further details. The first case may have been due to anaphylaxis which is a known risk of vaccination as discussed also below.

Adverse events of special interest (AESIs)

Case details of convulsions included 2 febrile convulsions and 1 convulsion. Case details were not provided in the PSUR. Febrile convulsions have just been included in the SPC for Pandemrix vaccine.

Serious unlisted events

The serious unlisted cases currently include a wide range of events from across all System Organ Classes with no clustering of cases suggestive of any specific signal. Most relate to possible symptoms of allergic reactions and flu-like illness.

Three reports of pyrexia, 1 report of convulsion and 1 report of febrile convulsion were reported in children aged under 2 years. An additional 16 cases of pyrexia were reported in children aged 2 to 8 years. No details of these cases were provided and so no comment on level of fever and dose relationship can be made. Pyrexia and febrile convulsions post dose 2 in children is currently being addressed as part of the Pandemrix SPC.

Twenty eight events in pregnant women were reported in this period. Other than 3 cases of premature birth, all events related to listed side effects, affecting the mother, and no adverse foetal events were reported.

Of the reported cases of anaphylaxis, 12 were received from the same public health physician, who was neither the treating nor vaccinating physician, and met Brighton Collaboration definition level 1 or 2 criteria. Seven of the reports (all from this physician) involved lot A80CA009A; black particles were observed in some vials from this lot and a manufacturing investigation of this lot was ongoing as of the submission of this report. One report described fatal outcome 8 days post-vaccination (onset of anaphylaxis was 85 minutes post-vaccination). Of the remaining 7 reports, 4 did not fulfil the Brighton Collaboration case definition of anaphylaxis and 3 did not provide enough detail for assessment.

The reporting rate for confirmed cases of anaphylaxis was 0.40/100,000 doses distributed. The overall reporting rate (confirmed, unconfirmed, and unknown) was 0.63/100,000 doses distributed. This is in line with the generally expected rate of anaphylaxis with vaccines in general of 1 to 10 cases per million doses.

After the data lock point of this report, the applicant was notified of 57 reports of anaphylaxis involving lot A80CA007A. Analyses of these reports by the applicant is ongoing. The applicant notified all consignees in Canada on 18 November 2009 to stop vaccinating with that lot until the analyses are complete. To date, the investigation has found no link between this vaccine lot and six confirmed anaphylaxis adverse events associated with this lot. No abnormalities or deviations from established specifications have been observed. The antigen and adjuvant vials used in lot A80CA007A have also been used, separately from one another, in other boxes with different lot numbers. No abnormally high rates of anaphylaxis or other adverse events have been seen with either the antigen or adjuvant from lot A80CA007A when used in a different box combination.

2nd sPSUR

The reporting period for this report is 17 November 2009 to 15 December 2009.
The applicant states that 15,630,060 doses were distributed to Canada and 5,550,000 doses were distributed to other countries (non-EU, inc. Japan and Morocco) during the reporting period. The cumulative number of doses distributed to the same countries at the data lock was 30,613,060 doses, however no data on vaccine uptake per country have yet been provided by the applicant.

During the reporting period, a total of 252 adverse event reports (68 serious, 3 fatal) were received by the applicant which were all from Canada. As well as Canada, Arepanrix has also been supplied to Japan and Morocco.

The cumulative total since 21 October is 565 adverse event reports (107 serious, 6 fatal).

The vast majority of events reported related either to the signs and symptoms of flu-like illness (including events specifically listed such as headache, nausea, vomiting, dizziness, fever, myalgia/arthralgia, fatigue, malaise, asthenia, chills, sweating), allergic ADRs (including dyspnoea and generalised rashes), lymphadenopathy, injection site reactions (including pain, swelling and localised paraesthesia or numbness) or 'psychogenic' events (i.e. events related to fear or anticipation of the injection process including syncope and related symptoms). Such events are all listed in the proposed SPC, or otherwise not unexpected, and the available information does not allow any assessment of a change in the expected frequency or severity of these events. No action is required on the basis of these cases at present. It was noted that 665 medically confirmed adverse events have been reported.
Five cases of cyanosis including one fatal case and 4 cases of syncope possibly of psychogenetic background are so far unlabelled in the proposed SPC of Arepanrix and the SPC of Pandemrix. The applicant committed to follow up these cases and to propose an update of the PI if appropriate

Fatal events

A 32 yr old female with a history of Crohn's disease and colitis died of an unknown cause 48 hours after vaccination with Arepanrix.
A10 month old male developed cough, cyanosis and died 3 hours after vaccination with Arepanrix. Autopsy found that the lungs were twice the normal weight but there was no evidence of obstruction.
A 43 yr old female experienced an unspecified haemorrhage within one week of vaccination with Arepanrix and died. The autopsy showed the subject died of an aneurysm.
The fatal cases in the 32 yr old and 10 month old contain insufficient detail to allow any assessment. The applicant committed to follow these reports up for further details and detailed post mortem findings as outlined in the Letter of Undertaking.

Adverse events of special interest (AESIs)

The following AESIs were reported:

Term (SMQ or PT)	Medically confirmed		Non-medically confirmed †	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
Facial palsy	2	2	0	0
SMQ-Anaphylaxis (SMQ)	69	122	5	15
SMQ-Convulsions (SMQ)	2	5	3	4
SMQ-Guillain-Barre syndrome (SMQ)	4	4	0	0
Total	**77**	**133**	**8**	**19**

† Only those cases that have been entered onto the database at data-lock.

The applicant stated that the SMQ for anaphylaxis includes all cases of urticaria, even in the absence of any signs of a serious anaphylactic or allergic event. Only 26 cases of anaphylaxis, including 3 cases of anaphylactic shock were actually reported in this period (46 cumulatively). Anaphylaxis is discussed further below.

The case details of convulsions were not provided in the PSUR. Febrile convulsions have just been included in the SPC for Pandemrix vaccine. The cases of GBS occurred 24 hours, 24 days and 3 days (the other case did not specify onset time) following vaccination. Insufficient detail was provided to allow an assessment of diagnostic certainty. Given the number of doses likely to have been used in Canada to date, the 4 cases of GBS do not currently indicate any signal of excess risk of GBS above expected background rate (this conclusion also applies to the most up to date analysis of GBS cases associated with Pandemrix).

Serious unlisted events

The serious unlisted cases currently include a wide range of events from across all System Organ Classes with no case clusters suggestive of any specific signal. Most relate to possible symptoms of allergic reactions, possible flu-like illness and possible 'psychogenic' events

Two cases of hepatitis were reported although no cased details were provided.

The CHMP noted that there are several clusters of event reports in SOCs which relate to events common in the clinical risk groups targeted for immunisation (i.e. cases of cardiac disorders, respiratory disorders and pregnancy outcomes). Many of these most likely reflect background event reporting, given the wide exposure amongst such populations.

Many other reports relate to possible symptoms of flu-like illness, localised events including injection-related events and paraesthesia and allergic reactions.

With regard to the 2 cases of hepatitis, given the previous assessment of possible autoimmune hepatitis associated with AS03 vaccines, the applicant should commit to provide details of these cases, and follow such cases up to rule out AIH as a diagnosis.

ADRs by age category

In children aged below 2 years, 30 events have been reported in this period, with 88 reports in the 2-8 year age group (the number of unique reports in this age group is not stated).

The CHMP considered that this does not raise any age-specific concerns at present. The majority of serious events have been reported amongst those aged above 9 years.

ADRs in pregnant women

Twenty five events in pregnant women were reported in this period (53 cumulatively). Other than 3 cases of premature labour/birth, all events related to listed side effects, affecting the mother, and no adverse foetal events were reported. The CHMP considered that this does not raise any specific concerns at present.

In the reporting period, the applicant conducted analyses of reports with fatal outcomes and reports of anaphylaxis (updated analysis), convulsions, dysgeusia, and facial palsy.

Regarding the cluster of reports of anaphylaxis highlighted in the last sPSUR involving lot A80CA007A, analyses of these reports by the applicant is ongoing. The applicant notified all consignees in Canada on 18 November 2009 to stop vaccinating with that lot until the analyses are complete.

The applicant's preliminary analysis of the cases associated with lot A80CA007A indicate a higher reporting rate of anaphylaxis. Both Health Canada and the applicant conducted testing on retained samples to determine whether a quality issue with this lot could be contributing to a higher rate of anaphylaxis. This found no abnormalities or deviations from established specifications; testing of samples returned from vaccination sites is ongoing. To date, the investigation has found no link between this vaccine lot and the confirmed anaphylaxis adverse events. The antigen and adjuvant vials used in lot A80CA007A have also been used, separately from one another, in other boxes with different lot numbers. No abnormally high rates of anaphylaxis or other adverse events have been seen with either the antigen or adjuvant from lot A80CA007A when used in a different box combination.

The apparent higher reporting rate of anaphylaxis associated with batch A80CA007A remains unexplained. The applicant committed to keep this under close review as outlined in the Letter of Undertaking.

Febrile convulsions have been included as a possible side effect in the Pandemrix SPC based on post marketing data.

The remaining case clusters reviewed do not indicate any specific signal of excess reporting above background at present.

Relevant safety data obtained with FluLaval (HA manufactured in Quebec)

In addition to the data from clinical studies with Q-Pan H5N1 the applicant summarised pertinent safety data relevant to use of the seasonal influenza vaccine *FluLaval* in adults to assist in an assessment of any possible impact of the differences in the manufacturing process of Q-Pan and D-Pan on the safety profile. The Q-Pan H5N1 antigen is manufactured according to the same process as the *FluLaval* antigens. *FluLaval* has been marketed in Canada since 1992 (as *Fluviral*) and in some countries in South America, Europe (Romania) and Asia. It was approved in the US in 2006. To date, more than 100 million doses of *FluLaval* have been distributed under different brand names.

The last PSUR on *Flu Laval* was submitted in February 2009 included the data for the period Dec 2007-Dec 2008 (attached in Annex 1 to the answer). During the period covered by this report there were 30.5 million doses distributed and 423 cases fulfilled the ICH E2C criteria for inclusion in the main line listings and summary tabulations. The review of reported cases did not raise new safety concerns.

Additional safety data have been obtained in four clinical studies (SPD707-104, IBD-707-105, IBD-707-106 and IBD-707-108) in which *FluLaval* was compared to either another trivalent inactivated vaccine (TIV) (*Fluzone* or *Vaxigrip*) or to placebo. Solicited and unsolicited symptoms plus SAEs were collected, analysed and described for 10,165 subjects, including 5277 who received *FluLaval*. In these four studies the incidence of solicited local symptoms was generally comparable between the *FluLaval* and placebo groups although there was a higher risk of pain among *FluLaval* subjects in the 4 days following vaccination. There were no significant differences between groups for any of the solicited general symptoms experienced during the 4 day follow-up period (see second table below).

During the 30-minute post-vaccination period the most frequently reported general symptoms in the *FluLaval* group during this period were red eyes (1.7%) and muscle or joint aches (1.6%). The incidence of these events appeared to be similar in the control groups. All other general symptoms were reported for ≤1.0% of subjects in the *FluLaval* and control groups during the 30-minute post-vaccination period.

During the 4-day post-vaccination period, the most frequently reported solicited general symptoms in the *FluLaval* group were fatigue (18.5%), headache (17.0%), and muscle or joint aches (16.6%). These were also the most frequently reported events in each of the control groups. No other events were reported for more than 10% of subjects in any group.

During the 43 day follow-up period, the proportions of subjects reporting at least one post vaccination AE were comparable across all treatment groups. In the *FluLaval* group, 25% of subjects had at least one AE compared with 23% in the placebo group and 31% in the control TIV group. The percentages of subjects who experienced Grade 3 events were low and rates were in the range 2-3%.

Unsolicited adverse events occurring in subjects who received *FluLaval* at an incidence of >2% included headache, pharyngolaryngeal pain, cough, upper respiratory tract infection and fatigue. Rates of these event rates were comparable to those in the pooled control arm. *FluLaval* subjects were significantly more likely than control subjects to report diarrhoea (RR=1.72), injection site erythema (RR = 3.00), injection site pain (RR = 3.06), injection site swelling (RR=3.58) and pharyngitis (RR=2.07). Each of these events was reported by more female than male *FluLaval* subjects and most events were mild or moderate in severity. However, the duration of these events appeared to be comparable or shorter in the *FluLaval* group versus the pooled control group.

No SAEs considered to be related to study vaccination occurred in these four studies. There were five deaths but none was considered to be related to vaccination by investigators and the details of these cases all point to underlying concurrent health problems.

There were 26 pregnancies in recipients of *FluLaval* reported from two of the four studies. A single pregnancy in one study is of unknown outcome since the subject was lost to follow-up. The other 25 pregnancies all occurred in one study of which four ended in spontaneous abortion, one ended with elective termination and one was lost to follow-up. The outcome also was unavailable for one other subject last reported to have a normal pregnancy. The outcomes for the 18 remaining pregnancies were term births with healthy infants.

The entity of oculo-respiratory syndrome (ORS) was initially described in Canada in the winter of 2000-2001. The syndrome definition included red eyes, cough, wheeze, chest tightness/difficulty breathing, sore throat, hoarseness or facial swelling. The pathogenesis of ORS remains unknown. It is

not an IgE-mediated hypersensitivity reaction and, while it may recur with subsequent vaccinations, it is not a predictor of serious hypersensitivity.

The initial reports linked ORS in Canada almost exclusively to *Fluviral* (i.e. *FluLaval*). Investigation of the product showed an unusual frequency of unsplit virions (most prominently for the A/Panama/2007/99 H3N2 strain, which was introduced in 2000). A modification of the detergent splitting conditions was introduced to resolve this issue. In addition, routine electron microscopy was introduced to ensure adequate viral disruption. These manoeuvres were associated with a decline in the rate of ORS reports over time.

Similar manifestations were reported at least once from Italy in the 1990s using a different vaccine. In the 2001-2002 influenza season a retrospective study in immunised healthcare workers in Quebec indicated no significant difference in the risk of ORS in recipients of *Fluviral* versus recipients of another manufacturer's vaccine. That study suggested that ORS could be a class effect, and could occur at a rate of approximately 5% among TIV recipients, which was consistent with earlier data descriptions. ORS was noted in a blinded clinical trial to have a vaccine-attributable incidence of approximately 2.9%, with the observation that many cases were sufficiently mild to escape detection under most (i.e. non-study) circumstances.

At present, the applicant believes that ORS may occur as a class effect of TIV but its occurrence has been reduced to background levels by the *Fluviral/FluLaval* manufacturing processes that are now in place.

The table below presents the pooled data relevant to ORS from the four randomised, controlled, blinded clinical trials in which adults received *Fluviral/FluLaval* or another TIV (either *Fluzone* or *Vaxigrip*) or placebo. Complaints consistent with ORS (along with other more typical reactogenicity symptoms) were actively solicited in each trial.

All of the components of ORS were reported and some were detected relatively commonly. However, the frequency was indistinguishable between the recipients of *Fluviral/FluLaval* and comparators – including the saline placebo. Therefore the applicant concluded that ORS does not represent a risk which is uniquely associated with the current formulation of *FluLaval*.

Discussion on safety

Based on the direct comparison made within study Q-Pan-001 the safety profile of Q-Pan H5N1 appears essentially the same as that previously described for D-Pan H5N1. Also, the data from the other reported studies with Q-Pan did not raise any new issues for the vaccine construct as a whole when compared to D-Pan. Based on these data, the differences in manufacturing process of the drug substance and in the excipients that are added during formulation of the antigen drug product do not seem to affect the safety profile of the vaccine.

As stated in the recent assessment report on the potential for the AS03 adjuvant to trigger the clinical onset of auto-immune diseases in predisposed individuals this remains under close scrutiny but so far without any definitive conclusion possible. Based on review of the individual case details from Q Pan and Flu NG trials the available information does not provide any new evidence to support an association between D or Q Pan and AIH or other autoimmune disorders. There is also no indication from the data provided that Q Pan carries any excess risk of liver disorders relative to D Pan.

The available safety data on Q-Pan H5N1 is already extensive. The clinical safety experience generated during clinical studies and routine use of *FluLaval* are reassuring. The safety of Q-Pan (H1N1) will be further assessed in the planned clinical studies and also through the large safety cohort study committed by the applicant and foreseen in the RMP.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

Following the approval of the core dossier, a revised description of the pharmacovigilance system was submitted during the assessment of the strain change variation. This version 3.05 (dated September 2009) included the name and registration certificate of the identified QPPV on Eudravigilance.

While the revised document did not fully address some other outstanding matters the CHMP agreed that the pharmacovigilance system could be considered to fulfil the legislative requirements provided that the remaining issues were rectified in an updated description of the pharmacovigilance system to be submitted within a month of the product being placed on the market (see section 2.7 Follow-up measures following the Marketing Authorisation).

Risk Management Plan

A risk management plan for the A(H1N1)v vaccine was submitted, which included a risk minimisation plan This was drafted in accordance with the CHMP core RMP for vaccines intended for use in a declared pandemic situation.

The CHMP, having considered the data submitted was of the opinion that the following activities are appropriate and necessary for the safe and effective use of the medicinal product as outlined in the Letter of Undertaking:

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

- The MAH commits to provide the results of the studies in pregnancy registries in both the UK and Canada in the simplified PSUR. The sPSUR will be continuously updated with all preliminary data and interim analysis resulting by these observational studies.

- The MAH commits to establish mechanisms to promptly investigate issues affecting the benefit-risk balance of the vaccine. The MAH should provide an inventory of all valuable databases ready to be use to promptly investigate issues affecting the benefit-risk balance of the vaccine. Details regarding databases (e.g., data sources, characteristics of the data, potential analysis) need to be reported. The characteristics and the validity of these sources, is to be agreed with EMEA within 1 month of the Commission Decision granting the Variation.

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

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

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

Table Summary of the Risk Management Plan

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anaphylaxis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs† o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 1/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	• Contraindication in the proposed labelling • Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components
Autoimmune hepatitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 20/100,000 doses distributed	NA*
Bell's palsy	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 24/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Convulsion	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 3,000/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA
Demyelinating disorders	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds published incidence rate • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA
Encephalitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 7/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Guillain-Barré syndrome	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed o Active monitoring in collaboration with national groups/agencies • Incidence will be estimated in participants of the post-authorisation safety study conducted in the EU • Study to establish a case-series in France, with possibility for case-control analysis, if needed • Monitoring within the Quebec provincial database	NA
Increased concentrations of hepatic enzymes	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if signal detected	NA
Neuritis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds published incidence rate • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Vasculitis	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period o Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed • Incidence will be estimated in participants of the post-authorisation safety studies conducted in the EU and Canada	NA
Vaccination failure	• Enhanced pharmacovigilance o Weekly signal detection o Use of targeted follow-up questionnaires o Individual reports expedited to regulators o Included in Table 3 of simplified PSURs o Cumulative analysis included in full PSUR following end of pandemic period • Incidence will be estimated in participants of the post-authorisation safety study conducted in the EU • Incidence will be estimated in the PCIRN Serious Outcome Surveillance Network (Canada)	NA
Vaccine effectiveness	• GSK Biologicals will support ECDC vaccine effectiveness project • GSK Biologicals will obtain results from the UK HPA project • PCIRN Severe Outcome Surveillance Network (Canada)	
Fever in children	• Additional clinical trials (H1N1-009, H1N1-010, H1N1-012, H1N1-023, H1N1-025) • Routine pharmacovigilance • Cumulative analysis in full PSUR prepared after the pandemic period	• No inclusion of children in the indication section of the proposed labelling • Statement in proposed labelling that there is no experience in children

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Missing data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy: • spontaneously reported by patients and HCPs • enrolled/observed during post-authorisation safety study • observed during clinical trials • reported via pregnancy registries in the EU and Canada	NA
Missing data in children	Conduct additional clinical trials • H1N1-009 (6 to 35 months) • H1N1-010 (3 to 17 years) • H1N1-012 (2 to 5 months) • H1N1-023 (3 to 17 years) • Post-authorisation safety study (depending on UK vaccination policy)	• No inclusion of children in the indication section of the proposed labelling • Statement in proposed labelling that there is no experience in children
Limited data in subjects with compensated underlying conditions; No data in subjects with severe underlying medical conditions and immunocompromise	• Routine pharmacovigilance • Post-authorisation cohort studiess in the EU and Canada: individuals will be included based on national recommendations, underlying medical conditions will be documented for *post hoc* analyses • Study in adults with HIV conducted by PCIRN (Canada)	NA

* NA = not applicable; † PSUR = periodic safety update report

The CHMP, having considered the data submitted in the MA application is of the opinion that the risk minimisation activities as detailed in section 2.3 of this CHMP Assessment Report are necessary for the safe and effective use of the medicinal product.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Clinical Context

In April 2009, a new strain of human influenza A(H1N1)v was identified and characterised. On 11 June 2009 the WHO declared an influenza pandemic.

Current estimates for the attack rate associated with the influenza A(H1N1)v virus vary from approximately 10-50 % in different geographical areas including local outbreaks such as in schools and kindergartens.

The development of Arepanrix was based on the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation applications (CPMP/VEG/4717/03) and the guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03).

In common with the approach taken for Pandemrix, the clinical data generated with Arepanrix (H5N1 and H1N1) can be used to support the licensure of Arepanrix in adults.

Clinical data submitted and assessed to support the MAA for Arepanrix include bridging studies between Pandemrix and Arepanrix H5N1 and H1N1 containing formulations in adults ≥ 18 years old and very limited bridging data from the two vaccines containing the AH1N1v strain.

Extrapolation of data from adults to other age groups

Extensive post-marketing experience from the use of Arepanrix in Canada in all age groups from 6 months onwards demonstrating no higher rates of ADR than expected support the safety conclusions from this dossier.

Further clinical data generated with Arepanrix in adults and clinical data in children will be submitted post-authorisation as commitments.

Quality

The manufacture of the A(H1N1)v antigen, the A(H1N1)v formulated vial and the AS03 (adjuvant) vial is appropriately controlled.
Adequate in-process controls, release and shelf life specifications have been set in line with relevant requirements (e.g. Ph.Eur.). The relevant quality data generated with the H5N1 vaccine construct can be considered supportive for the vaccine manufactured with the pandemic strain. Quality data required specifically for the pandemic strain have been provided and satisfactorily demonstrate the quality of the vaccine.
Commitments are made by the applicant to update some information when available, which does not impact on the risk/benefit assessment of this vaccine.

Non-clinical pharmacology and toxicology

The applicant discussed the mode of action of AS03 adjuvant and its use in prophylactic vaccines. The applicant also presented results of immunogenicity studies in mice and of homologous and

heterologous influenza challenge studies in ferrets, each using H5N1 vaccine, manufactured in eggs at the Quebec site.

The use of adjuvant in Q-Pan H1N1 is important as it is intended to allow a lower dose of antigen which will allow more subjects to be vaccinated for a given amount of antigen. The mode of action of AS03 is likely to be through an effect to augment the function of antigen presenting cells with release of pro-inflammatory cytokines that cause effects detected in animals in toxicity studies. Such effects are inherent in the mechanisms of action of AS03 adjuvant. The applicant provided numerous publications relating to the mechanism of action of adjuvants and their impact on immune system function, including that of antigen presenting cells. Use of AS03 adjuvant to augment immunogenicity is considered adequately justified.

Two immunogenicity studies were conducted in mice using H5N1 vaccine manufactured at the Quebec facility, adjuvanted with AS03. One used vaccine antigens from A/Vietnam/1194/2004 and the second used vaccine antigens from A/Indonesia/5/2005. Immunogenicity was greater in the presence of the adjuvant by both measures used (quantification of antigen-specific IgG in sera, haemagglutination inhibition tires) and a dose-response relationship was shown between antigen dose and serum IgG concentrations; however, there was no evidence of a dose-relationship using the functional antibody measure.

Vaccine efficacy studies were conducted in ferrets exposed to lethal challenge doses of homologous virus (A/Indonesia/5/2005), or heterologous virus (vaccine prepared from A/Indonesia/5/2005 H5N1 and the challenge virus was A/Hong Kong/156/97 H5N1) and a final experiment where the vaccine was based on H5N1 A/Vietnam/1194/04 and the challenge virus was A/Indonesia/05/2005 (10^5 TCID). All studies indicated that ASO3-adjuvanted vaccine conferred protection from lethal challenge with influenza virus, whereas without adjuvant, or with a half-dose of adjuvant, vaccine efficacy was compromised. Viral shedding, lung viral load measures and serology results were generally internally consistent, although in one experiment there was a lack of concordance between the test facility and the applicant's laboratory results for seroconversion. Cross-reactivity was indicated.

No concerns for human use was suggested by a safety pharmacology stud in rats conducted with intravenous dosing of Quebec-derived A-Wisconsin virus at 60 μg haemagglutinin /ml adjuvanted with AS03.

Two single dose and two repeat dose general toxicity studies have been reported and a further two repeated dose toxicity studies in rabbits are ongoing. Test material was Quebec-manufactured H5N1 vaccine, adjuvanted with AS03. Apart from pro-inflammatory changes at the injection site that are related to the primary mode of action of the AS03 adjuvant, there was no toxicity of note. These studies used the full human dose given intramuscularly to rabbits in a manner sufficient to support the intended clinical dosing.

Reproductive toxicity testing was described in rats and in rabbits. Testing suggested that the Quebec-manufactured vaccines tested did not adversely affect female fertility or pregnancy and no effect was indicated in the F1 generation. A study with H5N1 vaccine did not identify toxicity associated with vaccination in pregnancy animals when dosed from day 6 or pregnancy. Vaccination in early pregnancy, that is, prior and up to implantation of the embryo has not been directly studied. The applicant is conducting a study with AS03-adjuvanted vaccine to address this specifically.

Genotoxicity of the adjuvant was tested and indicated no positive findings.

The applicant provided results of a reproductive toxicity study with H5N1-AS03 adjuvanted vaccine in which there was proof of H5N1-antibody exposure; no toxicity was identified.

One remaining issue is that two general toxicity studies remain to be completed. One is a toxicity study in rabbits given three intramuscular injections of seasonal and pandemic influenza candidate vaccines with full, half and no dose of AS03 adjuvant, intended to support a quadrivalent vaccine with

two ‘A’ and two ‘B’ strains of influenza vaccine. The other is in rabbits given three intramuscular injections of Quebec-manufactured H5N1 vaccine with AS03 at the full human dose. Neither is considered critical to the approval of Arepanrix. The applicant committed to submit the study results.

Efficacy

The applicant has conducted a full clinical development programme with Arepanrix containing H5N1 antigens. Pandemrix and Arepanrix containing H5N1 strains have been shown to have comparable immunogenicity in adults in study Q-Pan-001 and there are also data in the elderly in study Q-Pan-002 that indicate comparable responses between Dresden and Quebec-manufactured vaccines.

As for the strain variation for Pandemrix during the October CHMP the Arepanrix H5N1 data can be extrapolated to the H1N1 containing vaccine when the rules of the core-mock-up principle are applied.

There are currently no clinical date with H1N1 containing Arepanrix in children.

As soon as further Arepanrix containing H1N1v strain specific data become available in any age group the CHMP will assess these and update its conclusions as necessary.

The available data (including the data on safety of *FluLaval*) indicate that the safety profiles of D-Pan and Q-Pan vaccines are comparable. Taking this into consideration, along with the comparable immune responses observed in adults to D-Pan (H5N1 and H1N1) and Q-Pan (H5N1 and H1N1), the CHMP concluded that the dose recommendations for Arepanrix in children can be aligned with those agreed for Pandemrix based on the following data:

Data supporting the use in the elderly (>60 years) was generated with Pandemrix (H1N1). The CHMP assessed data from this population in variation Pandemrix II-23 (study H1N1-008) and in II/34 post dose 1 immunogenicity and safety data from a phase III, randomised, single-blind study to evaluate the immunogenicity and safety of sequential administration of a licensed seasonal trivalent vaccine and Pandemrix administered in adults 61 years or above (DPAN-H1N1-020),.

Immunogenicity data in children and adolescents aged 3-17 years generated with Pandemrix (H1N1) has been assessed in variations Pandemrix II-32 and II-34. The data assessed included post dose 1 immunogenicity and safety data from study H1N1-010, that generated safety and immunogenicity data in children aged 3-17 years, and study H1N1-023, an open-label study to evaluate the safety and immunogenicity of a prime-boost schedule of Pandemrix H1N1 (using 1.9 µg HA and AS03B i.e. half adult doses) administered to subjects aged 3 to 17 years.

Data in children aged from 6 months to 9 years generated with Pandemrix H1N1 has been assessed within variation Pandemrix II/28 (post dose II safety and immunogenicity data from a phase II, randomised, open-label, multicentre study to evaluate the safety and immunogenicity of Pandemrix H1N1 following a homologous prime-boost schedule in children aged 6 to 35 months).

Overall the immune responses to Arepanrix and Pandemrix (both as H5N1 or H1N1 vaccine) can be considered to be broadly comparable.

Safety

Arepanrix and Pandemrix are not manufactured in an identical fashion.

Based on the limited data from the direct comparison made within study Q-Pan-001 the safety profile of Arepanrix H5N1 appears to be essentially the same as that described for Pandemrix H5N1. The data from the two reported studies with Arepanrix did not raise any completely new issues for the vaccine construct as a whole.

The data available with the H5N1 constructs cannot entirely predict the safety profile of H1N1v versions since there remains a possibility of ADRs associated with the antigenicity of the specific influenza strain.

Limited clinical safety data generated with Arepanrix indicate no safety concerns.

Safety data generated from FluLaval a seasonal vaccines which is manufactured in the same way like Arepanrix indicate also no safety concerns, as well as post-marketing data from Canada including over 5 million subjects including children and elderly vaccinated.

The safety of Arepanrix will be further assessed in 9000 subjects through a prospective non-interventional cohort safety study, which will occur in addition to the existing commitments for Pandemrix as outlined in the RMP

The safety data also suggested no important differences between vaccines. There was a higher rate of muscle aches in the Arepanrix group but some other symptoms showed higher rates in the Pandemrix group.

Overall the safety profiles appear to be comparable.

Study H1N1-017 is in keeping with the previous observations of comparable safety and immunogenicity between D-Pan and Q-Pan vaccines containing HA derived from H5N1 strains.

Having considered the safety concerns in the Risk Management Plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

User consultation

The applicant has performed readability testing on its Prepandemic H5N1 (Prepandrix) PL and bridged the Pandemrix H5N1 PL to the Prepandrix PL as the content, lay-out and writing style were similar than the Prepandrix PL. These testings were approved together with the May 2009 variations (EMEA/H/C/832/II/004-005-006). The Arepanrix PIL as submitted with the Rolling submission 2 in July 2009 corresponded to the approved Pandemrix H5N1 PL and has therefore not been retested.

The applicant further committed to perform a new readability test on the final approved Arepanrix PL and to provide the results as outlined in the Letter of Undertaking .This proposal was considered acceptable.

Risk-benefit assessment

Benefits

The CHMP considered that the real benefits of Arepanrix can only be assessed by effectiveness studies during the pandemic as outlined in the RMP. At present the benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination with a similar vaccine, Pandemrix plus data available from administration of Arepanrix A(H1N1)v vaccine during clinical trials and post-authorisation use in Canada.

Pandemrix and Arepanrix have shown (as H5N1 vaccine) to have comparable immunogenicity in adults and in the elderly that indicate comparable responses between Dresden and Quebec-manufactured vaccines.
In addition, the HI data at D21 in study H1N1-017 showed that both vaccines (as H1N1 vaccine) elicited immune responses that met the CHMP criteria in adults regardless of baseline serostatus and prior vaccination history.

There are limited data from clinical trials as yet in children with Arepanrix. An extrapolation of immunogenicity data on use of Pandemrix in children to use of Arepanrix in the same age groups might be considered on the basis of the comparable immunogenicity in adults. Therefore it is assumed based on immunogenicity considerations that the recommendations for Pandemrix H1N1v regarding use in children should also apply in principle to Arepanrix H1N1v.

Based on the data available with A(H1N1)v from clinical trials and post marketing with Arepanrix and Pandemrix the expected benefit of Arepanrix is to provide some protection against clinically-apparent infection due to A(H1N1)v.

Risks

Limited clinical data with Arepanrix do not suggest a different safety profile than Pandemrix or the one confirmed by clinical trials with Arepanrix or Pandemrix containing vaccine constructs manufactured using both H1N1 or H5N1 antigen.

Extensive use of Arepanrix H1N1 in Canada and Pandemrix H1N1 in Europe throughout all age groups from 6 months onwards can be considered sufficient to confirm the safety profile of Arepanrix to be favourable.

Conclusion

CHMP considers that the eligibility in accordance with Article 2(2) of Council Regulation (EC) No 507/2006 together with the criteria of conditional Marketing Authorisation in accordance with and 4 of Council Regulation (EC) No 507/2006 are fulfilled.

It can be further concluded that Arepanrix provides comparable immune responses and safety profile to the approved vaccine Pandemrix. The Benefit Risk ratio is considered positive

Recommendation

On the basis of the available data for Arepanrix the CHMP considered by consensus that the risk-benefit balance of Arepanrix A(H1N1)v for the prophylaxis of influenza in an officially declared pandemic situation, in accordance with official guidance, was favourable. Therefore CHMP recommended the granting of the conditional marketing authorisation.