European Medicines Agency
Evaluation of Medicines for Human Use

London, 24 September 2009
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CHMP ASSESSMENT REPORT
FOR
Pandemrix

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

Procedure No. EMEA/H/C/832/PU/17

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

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission history

The applicant GlaxoSmithKline Biologicals S.A. submitted on 2 February 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Pandemrix as an H5N1 mock-up vaccine, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

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 test(s) or study(ies)

The CHMP, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Pandemrix on 21 February 2008. The commission decision was issued on 20 May 2008.
The Applicant applied for the following indications: Prophylaxis of influenza in an officially declared pandemic situation.

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

A/California/07/2009 (H1N1)v like strain (X-179A)

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

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

CHMP Peer reviewer(s): Dr. Christian Schneider

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 2 February 2007.
- Accelerated Assessment procedure was agreed-upon by CHMP on 14 December 2006.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 May 2007.
- During the meeting on 22 May 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 May 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 31 October 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 December 2007.
- During a meeting of BWP Working Party on 14-15 January 2008, experts were convened to address the outstanding quality issues identified in the Joint response assessment report.
- During the CHMP meeting on 24 January 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 31 January 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 8 February 2008.
- During a meeting of BWP Working Party on 11-13 February 2008, experts were convened to address the responses to the outstanding quality questions.
- During the meeting on 18-21 February 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation under exceptional circumstances to Pandemrix on 21 February. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 19 February 2008.

- On 29 May 2009 the CHMP adopted a positive Opinion on a type II variation (II-04) to update sections 4.2, 4.4, and 5.1 of the summary of product characteristics (SPC) to include the possibility of administering one dose of Pandemrix after primary immunisation with the MAH's prepandemic vaccine containing H5N1 antigen from a different clade of the same influenza subtype, based on the data from clinical trials (H5N1-012 and -015). The package leaflet (PL) was updated accordingly. The European Commission adopted a positive Commission Decision for variation II-04 on 10 July 2009.

- On 29 May 2009, the CHMP adopted a positive Opinion on a type II variation (II-05) to update sections 4.2 and 5.1 of the SPC to include treatment in subjects aged 61 years and above based on clinical trial data. from study H5N1-010 Annex II and the PL were updated accordingly. . The European Commission adopted a positive Commission Decision for variation II-05 on 10 July 2009.

- On 29 May 2009, the CHMP adopted a positive Opinion on a type II variation (II-06) to update section 5.1 of the SPC regarding the interval between 2 doses for the primary vaccination schedule based on data from a clinical trial (H5N1-012). The PL was updated to reflect the results of user testing. The European Commission adopted a positive Commission Decision for variation II-06 on 10 July 2009.

- On 1 September 2009 an interim Opinion on a rolling review (RR/01) was adopted by the EMEA Task Force (ETF)/CHMP to include information supporting the introduction of paediatric data from study H5N1-009 (-022/023) in section 5.1 of the SPC for Pandemrix H1N1.

- On 21 September 2009 an interim Opinion on a rolling review (RR/02) was adopted by the ETF/CHMP to include information on the drug substance to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

- On 21 September 2009 an interim Opinion on a rolling review (RR/03) was adopted by the ETF/CHMP to include information on the drug product to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A); a revision of the Product Information (PI), responses to Questions from RR01 and RR02 the Pharmacovigilance and Risk Management Plan to support a change on the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A) and preliminary data from study H1N1-021.

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

- On 24 September 2009, the CHMP adopted a positive Opinion on a variation (PU-17) to change the pandemic strain vaccine composition to A/California/7/2009 (H1N1)v like strain (X-179A).

2. SCIENTIFIC DISCUSSION

2.1. Introduction

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which 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.

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

So far in this pandemic there has been a marked under-representation of infections in people over 65 years of age. In Europe, the median age has been 25 years in those who acquired the infection during travel and 13 years in those infected within the EU. Nearly 80% of cases have been in individuals under 30 years of age. Deaths have occurred in previously healthy subjects as well as in those with underlying conditions or pregnancy that would predispose them to complications of influenza. For more information about the known clinical features of the disease caused by influenza A(H1N1)v virus please see the updated Risk Assessment report from ECDC under:
http://ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf

Specific guidance has been developed for the fast track assessment procedure for pandemic influenza vaccines[2], which can only be used once WHO/EU have officially declared the pandemic (WHO Phase 6). The procedure involves the submission and evaluation of a core pandemic dossier during the inter-pandemic period that is based on a mock-up vaccine, followed by a fast track assessment of the data for replacing the antigens from the strain used to manufacture the mock-up vaccine with antigens from a recommended pandemic strain as a variation to the MAA.

The approval of a core dossier followed by a strain change variation 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.

[2] 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).

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

GlaxoSmithKline Biologicals received a Marketing Authorisation (core pandemic dossier) for the mock-up vaccine of Pandemrix in line with the above mentioned guidelines. The mock-up vaccine 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. The final formulation contains 3.75 µg haemagglutinin (HA) per 0.5 ml dose adjuvanted with AS03. Pandemrix is indicated for prophylaxis of influenza in an officially declared pandemic situation and for use in accordance with official guidance.

On 22 September 2009 GlaxoSmithKline Biologicals applied for a variation to change the strain used for manufacture of Pandemrix to A/California/07/2009 (H1N1)v. The strain used has been officially recommended by WHO and CHMP for the manufacture of vaccines during the current pandemic.

Pandemrix is based on the proposed new strain A/California/7/2009 (H1N1)v like strain (X-179A), which complies with the WHO[3] and CHMP[4] recommendations for the emergent novel A(H1N1)v influenza vaccine composition. In support of the strain change to A/California/07/2009 (H1N1)v, GlaxoSmithKline Biologicals submitted quality data in accordance with the quality requirements for a novel influenza A(H1N1)v vaccine, the *Guideline On Dossier Structure And Content For Pandemic Influenza Vaccine Marketing Authorisation* (CPMP/VEG/4717/03 Rev. 1) and *EMEA fast track procedure for community human influenza inactivated vaccines annual strain(s)* (CHMP/BWP/99698/07). The same manufacturing process, with the exceptions of strain dependant parameter, and safety precautions were applied to the production of H5N1 and A(H1N1)v, which includes the release and shelf-life specifications. The MAH provided quality data in support of this variation to demonstrate that the vaccine containing A/California/7/2009 (H1N1)v like strain (X-179A) is comparable, from the quality point of view, to the Mock-up containing H5N1 A/Vietnam/1203/2004.

The non-clinical data and most of the clinical data available at time of the strain variation were generated with vaccine constructs that included an influenza A H5N1 strain. The clinical data all pertained to use of H5N1 influenza strains. The first clinical data from an investigational formulation (with a higher amount of antigen but otherwise manufactured as for the mock-up vaccine) of Pandemrix including the A(H1N1)v strain were provided by the MAH on 09 September 2009 and are described and discussed in this report.

The first clinical data on the final formulation of Pandemrix A(H1N1)v (i.e. with the antigen content as specified for the mock-up vaccine and in the strain change variation) will be available by mid-October 2009 and will come from adults aged 18-60 years. Data from subjects aged > 60 years and from children and adolescents will follow at intervals. Submission of these data at specific time points is included in the Specific Obligations agreed for Pandemrix 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 Pandemrix influenza A(H1N1)v vaccine. The Pandemrix SPC summarises the existing clinical data. The Clinical Particulars will be updated as new data are submitted and reviewed.

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

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

2.2. Quality aspects

The quality section is divided into two parts of which chapter 3.2.1 describes quality characteristics pertaining to the initial Mock-up vaccine (developed with A/Vietnam/1203/2004 (H5N1) and chapter 3.2.2. describes quality characteristics submitted in support of the strain change variation to introduce the new pandemic strain A/California/07/2009 (H1N1)v like strain (X-179A).

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

Introduction

Pandemrix is a split virion inactivated influenza vaccine. The mock-up final formulation contains 3.75 µg haemagglutinin (HA) of A/VietNam/1194/2004 NIBRG-14 (H5N1) per 0.5 ml dose adjuvanted by AS03.

The mock-up reference virus is A/Vietnam/1194/2004 (H5N1) NIBRG-14 which was developed 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.

The mock-up vaccine consists of a suspension vial with the H5N1 antigen and an oil–in-water emulsion vial with the AS03 adjuvant, which are mixed extemporaneously. Thiomersal, 10 µg/ml (5 µg per dose), is added because of the multi-dose presentation.

Each 0.5 ml dose of vaccine has the following composition:

Active Ingredient:	
Purified antigen fractions of inactivated split virion A/Vietnam/1194/2004 NIBRG-14 (H5N1)	3.75 µg HA
Adjuvant:	
Squalene	10.69 mg
Alpha-tocopherol	11.86 mg
Polysorbate 80	4.86 mg
Other Ingredients:	
Octoxynol 10	
Sodium chloride	
Disodium phosphate	
Potassium dihydrogen phosphate	
Potassium chloride	
Magnesium chloride	
Thiomersal	
Water for injections	

Active Substance

- *Manufacture*

A master and working seed were prepared from the NIBRG-14 reference virus, received from the WHO Reference centre (NIBSC, UK). The manufacturing process for the monovalent bulks is similar to the manufacturing process for the monovalent bulks of the licensed product Fluarix (seasonal influenza virus) and can be divided into four main parts:

- Propagation of the working seed in fertilised hen's eggs, harvesting and pooling of infected allantoic fluids
- Purification of the whole virus bulk
- Splitting of the monovalent with sodium deoxycholate
- Inactivation of the monovalent split virus using sodium deoxycholate and formaldehyde, followed by ultrafiltration and sterile filtration

The process parameters are generally derived from the Fluarix process. Where needed these have been specifically determined for this H5N1 strain.

- *Control of Materials*

The following starting materials used in the production of the monovalent bulk are of biological origin: influenza seed virus, eggs and sodium deoxycholate (derived from bovine bile). The H5N1 working seed is derived from the A/Viet Nam/1194/2004 (H5N1) NIBRG-14 vaccine virus strain.

The testing of the virus and the eggs is the same as for Fluarix. Sufficient detailed information has been provided on the control and source of these starting materials. The genetic stability of the A/VietNam/1194/2004 (H5N1) NIBRG-14 obtained through Reverse Genetics has been satisfactorily addressed.

- *Process validation*

Critical steps of the drug substance production process have been identified and are sufficiently controlled. Process consistency has been demonstrated on three commercial scale batches.
Inactivation studies performed on different H5N1 strains have demonstrated that the proposed inactivation method (Sodium deoxycholate and formaldehyde) results in complete inactivation. Based on experience with Fluarix, the ability of the manufacturing process to inactivate avian leucosis and mycoplasma 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.
Controls include HA content, neuraminidase identity, sterility tests, tests for residual infectious viruses, residual sodium deoxycholate and test for disrupted virus particles (not routine) and are in line with Ph.Eur. monograph <0158>.
All analytical methods have been appropriately validated.
The monovalent bulks are filled and stored in 10 l glass Type I containers with polypropylene closures.

- *Stability*

Eighteen months of stability data at 2-8°C has been generated for three relevant batches.

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 consists of formulation of the final bulk with the excipients at SSW (Germany), transport from SSW (Germany) to GSK Biols (Belgium: Rixensart or Wavre sites and Canada: Quebec site for filling into final containers and then finally labelling and packaging at GSK Biols (Wavre).

Antigen bulk received is sterile. Bioburden is adequately controlled throughout the manufacturing process.
The sterile filtered H5N1 monovalent bulk (SSW, Dresden) and non-sterile excipients, are sterilised in-line, just prior to entering the mixing tank (SSW, Dresden). The resultant bulk is then transported in validated containers, initially to GSK Wavre for cold storage, and then for filling at GSK Rixensart or GSK Wavre or GSK Quebec. Formulation of final formulated bulk and subsequent filling into transport containers, and later, pooling of transported HDPE containers into the filling tank and subsequent filling is conducted under aseptic conditions. Stability data have been submitted to support the maximum storage period of the formulated bulk filling into bulk transport containers (30 days) and in the filling tanks (14days).

- *Product Specification*

Compliance with the product specifications has been shown on three batches representative of the final formulation and commercial scale manufacture
Specifications for excipients and analytical procedures are in line with the Ph.Eur. Controls of final bulks (sterility, HA, total protein, residual ovalbumin, thiomersal, residual formaldehyde and residual sucrose) and final containers (sterility, bacterial endotoxins, pH, volume, thiomersal and HA) of the antigen vial are acceptable (Ph.Eur. or in line with Fluarix). Methods are either in line with Ph.Eur. or are validated. Specificity in presence of thiomersal has been demonstrated.

HA content, sterility, thiomersal content, endotoxin content, pH and description, formaldehyde, ovalbumin and protein content are measured as part of the stability studies. Test methods and specifications are identical to those at release.
The proposed shelf life (i.e. 24 months) is accepted on basis of the updated stability results provided by the MAH.

An overage of 10 % HA will be applied at formulation of the commercials lots and supporting data and satisfactory justification have been provided.

Medicinal Product (AS03 adjuvant vial)

- 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 (formation of O/W emulsion using high shear and pressure homogenisation) 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, 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 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 extemporaneous dispensing, adjuvant is added to antigen vial. Data from 'withdrawable' volume studies conducted to support the required overfill for both antigen and adjuvant vials is provided. Information on long term storage (1 week) of mixed AS03 adjuvanted H5N1 is also provided.

Preservative efficacy of thiomersal concentration after mixing the content of the antigen container with AS03 adjuvant has been shown in line with Ph.Eur.

Sufficient compatibility/stability data has been provided in the dossier.

SDS PAGE and Western blot analysis performed show that profiles of the adjuvanted formulation are comparable to the non-adjuvanted formulation and remain unchanged after a period of 24 hours at 25°C. Interaction between antigen and adjuvant has been shown to be limited by various biophysical methods Uniformity of dose has been demonstrated for the 10-dose product.

In addition, non-clinical studies have shown similar immune responses were observed when antigen and adjuvant were administered separately (one hour apart at the same site, or simultaneously in 2 separate syringes in the same area) or after administration of pre-mixed antigen and adjuvant.

Therefore, it is accepted that there is no need to control antigen/adjuvant interaction for this product. Sufficient evidence has been provided that there is little/no effect of the reconstitution conditions (mixing time and conditions) on the essential characteristics of the antigen/adjuvant combination. The proposed in-use shelf life of 24 hours is considered justified based on stability/characterisation data provided.

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

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

The proposed influenza strain for Pandemrix is: A/California/7/2009 (H1N1)v like strain (X-179A). This vaccine strain complies with the WHO[5] and CHMP[6] recommendations for the emergent novel A(H1N1)v influenza vaccine composition and therefore is accepted.

The MAH provided quality data in support of this variation to ensure that the manufacture of the drug substance and drug product are 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.

The manufacturing process for A/California/7/2009 (H1N1)v like strain (X-179A) monovalent bulks is the same as the manufacturing process for A/Vietnam (H5N1) monovalent bulks (i.e. thiomersal-free monovalent bulk manufacturing process. Reference is made to the type II variation EMEA/H/C/000832/II/0010, positive opinion dated June, 25th 2009), with the exceptions of strain-dependant parameters. This is also the process used and approved to produce the monobulks of seasonal strains, used in *Fluarix*.

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. The master seed has been shown to be sterile and free from avian and human mycoplasmas in line with Ph.Eur 2.6.7. 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 approved for Pandemrix H5N1. Data on the results of safety tests in ferrets for the primary seed have been provided.

Eggs used for establishing seeds are SPF. The master seed prepared by GSK corresponds to E7/E1/E1. Commercial A(H1N1)v monobulks have been prepared with this master seed and also with working seeds derived from the master seed with up to 2 additional passages (i.e. up to E7/E1/E3). 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 (sodium deoxycholate (NaDoc) and formaldehyde) for the proposed strain and data are comparable to that seen for A/Indonesia H5N1. Splitting has been validated for three monovalent bulk lots using TEM and by analysis of sucrose gradient profiles for protein, HA and phospholipid partition for lots produced directly from the master seed.

The SRD method has been satisfactorily requalified using intended antigen and antisera. The MAH has demonstrated that the method is precise at 15µg/mL (100% concentration), and down to 25%. Sufficient assay validation data is provided to assure acceptable performance of SRD assay to quantify HA content in the monovalent bulk and as such also of the drug product.

Batch analysis results are provided for four commercial monovalent lots (produced using the strain-adapted process); produced at Building G and Building A/B using the master seed (using (E7/E1/E1). Batch analytical data are also provided for lots produced from the working seeds (E7/E1/E2 and E7/E1/E3). All batches demonstrate that registered specifications for Pandemrix are met.

[5] http://www.who.int/csr/resources/publications/swineflu/vaccine_recommendations/en/index.html
[6] EU recommendation for the emergent novel H1N1 influenza vaccine composition (EMEA/CHMP/BWP/3408312009 Rev 1). http://www.emea.europa.eu/pdfs/human/bwp/34083109enrev1.pdf

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 monobulks has been provided.
Real-time, real-temperature stability data are presented for up to two months for the four monovalent bulks produced from the master seed. Overall, the stability of the HA content during the period evaluated is satisfactory. The approved shelf-life for H5N1 monobulks is 18 months and this can be applied to the A(H1N1)v strain. The MAH 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.

Preservative: it contains 5 micrograms thiomersal

Other ingredients:
Suspension vial:
Polysorbate 80
Octoxynol 10
Sodium chloride (NaCl)
Disodium hydrogen phosphate (Na_2HPO_4)
Potassium dihydrogen phosphate (KH_2PO_4)
Potassium chloride (KCl)
Magnesium chloride ($MgCl_2$)
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
The approved specifications for final bulk and drug product have not been changed.

The A/California/7/2009 (H1N1)v like strain (X-179A) final bulks and final containers are respectively formulated and filled as approved for the H5N1 final bulks and final containers of Pandemrix H5N1. The same control processes as for Pandemrix H5N1 are applied to the antigen component of the MAH's A/California (H1N1)v influenza vaccine adjuvanted with AS03. The SRD method used for analysis of final bulks and final containers is the same as that used at the level of the monovalent bulks. QC release data for the A/California (H1N1)v final bulks and final containers presented conform to the specifications approved and in force for the antigen component of Pandemrix H5N1.

Compatibility of the split inactivated A/California (H1N1)v antigen with the AS03 adjuvant is demonstrated for the A(H1N1)v clinical lot being used in 10 trials across Europe, throughout the vaccine's in-use shelf life of 24 hours, as approved for Pandemrix. Results demonstrate the integrity of the HA antigen and the AS03 adjuvant upon formulation of the adjuvanted A(H1N1)v vaccine.

Stability data after storage for one month at 2-8°C are also available for 3 lots of final vaccine produced from the master seed. Preliminary accelerated stability data for A(H1N1)v A/California final containers stored at 30°C ± 3°C show a drop in HA content during the first week of storage, though this was also seen with H5N1 lots and is not representative for stability under long-term conditions. The confirmatory long-term stability program will cover 60 months storage at 5°C ± 3°C. The MAH is proposing an alignment to the shelf-life approved for the antigen and the adjuvant components of Pandemrix H5N1 (i.e. 24 months shelf-life at 2-8°C for the final antigen containers and 36 months at 2-8°C for the adjuvant), since the vaccine composition is unchanged apart form the vaccine strain. This is accepted.

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 Pandemrix 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 MAH's own Fluarix brand of seasonal influenza vaccine. This was approved in 1992 and over 200 million doses have been manufactured. As advised in regulatory guidance documents, preclinical testing with Fluarix can be used to support this application, based on the similarity of manufacture.

No new non-clinical studies with A(H1N1)v were submitted at the time of the strain variation.

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

Pharmacology

- Primary pharmacodynamics

Primary pharmacodynamic properties were investigated in mice, pigs and ferrets.

The studies demonstrate the ability of the AS03 adjuvant to augment immunological responses to the vaccine in mice and pigs. The data from the pig study show a statistically significant effect of dose of adjuvant in one of the three tested influenza strains, the B/Shangdong strain. A non-significant dose-response effect might be suggested with the A/Panama strain.
Efficacy of the vaccine was tested in a challenge test in ferrets. Survival data are compelling in that, where a sufficient dose of antigen was used, protection from a lethal challenge was obtained.
Consistent changes in serological and pathological parameters were detected and it can be concluded that the vaccine provided protection from virus-associated pathological changes.

- 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

No safety pharmacology studies were performed with Pandemrix vaccine. A study was reported in the anaesthetised rat, using trivalent influenza vaccine, adjuvanted with AS03, or saline. Single intramuscular injection of 0.1 ml of this vaccine administered to anaesthetised male Wistar rats (n = 4) did not produce any effects on cardiovascular or respiratory parameters in the 2 hour period following dosing. The vaccine used in this study contains 15 µg HA per strain and AS03. The dose represents 63 fold higher than the human exposure, on a µg/kg bodyweight comparison.

- Pharmacodynamic drug interactions

No studies were performed.

Pharmacokinetics

Experimental studies to demonstrate absorption, distribution, metabolism, and excretion of the active ingredients in Pandemrix 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

The MAH refers to the local tolerance study for consideration of single-dose toxicity.

- Repeat dose toxicity (with toxicokinetics)

Two studies in the rabbit using intramuscular injection have been performed. One used four doses of the adjuvanted vaccine and the second used two doses of a trivalent seasonal influenza vaccine, with the AS03 adjuvant.

Pandemic influenza vaccine: toxicity study in the rabbit after 4 injections

10 male and 10 female New Zealand White rabbits were injected with test item by the intramuscular route on Days 1, 15, 29 and 43 and were killed for pathological examination on either Day 46 or Day 71. Periodical assessments included mortality, clinical observations, injection site reactions, body weight, food consumption, ophthalmological examination, body temperature, haematology, clinical chemistry, organ weights and macro- and microscopic examination of tissues, including evaluation of spermatogenesis.
Very slight erythema and/or oedema occurred commonly but abated within 48 hours. On subsequent injections this was no more marked than the control group. There were no other clinical signs noted.
There was evidence of an inflammatory response in haematology, clinical chemistry and pathological parameters. Increases in fibrinogen and white blood cell counts were noted in temporal association with the erythema and oedema noted on observing the rabbits. Relative to body weight, the spleen weight was increased in all groups compared to the control (7 - 41%). This difference was much less marked from rabbits killed on Day 71, 28 days after the last injection, indicating reversibility.
Frequency and severity of fasciitis was higher in rabbits from the vaccine group. This toxicity was attributed to the adjuvant.

Seasonal influenza vaccine: toxicity study in the rabbit after 2 injections
10 male and 10 female New Zealand White rabbits were injected with 0.5 ml of test item by the intramuscular route on Days 1 and 24 and were killed for pathological examination on either Day 27 or Day 52.
There were no deaths and no clinical signs detected in this study, except one instance of very mild erythema shortly after injection of Fluarix. Minor changes indicative of an inflammatory response

were noted in clinical chemistry and haematology in rabbits dosed with AS03 or with the trivalent influenza vaccine. These changes reduced over time, indicating recovery.

- 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

Preliminary immunogenicity studies were performed in the rat in which the immunogenic responses of the dams, foetuses and pups were confirmed, demonstrating that the rat is a suitable species for assessing toxicity of the vaccine.

In this study, six groups of 48 female rats were given a single intramuscular dose on Day -30 and paired with males and 44 rats with a positive indication of mating were treated on Days 6, 8, 11 and 15 after mating. 22 were killed at Day 20 and 22 were allowed to deliver and rear their young to Day 25 of age. Measures of reproductive toxicity and maternal health were assessed. The six groups were dosed with:

1 saline, 200 µl
2 AS03 adjuvant, 200 µl
3 saline / split H5N1/AS03, 200 µl
4 split H5N1 / AS03, 200 µl
5 saline /whole H5N1/A1, 100 µl
6 whole H5N1/A1, 100 µl

There was one unexpected death in a maternal rat: however, this was judged unrelated to the vaccine. Treatment of maternal rats did not adversely affect their clinical condition, bodyweight or food consumption throughout the study. Mating performance, fertility of maternal rats, and length of gestation or ability to give birth to a live litter were unaffected. Embryo-foetal survival, growth and development were not affected by vaccination. In neonates, the reflex development was unimpaired, but among offspring from dams treated with AS03 13 offspring from 7 litters did not show the air righting reflect before day 21 of age and this effect may be related to treatment. However, AS03 did not affect the attainment of the surface righting reflex or the ability of the offspring to show startle response reflexes or the pupil reflex. No abnormalities were evident on macro pathological examination of the offspring. This is considered a suitable study to assess the reproductive toxicity of the vaccine.

As no administration around implantation phase of the embryos was performed, the use of AS03-adjuvanted vaccine in early pregnancy was considered not directly supported by the study. The MAH has agreed to conduct a study where the vaccine will be given to pregnant animals, early in their pregnancy. The MAH argues that the adjuvant is not expected to have adverse effects on early pregnancy primarily because the innate immune response is local to the site of injection and on injection of the adjuvanted vaccine, there is no systemic cytokine response detectable. However, the effect of adjuvant plus antigen in the vaccine has not been directly studied in early pregnancy. No effects of concern were identified in later pregnancy. The SPC statements adequately reflect that animal studies did not indicate harmful effects with respect to fertility, pregnancy or embryofetal development.

This vaccine will be widely used in a healthy population at risk of infection with a virus that may cause severe disease, or may yet be mild in most cases. Pregnant women are considered more at risk

from influenza than the general population and are thus more likely to be vaccinated early in vaccination campaigns. The present concern relates to early pregnancy as there are data from exposure post-implantation from animals. Risk-benefit considerations include that additional data from animals do not directly predict what happens in humans and that in some cases women will not know they are pregnant at the time of vaccination. Although the MAH's expectation that harmful effects will not be identified is reasonable, this should be tested experimentally, rather than inferred, especially where the population to be exposed are healthy and large in number. The MAH committed to investigate this matter further.

- Local tolerance

The test items in this study were the adjuvant, AS03, a candidate trivalent influenza vaccine adjuvanted with AS03, and Fluarix, which is the MAH's approved inactivated influenza vaccine and which is not adjuvanted. Thus, the vaccine intended to be marketed was not used in this test. This study also served as the assessment of single dose toxicity.

Single intramuscular injection of the test items (n = 3) or of saline (n = 2) into the thigh muscle of New Zealand White rabbits was followed by clinical observation for dermal reactions (erythema and oedema were each graded separately on 5 point scales) and clinical signs until Day 4 when rabbits were killed and subject to microscopic examination of the injection sites. Dose volumes of 0.5 ml were used, injected into the upper and the lower thigh. 7.5 and 15 μg of trivalent influenza was used (the clinical dose of the monovalent vaccine is 3.75 μg).

There were no deaths or clinical signs in the study. On visual examination, dermal reactions were unremarkable, with very slight oedema noted in one rabbit 3 hours after injection of the adjuvant AS03, and also in another rabbit injected with the trivalent vaccine. Very slight erythema was noted commonly in all groups. On microscopic examination, the adjuvant was associated with multifocal or diffuse infiltrating low grade sub-acute fasciitis with macrophage infiltration. Fasciitis of the skin was also evident. These effects were more evident than in tissues from rabbits injected with either saline or Fluarix. Such changes were also noted in tissue from rabbits injected with the trivalent vaccine, to a similar degree.

- Other toxicity studies

Immunogenicity described under pharmacology. Other studies were not reported.

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

Introduction

The avian influenza strain H5N1 strain was initially considered as a possible candidate to cause the next influenza pandemic. Therefore the MAH decided to base the mock-up dossier on clinical studies performed (immunogenicity and safety) with vaccine containing antigens from A/Vietnam/1194/2004 (H5N1). The MAH also performed studies with vaccine containing antigen from A/Indonesia/5/2005 (H5N1), results of which were assessed via the appropriate regulatory procedures.

Since then, Phase 6 of the influenza pandemic has been declared and the strain A/California/07/2009 (H1N1)v was officially recommended. The first clinical data from an investigational formulation (with a

higher amount of antigen) of the vaccine including the A(H1N1)v strain were submitted and considered during the review of this application. Clinical data on the approved formulation of Pandemrix A(H1N1)v are expected in accordance with agreed timelines.

GCP

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

Pharmacokinetics

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

Pharmacodynamics

In relation to vaccines, the pharmacodynamic studies consist of assessments of the immune responses. The data on the immunological response to Pandemrix mock-up vaccine and final pandemic strain vaccine obtained during clinical studies are described and discussed below.

Clinical efficacy

Pre-licensure clinical trials that evaluate the protective efficacy of the Pandemrix mock-up vaccine or final pandemic strain vaccine cannot be performed. Therefore the assessment of the potential protective efficacy of Pandemrix was based mainly on the detailed characterisation of the immunological response to the mock-up vaccine containing H5N1 strains (either A/Vietnam or A/Indonesia).

The available data on the H5N1 mock-up vaccine up to the time of approval of the core dossier came from three studies as shown below. Data were available at Day 42 from each study and some antibody persistence data were available up to day 180 from studies 007 and 008/011. Additional longer-term data from study 011 and also from H5N1-030 (the continuation phase of study 002) were submitted after first approval of the core dossier but for convenience they have been described with the primary series data below.

Study	Primary Objective(s) Countries	Population/ age of subjects	Study vaccines	N safety	N immuno
H5N1-007 And ext study 015	Immunogenicity Reactogenicity/safety Belgium only	Unprimed population 18-60 years	Monovalent split vaccine (H5N1). 30 µg, 15 µg, 7.5 µg or 3.8 µg HA * with or without AS03 2-dose schedule 21 days apart	400	394
H5N1-008 And ext study 011	Reactogenicity/safety Germany, Estonia, France, Netherlands, Russia, Spain, Sweden	Unprimed population > 18 years	Monovalent split vaccine (H5N1) 15 µg HA with AS03 or Fluarix (first dose), placebo (second dose) 2-dose schedule 21 days apart	3802 1269	455 154
H5N1-002 And ext study 030	Immunogenicity - lot consistency Reactogenicity/safety Taiwan, Thailand, Singapore and HongKong.	Unprimed population 18-60 years	Monovalent split vaccine (H5N1). 3.8 µg HA with or without AS03 2-dose schedule 21 days apart	954 with AS03 245 without AS03	933 with AS03 236 without AS03

N safety = Total vaccinated cohort;
N immuno = ATP cohort for immunogenicity
*: Vaccine doses were expressed using only one digit throughout the clinical documentation, i.e. 3.75 µg Haemagglutinin [HA] was rounded up to 3.8 µg HA in the dossier.

After first approval the MAH provided additional data from the following studies with the H5N1 mock-up vaccine:

H5N1-012 was an open, randomised study in healthy adults aged 18-60 years. The data were provided to support the possibility of administering one dose of Pandemrix after primary immunisation with one or two doses of the same vaccine formulation except that the H5N1 antigen was derived from a different clade of the virus.

H5N1-015 was a continuation (boosting phase) of the dose-finding study 007. Boosting in study 015 occurred at approximately 14 months after the two priming doses. The data from this study are described separately below since there was an additional group.

H5N1-010 was an open label study that compared administration of two single or two double doses of vaccine on Day 0 and on Day 21 in subjects aged 61 years and above. The comparative groups received single or double doses of non-adjuvanted vaccine of the same HA content.

H5N1-009 (-022/023) enrolled children aged from 3-9 years to receive two doses at Day 0 and Day 21 of either the adult dose of the H5N1 mock-up vaccine, half the adult dose or half the amount of HA but the same amount of AS03 adjuvant as in the adult dose.

In September 2009, just before approval of the strain change variation to the mock-up vaccine, the MAH provided preliminary data from **H1N1-021**, which was conducted with Pandemrix containing A(H1N1)v antigen from an approved pandemic strain for vaccine manufacture. The antigen content was slightly higher than that in the final vaccine because a preliminary method for estimating the antigen content had been used. The data were limited to HI responses at 21 days after a single dose. These data were taken into account in drafting the final SPC for the A(H1N1)v vaccine.

Assays

Anti-haemagglutinin antibody titres (HI titres) were measured using the method described by the World Health Organization Collaborating Centre for Influenza, Centres for Disease Control, Atlanta, USA (1991). All assays were performed in duplicate. The following parameters were assessed:

- Seropositivity rate defined as the percentage of vaccinees with a minimum titre of 1:10.
- Seroconversion factor (SCF) defined as the ratio of the post-vaccination GMT divided by the pre-vaccination GMT.
- Seroconversion rate (SCR) defined as the proportion that was either seronegative prior to vaccination and had a post-vaccination titre ≥ 1:40 or seropositive prior to vaccination and had at least a 4-fold increase in titre post-vaccination.
- Seroprotection rate (SPR) defined as the proportion with post-vaccination titres ≥ 1:40.

The results were compared against the CHMP criteria applied to the assessment of seasonal influenza vaccines for age groups 18-60 years and > 60 years.

Virus neutralisation titres (NA titres) were determined in a micro-neutralisation assay. Each serum was tested in triplicate. A standardised amount of virus was mixed with serial dilutions of serum and incubated to allow binding of the antibodies to the virus. Results of neutralising serum antibodies were expressed as follows:

- Seropositivity rate defined as the percentage of vaccinees with a minimum titre of 28 (1/dil).
- Seroconversion rate (with 95% CI) defined as the percentage of vaccinees with a minimum 4-fold increase in titre from pre- to post-vaccination
- GMTs of serum neutralising antibodies pre- and post-vaccination (with 95%CI)

Influenza-specific cellular responses were assayed using a method that involved stimulation of peripheral blood antigen-specific CD4 and CD8 T cells *in vitro* to produce cytokines on incubation with corresponding antigen. Antigen-specific CD4 and CD8 T cells were enumerated by flow cytometry following conventional immunofluorescence labelling of cellular phenotype (using anti CD8 APC Cy7 / anti CD4 PerCP) as well as intracellular cytokine production. Results were expressed as a frequency of cytokine(s)-positive CD4 or CD8 T cells within the CD4 or CD8 T cell population.

Studies with the H5N1 mock-up vaccine submitted before approval of the core dossier

Studies **H5N1-002 and -007** enrolled healthy males and females aged 18 to 60 years while study **008** also enrolled subjects aged > 60 years. Study groups were as in the table above.

In **study 007** immunogenicity (HI) and safety were co-primary objectives. The randomisation algorithm used a minimisation procedure accounting for centre and age and subjects were stratified according to age (18-30 years old or 31 to 60 years old). The target sample size was 400 (i.e. 50 for each of the eight groups) to provide 360 evaluable subjects.

In **study 008** the primary objective was to evaluate the safety of a 15 µg/AS03 candidate vaccine but immunogenicity was evaluated in a subset. The randomisation algorithm used a minimisation procedure accounting for centre and age and employed three strata (18-30, 31-60 and > 60 years). There was a 3:1 allocation ratio in favour of the candidate vaccine. The sample size was calculated at 5052 subjects to provide 4800 evaluable taking into account a 5% dropout rate. This number was to include 4526 subjects aged between 18-60 years and 526 aged 61 years or above.

In **study 002** the primary objective was to demonstrate the consistency of the HI immune response elicited by four lot groups derived from mixing of 2 lots of HA and 2 lots of AS03. The target sample size was 1090 enrolled subjects (four groups of 218 subjects plus two control groups of 109 subjects that received unadjuvanted HA) in order to reach 980 evaluable subjects.

Studies were observer-blinded due to differences in the appearances of the vaccines. Study personnel who vaccinated the subjects were not involved in the evaluation of endpoints and access to the vaccines was restricted to the person(s) in charge of accountability, preparation and administration.

The following populations were defined:

- Total Vaccinated cohort: all vaccinated subjects for whom data were available.
- According-To-Protocol (ATP) for safety: all vaccinated with sufficient safety data for analysis.
- ATP for immunogenicity: all evaluable subjects with immunogenicity data available.

Immunogenicity Results

H5N1-007

This study was initiated at a single site in Belgium (Ghent) in March 2006. There were 400 subjects enrolled, with 49-51 randomised to each dose/adjuvant group. Of these 400, 399 were evaluable for safety and 394 met the criteria for the ATP immunogenicity analysis.

Pre-vaccination, nine subjects were seropositive for **HI antibody** to A/Vietnam/1194/2004 but only three were seroprotected. The 70% threshold for the SPR was not reached in any group after one dose. After two doses the 70% threshold was exceeded in all four adjuvanted formulation groups (range 84 – 96%) but in none of the non-adjuvanted vaccine groups.

Seroprotection rates against A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)

				≥ 40 1/DIL			
				n	%	95%CI	
Antibody	Group	Timing	N			LL	UL
A/Vietnam	H5N1/30	PRE	49	0	0.0	0.0	7.3
		PI(D21)	49	14	28.6	16.6	43.3
		PII(D42)	49	21	42.9	28.8	57.8
	H5N1/15	PRE	49	1	2.0	0.1	10.9
		PI(D21)	49	10	20.4	10.2	34.3
		PII(D42)	49	17	34.7	21.7	49.6
	H5N1/7.5	PRE	49	0	0.0	0.0	7.3
		PI(D21)	49	4	8.2	2.3	19.6
		PII(D42)	49	8	16.3	7.3	29.7
	H5N1/3.8	PRE	50	0	0.0	0.0	7.1
		PI(D21)	50	0	0.0	0.0	7.1
		PII(D42)	50	2	4.0	0.5	13.7
	H5N1/30/AS03	PRE	48	0	0.0	0.0	7.4
		PI(D21)	48	28	58.3	43.2	72.4
		PII(D42)	48	41	85.4	72.2	93.9
	H5N1/15/AS03	PRE	49	0	0.0	0.0	7.3
		PI(D21)	49	24	49.0	34.4	63.7
		PII(D42)	49	47	95.9	86.0	99.5
	H5N1/7.5/AS03	PRE	50	1	2.0	0.1	10.7
		PI(D21)	50	25	50.0	35.5	64.5
		PII(D42)	50	45	90.0	78.2	96.7
	H5N1/3.8/AS03	PRE	50	1	2.0	0.1	10.7
		PI(D21)	50	13	26.0	14.6	40.3
		PII(D42)	50	42	84.0	70.9	92.8

After the second vaccination with all adjuvanted formulations and with non-adjuvanted formulations containing 30 or 15 µg HA the SCFs exceeded 2.5 but ranged from 27.9 to 60.5 for adjuvanted vaccines compared to a maximum value of only 3.9 among non-adjuvanted formulations.

After both the first and second vaccinations the SCR rates were significantly superior in groups vaccinated with adjuvanted formulations. There was no significant difference in the post-vaccination anti-HA antibody titre between the four groups that received adjuvanted formulations. For each dose of HA, a significant difference was detected between the adjuvanted and non-adjuvanted groups.

SPRs to A/Vietnam/1194/2004 for the adjuvanted vaccine groups at D180 ranged from 54 - 64 %. In the 3.8 µg HA +AS03 group the seroprotection rates were 84% at D42 and 54% at D180 (see below).

Seroprotection rates (SPR) for anti-HA antibody titer against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains at Day 180 (ATP cohort for persistence)

			SPR			
					95% CI	
Antibodies against	Group	N	n	%	LL	UL
A/Vietnam	H5N1/30	48	18	37.5	24.0	52.6
	H5N1/15	48	12	25.0	13.6	39.6
	H5N1/7.5	49	7	14.3	5.9	27.2
	H5N1/3.8	50	2	4.0	0.5	13.7
	H5N1/30/AS03	48	30	62.5	47.4	76.0
	H5N1/15/AS03	49	30	61.2	46.2	74.8
	H5N1/7.5/AS03	50	32	64.0	49.2	77.1
	H5N1/3.8/AS03	50	27	54.0	39.3	68.2
A/Indonesia	H5N1/30	48	0	0.0	0.0	7.4
	H5N1/15	48	0	0.0	0.0	7.4
	H5N1/7.5	49	0	0.0	0.0	7.3
	H5N1/3.8	50	0	0.0	0.0	7.1
	H5N1/30/AS03	48	2	4.2	0.5	14.3
	H5N1/15/AS03	49	2	4.1	0.5	14.0
	H5N1/7.5/AS03	50	3	6.0	1.3	16.5
	H5N1/3.8/AS03	50	0	0.0	0.0	7.1

Day 180 SCFs against A/Vietnam/1194/2004 were reduced compared to values obtained at Day 42 in both adjuvanted and non-adjuvanted vaccine groups. In the 3.8 µg/AS03 vaccine group the SCFs were 27.9 at D42 and 4.4 at D180.

Pre-vaccination, between one fifth and one third per group already had NA titres of at least 1:28 while 10 to 25% per group had titres ≥1:40 and 2 to 10% had titres ≥1:80. GMTs increased significantly after the first and second vaccinations with adjuvanted formulations.

At D42 most subjects in the adjuvanted groups had NA titres above these two cut-offs (i.e. 97.9% - 100% at 1:40 and 91.5% - 100% at 1:80). Similarly, seroconversion rates were higher in groups vaccinated with adjuvanted formulations. An HA dose effect was detected in the non-adjuvanted groups only.

NA titres against the A/Vietnam/1194/2004 (H5N1) strain (ATP cohort for immunogenicity)

				≥ 28 1/DIL				GMT				
						95% CI			95% CI			
Strain	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
A/Vietnam/1194/2004	H5N1/30/AS03	PRE	48	9	18.8	8.9	32.6	17.3	15.1	20.0	<28.0	90.0
		PI(D21)	47	45	95.7	85.5	99.5	146.6	113.3	189.8	<28.0	905.0
		PII(D42)	47	47	100	92.5	100	258.2	205.5	324.5	28.0	1420.0
	H5N1/15/AS03	PRE	49	16	32.7	19.9	47.5	22.0	17.9	27.0	<28.0	180.0
		PI(D21)	49	49	100	92.7	100	181.3	144.6	227.3	45.0	905.0
		PII(D42)	49	49	100	92.7	100	400.1	319.3	501.4	113.0	2260.0
	H5N1/7.5/AS03	PRE	50	17	34.0	21.2	48.8	23.3	18.4	29.4	<28.0	284.0
		PI(D21)	49	47	95.9	86.0	99.5	134.6	101.3	178.7	<28.0	1420.0
		PII(D42)	50	49	98.0	89.4	99.9	343.0	260.5	451.5	<28.0	1440.0
	H5N1/3.8/AS03	PRE	50	16	32.0	19.5	46.7	21.7	17.8	26.4	<28.0	113.0
		PI(D21)	50	48	96.0	86.3	99.5	117.9	93.7	148.3	<28.0	905.0
		PII(D42)	49	48	98.0	89.1	99.9	314.7	243.1	407.3	<28.0	1420.0

At D180 all except one of the subjects from the adjuvanted groups were seropositive for NA to the vaccine strain and 98% were seropositive in the group that received the 3.8 µg HA + AS03 vaccine.

Seropositivity rates and GMTs (with 95%CI) for the neutralizing antibodies against the vaccine strain (A/Vietnam/1194/2004 strain) at Day 180 (ATP cohort for Persistence)

			>= 28 1/DIL				GMT				
					95% CI			95% CI			
Antibodies against	Group	N	n	%	LL	UL	value	LL	UL	Min	Max
A/Vietnam	H5N1/30	49	45	91.8	80.4	97.7	81.7	61.9	107.9	<28.0	905.0
	H5N1/15	49	32	65.3	50.4	78.3	38.3	29.2	50.3	<28.0	453.0
	H5N1/7.5	48	28	58.3	43.2	72.4	32.8	25.6	42.1	<28.0	284.0
	H5N1/3.8	50	21	42.0	28.2	56.8	23.5	19.0	29.0	<28.0	226.0
	H5N1/30/AS03	48	48	100	92.6	100	130.8	109.7	155.9	28.0	569.0
	H5N1/15/AS03	49	49	100	92.7	100	130.0	106.0	159.5	28.0	720.0
	H5N1/7.5/AS03	50	50	100	92.9	100	116.3	97.7	138.4	28.0	360.0
	H5N1/3.8/AS03	50	49	98.0	89.4	99.9	101.8	84.8	122.3	<28.0	453.0

HI and NA titres were also assessed against heterologous H5N1 strains (i.e. H5N1 viruses of a different clade to the vaccine strain) to assess cross-protection.

Pre-vaccination, no subject was seropositive (HI titre ≥ 10) for A/Indonesia/5/2005 (H5N1) i.e. a clade 2 sub-clade 1 strain.

- By D42 HI GMTs approximately doubled in the adjuvanted formulation groups and the number of seropositive subjects increased significantly to reach 26.5 to 48% per group. D42 SCFs ranged from 2.0 to 2.8. The percentage of vaccinees that seroconverted after the second vaccination ranged from 20% to 32% per group.
- After both the first and second vaccinations with non-adjuvanted formulations, the seroconversion factors were equal to 1.0 and no subjects seroconverted.
- At D180 seropositivity rates for anti-HA against the A/Indonesia/5/2005 strain were ≤ 10% for both adjuvanted and non-adjuvanted vaccine groups and seroprotection rates were all ≤ 6%.

Cross-reactivity was assessed against two additional H5N1 drifted clade 2 strains - A/Anhui/01/2005/subclade 3 and A/Turkey/Turkey/1/2005 - NIBRG23/subclade 2. Assays were performed on sera from a subset of 40 subjects who received 3.8 µg HA with or without AS03.

- No subject was seropositive based on HI for either strain before the first dose. Adjuvanted vaccine mediated a significant increase in GMT at D42 against both strains, although the absolute titres were low, and 55% - 65% were seropositive at this time point.
- At D42, HI seroconversion and seroprotection rates in the adjuvanted group were both 35% against A/Anhui/01/2005 and 60% against A/Turkey/Turkey/1/2005 but rates were ≤ 5% by D180. In the adjuvanted vaccine group the D42 seroconversion factors were 3.4 and 4.7 for respective strains.

For NA against A/Indonesia/5/05 (H5N1) 0-8.3% in 7/8 groups were seropositive with respect to this strain pre-vaccination but the rate was 21.3% (10/47) in the 7.5/AS03 group. At least 88% were seropositive after two doses and 79 – 83% had a titre ≥ 1:40 while 46 – 58% had ≥ 1:80. Seroconversion rates increased significantly (up to 63-77%) after the second vaccination.

NA seropositivity rates and GMTs against A/Indonesia/5/2005 (H5N1) (ATP)

				≥ 28 1/DIL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
	H5N1/30/AS03	PRE	47	0	0.0	0.0	7.5	14.0	14.0	14.0	<28.0	<28.0
		PI(D21)	46	38	82.6	68.6	92.2	54.6	42.5	70.1	<28.0	284.0
		PII(D42)	46	42	91.3	79.2	97.6	66.8	53.4	83.5	<28.0	226.0
	H5N1/15/AS03	PRE	44	1	2.3	0.1	12.0	14.2	13.8	14.7	<28.0	28.0
		PI(D21)	44	35	79.5	64.7	90.2	38.1	30.0	48.5	<28.0	287.0
		PII(D42)	44	41	93.2	81.3	98.6	72.9	58.5	90.9	<28.0	226.0
	H5N1/7.5/AS03	PRE	47	10	21.3	10.7	35.7	17.3	15.2	19.5	<28.0	57.0
		PI(D21)	47	34	72.3	57.4	84.4	43.7	33.7	56.6	<28.0	284.0
		PII(D42)	46	45	97.8	88.5	99.9	95.7	75.3	121.7	<28.0	453.0
	H5N1/3.8/AS03	PRE	48	4	8.3	2.3	20.0	15.8	13.9	17.9	<28.0	113.0
		PI(D21)	48	32	66.7	51.6	79.6	36.6	28.8	46.5	<28.0	226.0
		PII(D42)	48	42	87.5	74.8	95.3	80.3	62.0	103.9	<28.0	284.0

At D180 the NA seropositivity rates against the A/Indonesia/5/2005 strain in the adjuvanted groups were 82% to 92% compared to 6 – 49% in the non-adjuvanted groups. For the 3.8 µg HA + AS03 vaccine the rates were 87.5% at D42 and 82% at D180. There was no antigen dose effect in the adjuvanted groups for seropositivity rates, GMTs or seroconversion rates.

Seropositivity rates and GMTs (with 95%CI) for the neutralizing antibodies against the A/Indonesia/5/2005 strain at Day 180 (ATP cohort for Persistence)

			>= 28 1/DIL				GMT				
					95% CI			95% CI			
Antibodies against	Group	N	n	%	LL	UL	value	LL	UL	Min	Max
A/Indonesia	H5N1/30	49	24	49.0	34.4	63.7	25.4	20.7	31.2	<28.0	226.0
	H5N1/15	49	16	32.7	19.9	47.5	19.9	16.8	23.5	<28.0	113.0
	H5N1/7.5	49	12	24.5	13.3	38.9	18.5	15.7	21.9	<28.0	226.0
	H5N1/3.8	50	3	6.0	1.3	16.5	14.7	13.9	15.5	<28.0	36.0
	H5N1/30/AS03	48	44	91.7	80.0	97.7	48.7	40.1	59.2	<28.0	226.0
	H5N1/15/AS03	49	43	87.8	75.2	95.4	52.9	41.7	67.2	<28.0	284.0
	H5N1/7.5/AS03	50	41	82.0	68.6	91.4	45.8	37.5	55.9	<28.0	180.0
	H5N1/3.8/AS03	50	41	82.0	68.6	91.4	46.1	36.9	57.6	<28.0	180.0

NA assays performed against A/Anhui/01/2005/subclade 3 and A/Turkey/Turkey/1/2005 - NIBRG23/subclade 2 showed that 0-4 subjects per group had detectable antibody before vaccination. By D42 1-2 subjects in the non-adjuvanted groups had become seropositive but none met the criteria for seroconversion and there was no change in GMTs. The adjuvanted vaccine elicited significant increases in GMTs after the first and second doses. At D42 all subjects were seropositive for NA against these strains and 75% and 85% had seroconverted against A/Anhui/01/2005 and A/Turkey/Turkey/1/2005, respectively. At D180 all except one subject in the adjuvanted groups remained seropositive for both strains and 60% and 70% still met the seroconversion criterion although GMTs had declined by about one third.

Pre-vaccination frequencies of influenza-specific CD4 T-cells were similar across groups. On stimulation with split A/Vietnam/1194/2004 frequencies of influenza-specific CD4 T-cells significantly increased in all groups after the first vaccination but essentially remained unchanged after the second dose. This lack of detectable increment after the second dose might have occurred because the sample was taken after the peak response occurred. The frequencies of influenza-specific CD4 T-cells were higher in adjuvanted compared with non-adjuvanted formulation groups. No significant effect of antigen dose was detected.

At D180 frequencies of influenza-specific CD4 T-cells remained high compared to the pre-vaccination levels. Values were higher after vaccination with the AS03 adjuvanted compared to non-adjuvanted formulations. Individual differences between D180 and D0 in CD4 responses showed a statistically significant difference between adjuvanted and non-adjuvanted groups for both 3.8 µg and 7.5 µg formulations for all types of cytokines except IFNγ.

The pre-vaccination frequency of influenza-specific CD8 T-cells was essentially similar in all groups. No significant effect of vaccination was observed on the frequency of influenza-specific CD8 T-cells at D42 or at D180 whatever the formulation received.

The 3.8 µg HA/AS03 formulation induced a cross-reactive CD4+ T cell response to the heterologous clade 2 H5N1 A/Indonesia/05/05 strain that was similar to that against the vaccine strain. The response to both strains was higher in the adjuvanted vaccine group at the same HA level. There was also a limited CD4+ T cell response to the heterologous split virions H3N2 New-York (NY) and H1N1 New Caledonia (NC). It is not known whether the cross-recognised domains belong to the split virion backbone (PR8) and/or represent conserved T cell epitopes on haemagglutinin and/or neuraminidase proteins. T-cell cross-reactivity against pools of peptides derived from the HA of the vaccine strain, the H5N1 drifted clade 2 subclade 1 A/Indonesia/5/2005 and the Anhui clade 2 subclade 3 (A/Anhui/01/2005) strain showed a weak response with respect to each strain in the non-adjuvanted group. The adjuvanted vaccine elicited a significant increase in the response against HA peptides from A/Vietnam, A/Indonesia and A/Anhui.

H5N1- 008 (and extension to D180 as study 011)
Thus study was initiated at 41 sites in seven countries (6 EU MS plus Russia) in May 2006. There were 5075 subjects enrolled of which 5071 subjects were vaccinated and 4904 completed to D51. Immunogenicity was assessed up to D180 in a subset of the total enrolled.

Pre-vaccination 0-2.5% of subjects aged < 60 years but 10-18% aged > 60 years were already seropositive according to HI titres. Due to the baseline seropositivity rates the data shown below refer only to subjects who were initially seronegative.

In adults aged between 18 and 60 years, the SPR against the vaccine strain exceeded the 70% threshold after the second vaccination. In adults aged > 60 years, the 60% threshold was exceeded after the first vaccination (61.4%). In both age strata SPRs reached 91.4% at D42.

In both age-strata the SCFs exceeded the relevant CHMP thresholds after the first dose of 15µg/AS03. After the second dose the SCFs significantly increased in both age-strata but the increment and the final GMT were higher in adults aged between 18 and 60 years than in those aged > 60 years. There were no appreciable changes in GMTs after Fluarix was given in either age group.

Initially seronegative subjects: Seroprotection rates for anti-HA (ATP cohort)

Antibody	Group	Timing	N	n	SP with 95%CI			n UNPROT	% UNPROT
					%				
A/Vietnam	H5N1 18-60	PRE	269	0	0.0	0.00	1.36	269	100.0
		PI(D21)	269	147	54.6	48.49	60.70	122	45.4
		PII(D42)	268	245	91.4	87.40	94.48	23	8.6
	H5N1 >60	PRE	146	0	0.0	0.00	2.49	146	100.0
		PI(D21)	145	89	61.4	52.94	69.34	56	38.6
		PII(D42)	140	128	91.4	85.51	95.49	12	8.6
	Fluarix 18-60	PRE	96	0	0.0	0.00	3.77	96	100.0
		PI(D21)	97	5	5.2	1.69	11.62	92	94.8
		PII(D42)	96	3	3.1	0.65	8.86	93	96.9
	Fluarix >60	PRE	50	0	0.0	0.00	7.11	50	100.0
		PI(D21)	49	5	10.2	3.40	22.23	44	89.8
		PII(D42)	50	6	12.0	4.53	24.31	44	88.0

At D180 58% of those aged < 60 years and 79% aged > 60 years in the group that had received 15µg/AS03 were seroprotected. The SPR at D180 was the same (58%) for the 18-30 and 31-60 years groups. In contrast only 2% of those aged < 60 and 18% of those > 60 years who had been primed with Fluarix were seroprotected at D180. The SCRs were 57% and 74% for the younger and older age groups, respectively, who had received 15µg/AS03 compared to 2% and 9% in the control group. The corresponding SCFs were 5.2 and 8.3 compared to 1.1 and 1.5 in the control group.

Seroprotection rates (SPR) for anti-HA at each time point (ATP cohort for persistence)

					SPR			
							95% CI	
Vaccine strain	Group	Sub-group	Timing	N	n	%	LL	UL
FLU A/VIET/04 AB	H5N1	18-60	PRE	279	4	1.4	0.4	3.6
			PII(D180)	279	161	57.7	51.7	63.6
		>60	PRE	170	18	10.6	6.4	16.2
			PII(D180)	171	135	78.9	72.1	84.8
	Fluarix	18-60	PRE	94	0	0.0	0.0	3.8
			PII(D180)	95	2	2.1	0.3	7.4
		>60	PRE	54	3	5.6	1.2	15.4
			PII(D180)	55	10	18.2	9.1	30.9

H5N1 = H5N1 15µg HA + AS03
Fluarix = Fluarix/Placebo at the 2nd dose

In subjects aged 18 to 60 years 45.0% in the H5N1/AS03 group (21.4% with a titre of at least 1:80) and 44.7% in the Fluarix group (27.7% with at least 1:80) were seropositive for NA against A/Vietnam at baseline.

NA GMTs in H5N1/AS03 recipients peaked at Day 42 (827.8) and then declined to 134.9 at Day 180. Within the Fluarix group, there was also a significant increase in GMTs from pre-dose to 21 days after the first and second vaccinations but values were much lower (>10-fold difference). At Day 180 there was still a 4-fold difference between groups. Correspondingly at Day 180 98.6 % of subjects from the H5N1/AS03 group were still seropositive for NA compared to 44.2% in the Fluarix/placebo group.

At Day 21, 83.2% of subjects had seroconverted in the H5N1/AS03 group compared to 38.3% in the Fluarix group. The SCR showed a further significant increase at Day 42 in the H5N1/AS03 group to reach 92.1% compared to 29.8% in the Fluarix group (29.8% at Day 42). At D180 the SCRs were 58 % and 16% in respective groups.

Seroconversion rate (SCR) for Neutralising antibodies against the vaccine strain (A/Vietnam/1194/2004) at post vaccination day 21, day 42, and day 180 in subjects aged 18-60 years (ATP cohort for persistence)

				SCR			
						95% CI	
Antibodies against	Group	Timing	N	n	%	LL	UL
A/Vietnam/1194/04	H5N1	PI(D21)	280	233	83.2	78.3	87.4
		PII(D42)	279	257	92.1	88.3	95.0
		PII(D180)	279	162	58.1	52.0	63.9
	Fluarix/Placebo	PI(D21)	94	36	38.3	28.5	48.9
		PII(D42)	94	28	29.8	20.8	40.1
		PII(D180)	94	15	16.0	9.2	25.0

HN AS03 = H5N1 15µg HA + AS03; Fluarix/Placebo = Control; Seroconversion defined as: antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre; 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; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination dose 1; PI(D21) = Post-vaccination at day 21; PII(D42) = Post-vaccination at day 42; PII(D180) = Post-vaccination at Month 6

The proportions with NA titres of at least 1:40 and 1:80 increased significantly at Day 21 and Day 42 in both H5N1/AS03 and Fluarix groups although the increase was greater in the H5N1/AS03 group.

At D180, 92.5 % and 71 % had titres of 1:40 and 1:80, respectively, in the H5N1/AS03 group compared to 34.7% and 22.1% in the Fluarix group.

Percentage of subjects that reached neutralising antibody titres of 1:40 and 1:80 against A/Vietnam/1194/2004 strain at day 0, day 21, day 42, and day 180 in subjects aged 18-60 years (ATP cohort for persistence)

				≥1:40 1/DIL				≥ 1:80 1/DIL			
						95% CI				95% CI	
Antibodies against	Group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Vietnam/1194/04	H5N1	PRE	280	106	37.9	32.2	43.8	60	21.4	16.8	26.7
		PI(D21)	280	280	100	98.7	100	274	97.9	95.4	99.2
		PII(D42)	279	279	100	98.7	100	277	99.3	97.4	99.9
		PII(D180)	279	258	92.5	88.7	95.3	198	71.0	65.3	76.2
	Fluarix/Placebo	PRE	94	39	41.5	31.4	52.1	26	27.7	18.9	37.8
		PI(D21)	95	70	73.7	63.6	82.2	54	56.8	46.3	67.0
		PII(D42)	94	64	68.1	57.7	77.3	51	54.3	43.7	64.6
		PII(D180)	95	33	34.7	25.3	45.2	21	22.1	14.2	31.8

HN AS03 = H5N1 15µg HA + AS03; Fluarix/Placebo = Control; 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; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination dose 1; PI(D21) = Post-vaccination at day 21; PII(D42) = Post-vaccination at day 42; PII(D180) = Post-vaccination at Month 6

In the age group > 60 years the majority (82% and 91% per group) were already seropositive for NA to the vaccine strain at baseline. The percentages with pre-vaccination titres ≥ 1:40 or ≥ 1:80 were similar between the 15 µg HA/AS03 and the Fluarix control group (i.e. 69.5% and 67.3% at 1:40, with 44.6% and 40.0% at 1:80).

After a single dose of the adjuvanted H5N1 vaccine all except one subject was seropositive. After a second dose there were further and significant increments in GMT and SCR. In the 15 µg HA/AS03 group the percentages with ≥ 1:40 and ≥ 1:80 at D21 were 99.4% and 93.8%, respectively. At D42 these percentages were 100% and 99.4%. At D21 and D42 there was a statistically higher immune response in the 15 µg HA/AS03 group.

Percentage with NA titres ≥ 1:40 and ≥ 1:80 at each time point against vaccine strain H5N1 A/Vietnam/1194/2004 in H5N1-008 (ATP cohort for Immunogenicity)

			≥40 1/DIL				≥80 1/DIL			
		N	n	%	95%CI		n	%	95%CI	
Group	Timing				LL	UL			LL	UL
H5N1 15/AS03	PRE	177	123	69.5	62.1	76.2	79	44.6	37.2	52.3
	PI(D21)	176	175	99.4	96.9	100.0	165	93.8	89.1	96.8
	PII(D42)	170	170	100	97.9	100.0	169	99.4	96.8	100.0
Fluarix/Placebo	PRE	55	37	67.3	53.3	79.3	22	40.0	27.0	54.1
	PI(D21)	53	48	90.6	79.3	96.9	35	66.0	51.7	78.5
	PII(D42)	53	46	86.8	74.7	94.5	31	58.5	44.1	71.9

At D180 all except one subject aged > 60 years who had received the 15µg + AS03 vaccine and 82% in the control group had NA titres to the vaccine strain ≥ 1:28. The seroconversion rates at D180 in this age group were 43% for the 15µg/AS03 group compared with 6% for the control group.

H5N1-002 (and extension study 030 to D180 + boosting)
The study was initiated on 24 March 2007 in four SE Asian countries. There were 1206 subjects enrolled into the study and 1190 completed primary immunisation.

Consistency among the four adjuvanted vaccine lots based on pre-defined criteria applied to D42 HI data was demonstrated. GMTs for anti-HA antibody were very similar between the four adjuvanted groups on D0, D21 and D42 for the homologous vaccine strain and were also similar between groups but much lower against A/Indonesia/5/2005. Results for the two non-adjuvanted groups were similar to each other but showed a very small anti-HA response to the vaccine strain and no discernible response to the heterologous strain.

The SCF threshold of ≥ 2.5 was reached in the pooled H5N1 adjuvanted AS03 vaccine group after the first dose (4.1) and the second dose (39.8) for the A/Vietnam strain but only after the second dose (4.9) for the A/Indonesia strain. The SCR in the pooled adjuvanted group at D42 was 94% for the vaccine strain and 50% for the heterologous strain and the required 40% threshold rate was reached after a single dose.

GMTs of Anti-HA antibody titres at days 0, 21 and 42 by H5N1 strain
Pooled vaccine groups (ATP cohort for immunogenicity)

				>= 10 1/DIL				GMT				
						95% CI			95% CI			
Antigen	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
H5N1 (A/VIET)	HN-AS03	PRE	933	59	6.3	4.8	8.1	5.5	5.4	5.7	<10.0	320.0
		PI(D21)	925	544	58.8	55.6	62.0	22.8	20.7	25.0	<10.0	1280.0
		PII(D42)	924	881	95.3	93.8	96.6	219.4	203.3	236.9	<10.0	5120.0
	HN DIL	PRE	236	17	7.2	4.3	11.3	5.6	5.3	5.9	<10.0	57.0
		PI(D21)	234	33	14.1	9.9	19.2	6.7	6.0	7.4	<10.0	320.0
		PII(D42)	234	50	21.4	16.3	27.2	7.5	6.7	8.3	<10.0	320.0
H5N1 (A/IND)	HN-AS03	PRE	933	8	0.9	0.4	1.7	5.1	5.0	5.1	<10.0	40.0
		PI(D21)	925	111	12.0	10.0	14.3	6.0	5.8	6.2	<10.0	453.0
		PII(D42)	924	587	63.5	60.3	66.6	24.9	22.8	27.3	<10.0	640.0
	HN DIL	PRE	236	2	0.8	0.1	3.0	5.0	5.0	5.1	<10.0	20.0
		PI(D21)	234	7	3.0	1.2	6.1	5.2	5.0	5.3	<10.0	28.0
		PII(D42)	234	7	3.0	1.2	6.1	5.2	5.0	5.4	<10.0	40.0

HN-AS03 = pooled adjuvanted group (H5N1_AX, H5N1_AY, H5N1_BX, H5N1_BY)
HN DIL = pooled un-adjuvanted group (H5N1_AD, H5N1_BD)

A small proportion (15; 1.6%) had seroprotective anti-HA antibody before vaccination. The threshold of 70% was reached in the pooled H5N1 adjuvanted group (94.3%) after the second dose (D42) for the A/Vietnam strain but the D42 seroprotection rate against the heterologous strain was 50.2%.

SPRs for anti-HA antibody – Pooled vaccine groups (ATP cohort for immunogenicity)

				SPR			
						95% CI	
Antigen	Group	Timing	N	n	%	LL	UL
H5N1 (A/VIET)	HN-AS03	PRE	933	15	1.6	0.9	2.6
		PI(D21)	925	412	44.5	41.3	47.8
		PII(D42)	924	871	94.3	92.6	95.7
	HN DIL	PRE	236	5	2.1	0.7	4.9
		PI(D21)	234	16	6.8	4.0	10.9
		PII(D42)	234	24	10.3	6.7	14.9
H5N1 (A/IND)	HN-AS03	PRE	933	1	0.1	0.0	0.6
		PI(D21)	925	27	2.9	1.9	4.2
		PII(D42)	924	464	50.2	46.9	53.5
	HN DIL	PRE	236	0	0.0	0.0	1.6
		PI(D21)	234	0	0.0	0.0	1.6
		PII(D42)	234	1	0.4	0.0	2.4

HN-AS03 = pooled adjuvanted group (H5N1_AX, H5N1_AY, H5N1_BX, H5N1_BY)
HN DIL = pooled un-adjuvanted group (H5N1_AD, H5N1_BD)

Before vaccination 17 - 20% of subjects were seropositive for NA against the vaccine strain while 5 - 11% of subjects were seropositive for NA against A/Indonesia/2005. For the individual adjuvanted groups the percentages with titres ≥1:28 at D42 ranged from 98-100% for the vaccine strain and 92-100% for the heterologous strain. In contrast, percentages with titres ≥1:28 at D42 in the two non-adjuvanted groups were 42% and 54% for the vaccine strain and 17% and 11% for the heterologous strain.
For the pooled adjuvanted vaccine groups the D42 seroconversion rate was 96% for the H5N1 A/Vietnam strain and 91.4% for A/Indonesia/2005.

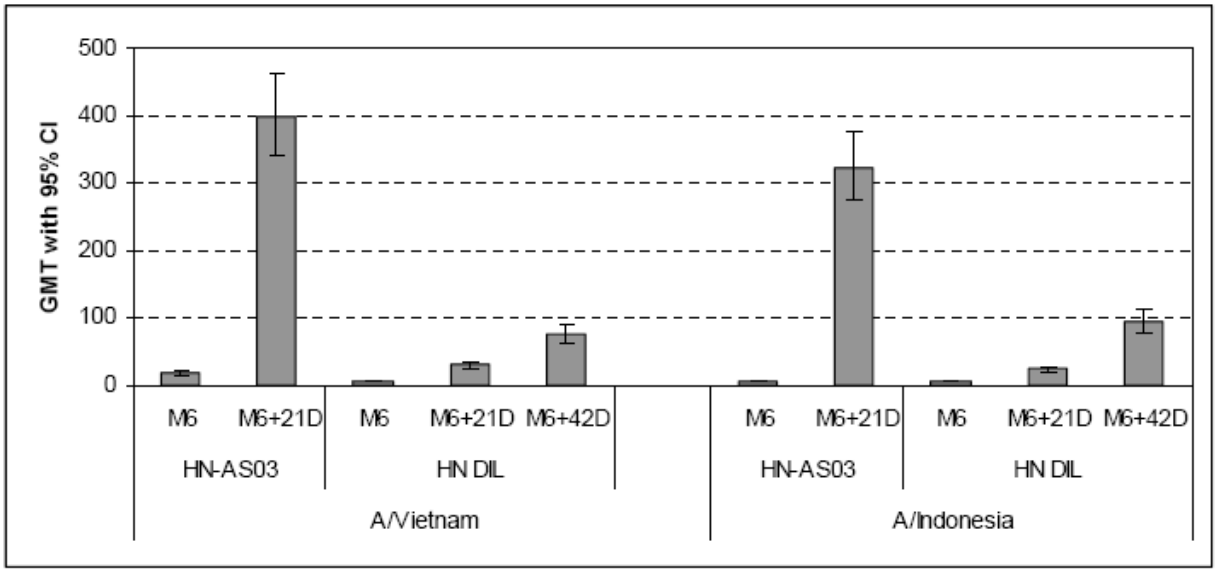
Seropositivity rates and GMTs for NA at D0 and D42 (ATP cohort for immunogenicity)

				>= 28 1/DIL				GMT				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
FLU A/VIET/04 AB	HN-AS03	PRE	279	56	20.1	15.5	25.3	17.5	16.5	18.7	<28.0	360.0
		PII(D42)	277	276	99.6	98.0	100	308.4	283.1	336.1	<28.0	4530.0
	HN DIL	PRE	71	12	16.9	9.0	27.7	17.7	15.4	20.4	<28.0	226.0
		PII(D42)	71	34	47.9	35.9	60.1	29.0	23.4	35.9	<28.0	226.0
FLU A/IND/05 AB	HN-AS03	PRE	279	15	5.4	3.0	8.7	14.9	14.3	15.4	<28.0	569.0
		PII(D42)	279	266	95.3	92.2	97.5	84.0	77.1	91.4	<28.0	720.0
	HN DIL	PRE	71	8	11.3	5.0	21.0	15.6	14.4	16.7	<28.0	57.0
		PII(D42)	71	10	14.1	7.0	24.4	16.2	14.8	17.8	<28.0	71.0

The extension study 030 involved the administration of one or two doses of AS03-adjuvanted vaccine containing A/Indonesia/05/2005 to subjects aged 19-61 years who had received two doses of AS03-adjuvanted (HN-AS03) or non-adjuvanted (HN-DIL) A/Vietnam vaccine, respectively, in study 002. The pre-dose data from Month 6 allowed for an assessment of antibody persistence. Of 1181 subjects that entered study 030, 509 (265 from the original HN-AS03 group and 236 from the original HN-DIL group) were to be boosted and 672 (all from HN-AS03 group) were not boosted.

HI titres were measured at Month 6 and then at 21 days after the first dose (i.e. M6 + 21D). In the HN-DIL group, which received two doses of adjuvanted A/Indonesia vaccine in study 030, an additional sample was obtained at 21 days after the second dose (i.e. M6 + 42D). At Month 6 all HI GMTs had dropped compared to day 42 of study 002. Seropositivity rates were higher in the HN-AS03 group (62.1% for A/Vietnam and 18.4% for A/Indonesia) than in the HN-DIL group (9.2% and 1.3%, respectively).

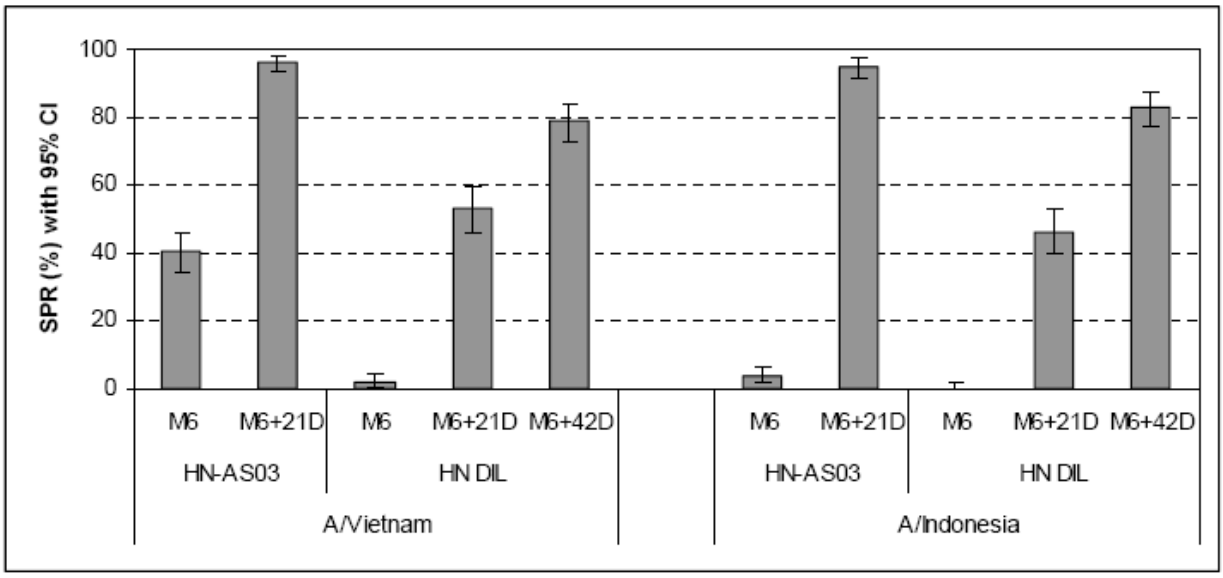
GMTs for HI antibodies against A/Vietnam and A/Indonesia - boosted subjects (ATP Cohort for Immunogenicity)



At M6 + 21D the GMTs had increased markedly and were significantly higher in the HN-AS03 group (397.4 for A/Vietnam and 321.3 for A/Indonesia) compared to the HN-DIL group (30.1 and 24.8). At 21 days after a second dose in the HN-DIL group there was a further increment in GMT against both strains.

After a single dose the SCRs in the HN-AS03 group exceeded 40% against each strain (96.1% for A/Vietnam and 94.9% for A/Indonesia) and the HN-DIL group (48.5% and 46.3%). The > 2.5 SCF threshold was exceeded at day 21 against each strain in the HN-AS03 group (74.0 and 63.8) and the HN-DIL group (5.3 and 4.9). The > 70% SPR threshold was exceeded at day 21 against each strain in the HN-AS03 group (96.5% for A/Vietnam and 94.9% for A/Indonesia). The SPR threshold was exceeded only after a second dose in the HN-DIL group (78.9% and 82.9%, respectively).

SPR A/Vietnam and A/Indonesia - boosted subjects (ATP Cohort for Immunogenicity)



Comparison of results with adjuvanted vaccine in studies 002, 007 and 008

In subjects aged 18-60 years the HI titres against the vaccine strain tended to be higher for the 924 subjects tested in study 002 with final production lots compared to the 50 tested in study 007 with preliminary manufactured vaccine. On comparing study 002 with the results for the 15 µg HA/AS03 vaccine used in study 008 the GMT and SCF were higher (95% CI do not overlap) in 008 but the SCRs and SPRs were comparable despite the difference in HA content. The D21 and D42 data from each study showed that two doses of AS03-adjuvanted vaccine were needed to meet all three CHMP criteria with respect to HI antibody against the vaccine strain.

D42 HI against vaccine strain in adults aged 18-60 years from H5N1-007, H5N1-008 and H5N1-002 (ATP immunogenicity cohort) compared to CHMP criteria

Study	HA (µg per dose)	N	GMT			SCF >2.5 <60 years of age >2.0 > 60 years of age			SCR >40% <60 years of age >30% > 60 years of age			SPR >70% <60 years of age >60% > 60 years of age		
			Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
				LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007	3.8	50	149.3	93.2	239.1	27.9	17.2	45.2	82.0	68.6	91.4	84.0	70.9	92.8
H5N1-008	15	275	312.8	264.2	370.4	58.6	49.4	69.5	91.6	87.7	94.6	91.6	87.7	94.6
H5N1-002	3.8	924	219.4	203.3	236.9	39.8	36.8	43.1	93.7	92.0	95.2	94.3	92.6	95.7

The HI SPRs against the vaccine strain in subjects aged 18-60 years at D180 were 54% after priming with 3.8 µg/AS03 in study 007 compared to 58% primed with 15 µg/AS03 in study 008. The respective HI GMTs at D180 were 23.3 and 27.2. These data suggested no advantage for the higher HA dose. In study 002 the HI seropositivity rate in the HN-AS03 group at D180 were 62.1% for A/Vietnam and 18.4% for A/Indonesia and 40% were seroprotected with respect to the vaccine strain.

The D42 NA response against the vaccine strain was similar between 002 and 007 (all 95% CI overlap). At least 98% were seropositive with respect to the vaccine strain while the seropositivity rate with respect to the heterologous strain was numerically higher in 002. The SCRs were numerically or (borderline) significantly greater with respect to homologous and heterologous strains, respectively, in study 002. However, the GMTs were the same between studies for each of the homologous and heterologous strains and about 4-fold higher for the former than for the latter strain.

NA against vaccine strain and H5N1 A/Indonesia/5/2005 in adults aged 18-60 years in H5N1-002 and H5N1-007 (ATP immunogenicity cohort)

Study	HA (µg per dose)	N	≥ 1:28			SCR			GMT		
			%	95% CI		%	95% CI		Value	95% CI	
				LL	UL		LL	UL		LL	UL
Vietnam											
H5N1-002	3.8	277	99.6	98.0	100.0	96.0	93.0	98.0	308.4	283.1	336.1
H5N1-007	3.8	49	98.0	89.1	99.9	85.7	72.8	94.1	314.7	243.1	407.3
Indonesia											
H5N1-002	3.8	279	95.3	92.2	97.5	91.4	87.5	94.4	84.0	77.1	91.4
H5N1-007	3.8	48	87.5	74.8	95.3	77.1	62.7	88.0	80.3	62.0	103.9

Overall the data from these studies indicated that for H5N1 mock-up vaccine two doses of Pandemrix were needed to meet the CHMP criteria for HI antibody. The addition of the AS03 adjuvant greatly enhanced the antibody responses for HI and NA against the vaccine strain and drifted variants of H5N1 regardless of baseline serostatus. In the dose-finding study the addition of adjuvant indicated that the lowest dose tested was satisfactory, allowing for an antigen-sparing approach.

Studies with the H5N1 mock-up vaccine submitted post authorisation

H5N1- 012

This was an open, randomised study conducted in Germany with eight parallel groups of healthy adults aged 18-60 years. The study examined the possibility of administering one dose of Pandemrix after primary immunisation with the same vaccine containing H5N1 antigen from a different clade of the same influenza subtype.

Eight groups were vaccinated (VT=A/Vietnam; IN=A/Indonesia):
Four groups primed with a single dose at D0

- VT/VT/6Mo = one VT dose for priming and one VT booster at Month 6.
- VT/VT/12Mo = one VT dose for priming and one VT booster at Month 12.
- VT/IN/6Mo = one VT dose for priming and one IN booster at Month 6.
- VT/IN/12Mo = one VT dose for priming and one IN booster at Month 12.

Four groups primed with 2 doses at D0 and D21

- 2VT/VT/6Mo = two VT doses for priming and one VT booster at Month 6.
- 2VT/VT/12Mo = two VT doses for priming and one VT booster at Month 12
- 2VT/IN/6Mo = two VT doses for priming and one IN booster at Month 6.
- 2VT/IN/12Mo = two VT doses for priming and one IN booster at Month 12.

The study enrolled 512 subjects aged 18-60 years (63 to 66 per group) and all were vaccinated. At pre-vaccination no subject was seropositive with respect to HI antibody against A/Indonesia and 0-2 subjects per group were seropositive with respect to A/Vietnam. The data available were reported up to Month 6 boosting doses; data on boosting at one year will follow.

- At Day 21, GMTs for H5N1 HI antibodies against the homologous strain A/Vietnam were higher (15.8 - 33.6) than against the A/Indonesia strain (5.3 - 6.8). At Day 42 in the groups that received two primary doses the GMTs increased significantly against homologous and heterologous strains (178.3 - 289.1 and 18.4 - 28.0, respectively). At Month 6, the GMTs against the homologous strain in the four groups primed with a single dose were 9.7 - 13.2 and those for the heterologous strain were 5.3 - 5.7. Corresponding GMTs for the four groups primed with two doses were 24.0 - 38.4 and 6.5 - 10.2.

- The D21 SCRs against A/Vietnam exceeded 40% in 5/8 groups (max 60%) while all SCRs were < 10% against A/Indonesia. At Day 42 the SCRs against homologous virus in the groups primed with two doses were 89.6% - 93.2 % and also exceeded 40% against the heterologous strain (41.5 % - 54.5 %). At Month 6 a SCR >40 % was only maintained against homologous virus and only in groups that had received two primary doses (47.1 % - 67.3 %).

- At Day 21, the >2.5 SCF threshold was met for all groups against the homologous strain (3.1 - 6.5) but no group met the criterion for A/Indonesia. At Day 42 the >2.5 SCF threshold was met in the four groups primed with two doses against homologous virus (34.4 - 49.2) and for A/Indonesia (3.7 - 5.6). At Month 6 the >2.5 SCF threshold was still met by groups primed with two doses against A/Vietnam (4.6 and 7.5). No group met the criterion for A/Indonesia.

- The pre-vaccination SPRs ranged from 0-4.2% to both homologous and heterologous strains. At Day 21, SPRs were between 30.9 % - 60.0 % against A/Vietnam but only from 0.0 % - 8.6 % against A/Indonesia. SPRs in the four groups primed with one dose of VT were all < 50%. At Day 42, SPRs were from 89.6 % - 93.2 % against A/Vietnam but only 41.5 % - 54.5 % against A/Indonesia in groups primed with two doses. At Month 6 SPRs against A/Vietnam were 47.1% - 69.2% in groups primed with two doses but only 14.3% - 25.5% in groups primed with a single dose. Corresponding rates for A/Indonesia were 2.0 % -13.5 % and 0.0 % -1.8 %, respectively.

In the four groups that received a booster dose with VT or IN vaccine at Month 6 the results at Month 6 + 21 days showed that the response against A/Indonesia was significantly higher for the two groups boosted with IN vaccine (GMTs 303.4 - 392.9) compared with the two groups boosted with VT

vaccine (GMTs 92.4 - 127.7). In contrast the response against A/Vietnam was not significantly different between groups.

The SPRs at Month 6 + 21 days were 85.4 % - 98.1 % and there were only marginal increases in seropositivity rates for all groups compared to Month 6 + 7 days. The SCRs against A/Vietnam and A/Indonesia were high at Month 6 + 21 days (83.3 % - 98.1 %). SPRs exceeded 70% to both strains in all groups. The SCFs exceeded 2.5 in all groups against A/Vietnam and A/Indonesia. Responses were very good even at 7 days post-boost but tended to be higher by 21 days after the dose was given.

Analyses by age groups indicated generally higher responses for most parameters in those aged < 30 years compared to those aged > 30 years at D42 and after a booster dose. There was less or no appreciable difference between subgroups aged 31-45 and 46-60 years.

In this adult German population the pre-vaccination NA seropositivity rates against A/Vietnam ranged from 20- 33% but GMTs were ≤ 22. Similarly, against A/Indonesia the baseline seropositivity rates ranged from 4.2% to 14.3% and GMTs were ≤ 20.

At Day 42 the groups primed with two doses of VT vaccine showed increases in GMTs against both strains but the increment was greater for NA against the homologous strain. At Month 6, the GMTs were similar to or within 4-fold the baseline GMTs. At Month 6 + 21 days the GMTs against A/Indonesia were significantly (about 2-fold) higher in the groups boosted with IN vaccine compared to the groups boosted with VT vaccine.

After one dose of VT vaccine the Day 21 SCR were from 50.0% to 71.4 % against A/Vietnam and from 9.1% to 36.4% against A/Indonesia. After two doses the Day 42 SCRs ranged from 91.5% to 95.5% against A/Vietnam and from 66.7% to 73.7% against A/Indonesia. At Month 6 the seroconversion rates had dropped in all groups but were higher in groups primed with two doses than in groups primed with one dose.

The study showed that two doses of AS03-adjuvanted vaccine given 6 months apart elicited comparable immune responses after the second dose to two doses given 21 days apart. The potential advantage of a 2+1 regimen (i.e. D0, D21 and then a third dose later on) over a 1+1 regimen (i.e. a dose at D0 and a second dose later on) was that a higher level of protection might be expected between the second and third doses of a 2+1 regimen compared to the interval between doses in a 1+1 regimen.

Study H5N1-015

This was the boosting phase of the dose-finding study 007. Boosting occurred at approximately 14 months after the two priming doses. Data were reported at day 21 post-boost and also at day 180 after boosting.

The four dose groups that had been primed with adjuvanted vaccine received a single dose of adjuvanted vaccine containing A/Indonesia/05/2005. The booster dose consisted of 3.8 µg HA regardless of the dose received for priming (i.e. 3.8, 7.5, 15 or 30 µg HA + AS03 adjuvant). Blood samples were obtained at Days 0, 7, 14 and 21 after the booster.

The four groups that had been primed with non-adjuvanted vaccine received two doses of adjuvanted vaccine containing A/Indonesia/05/2005 at D0 and D21 of study 015. The booster dose consisted of 3.8 µg HA regardless of the dose received for priming and blood samples were obtained at Days 0, 7, 14, 21, 35 and 42.

An additional control group (no previous doses of H5N1 vaccine) was enrolled into this study. This group received two doses of the same adjuvanted vaccine containing A/Indonesia/05/2005 as used for boosting the eight groups derived from study 007. Doses were given at D0 and D21 and blood samples were obtained at D42.

The boosting phase enrolled 350 subjects 19-61 years of age (35 to 50 subjects per group).

For the main analysis concerning the group primed with 3.8 µg HA + AS03 the CHMP criteria were each exceeded at 21 days following the booster for HI responses to the booster homologous strain i.e. A/Indonesia. The HI responses to a single dose of IN vaccine strongly suggested that these subjects had been primed for A/Indonesia by vaccination 14 months earlier with two doses of VT vaccine.

- At D0 in study 015 GMTs against A/Indonesia and against A/Vietnam were all low (<10).
- At Day 7 there were significant increases in GMTs against A/Indonesia in all except the control group with actual GMTs that were highest in the groups that had been primed with adjuvanted vaccine (118.5 to 193.3).
- At Day 21 the GMTs against A/Indonesia were significantly higher in the four groups primed with adjuvanted vaccine (208.4 - 429.5) compared to those primed with non-adjuvanted vaccine and controls (31 - 77). There were no significant differences between the four dose groups primed with adjuvanted vaccine and no significant differences between the four dose groups primed with non-adjuvanted vaccine. Therefore, priming with adjuvanted vaccine was considered the important factor and not the HA dose administered.

  The GMT against A/Indonesia in the Control group at Day 42 (443) was significantly higher than the values observed at Day 42 for the four groups that had been primed with non-adjuvanted vaccine (54.3 - 141.4). This unexpected finding was not considered relevant for use of the MAH's adjuvanted vaccine but could have implications for interchangeability of vaccines in a pandemic situation.

At Day 7, the increases in GMTs against A/Vietnam after a single dose of adjuvanted vaccine containing A/Indonesia were significant for the groups primed with A/Vietnam 3.8 µg HA with or without AS03. The actual GMT at day 7 was much higher in the former group (176.8 versus 20.8, respectively) and GMTs in this group remained higher at Day 14 (343.7) and Day 21 (352.8). The GMT reached 58.3 at Day 42 (i.e. 21 days after the second dose) in the group primed with non-adjuvanted vaccine. The GMT for the control group began to rise after the second dose to reach 27.1 to 31.7 from Day 28 up to Day 42. In line with the low GMTs at D0 of study 015 the seropositivity rates for A/Indonesia were low (< 10%) before the booster dose.

SCRs against A/Indonesia exceeded 40% at Day 7 for the four groups that had been primed with adjuvanted vaccine (84.2 - 93.9 %) and in three groups primed with non-adjuvanted vaccine (44.7 % - 60.7 %). The SCR at Day 7 was 35.3% in the group that had been primed with 3.8 µg HA without AS03 but reached 64.7% by day 14. The Control group achieved a SCR > 40% at Day 21 (59.2 %) and by Day 42 the rate had reached 98.0 %. This compares with a SCR at D42 of about 64% in the group primed with 3.8 µg HA without AS03.Against A/Vietnam the SCR was 81.6% at Day 7 for the group primed with 3.8 µg + AS03 while the corresponding dose group primed with non-adjuvanted vaccine exceeded 40% at Day 14 (61.8 %). The threshold was only reached by the Control group after the second dose (Day 28 rate = 59.2 %).

The SCF against A/Indonesia was > 2.5 in all previously vaccinated groups by day 7. The criterion was also exceeded at Day 14 in the Control group (2.7) and then increased greatly to 88.6 at Day 42. In contrast the D42 SCF in the group primed with 3.8 µg HA without AS03 was about 10.Against A/Vietnam the > 2.5 criterion was met in all primed groups at day 7 and at Day 28 in the Control group (6.3). SCFs for the group primed with 3.8 µg + AS03 (21.0 - 42.5) were significantly higher than for the corresponding non-adjuvanted dose group (3.7 - 10.3) and the Control group (1.1 - 6.5) at all time points.

The SPRs against A/Indonesia were all 0-3% at D0. The rate exceeded 70% in the four groups primed with adjuvanted vaccine by Day 7 (84.2 % - 93.9 %). The threshold was reached at Day 14 for groups primed with 7.5 µg HA alone (73.7 %) and 30 µg HA alone (75.0 %), at Day 35 for the group primed with 15 µg alone (71.9 %) and at Day 28 for the Control group (100%). The threshold was not reached for the group primed with 3.8 µg alone at any time-point. SPRs against A/Vietnam were low at D0 (0 % - 10.3 %) but had increased significantly by Day 7 in the groups primed with 3.8 µg HA with or without AS03.

A significant increase in SPR was observed on Day 28 in the Control group. However, a SPR > 70% was reached only in the group primed with 3.8 µg HA + AS03 (84.2 % at Day 7 and 89.7 % at Day 21).

NA titres were measured against A/Indonesia/05/2005 in the groups primed with 3.8 µg HA with or without AS03 and in the Control group. The D0 GMT was significantly higher in the group primed with 3.8 µg HA + AS03 (157.8) than in the group primed with 3.8 µg HA alone (47.0) and the Control group (19.9). At D21 significant increases in GMTs occurred in all groups to reach 3708.9, 692.4 and 307.3 in respective groups. At D42 there was a significant increase in GMT in the Control group only (to 1606.4). The actual GMT was higher than that (933.1) in the group primed with 3.8 µg HA alone and the 95% CI only just overlapped. This finding mirrors the unexpected HI findings noted above. All subjects in the group primed with 3.8 µg HA + AS03 were seropositive at Day 0 and 92% had a titre ≥1:80 compared to 35% in the group primed with non-adjuvanted HA and 6.1% of controls. All subjects in the three groups were seropositive by Day 21, at which time all had titres ≥1:80. Seroconversion rates for NA were all above 85.0 % and did not differ significantly between groups after one vaccination dose.

At Day 180 after the booster doses were given the HI results against A/Indonesia showed:

- GMTs for the H5N1 AD groups (42.1 - 82.5) were higher than those observed for the H5N1 non-AD (17.6- 24.3) and Control groups (17.8). .
- SCRs for the H5N1 AD groups (50.0 % - 75.0%) were higher than those observed for the H5N1 non-AD (30.0 %- 41.7%) and Control groups (32.6%). The >40% SCR threshold was exceeded in all H5N1 AD groups and in the H5N1 15µg and H5N1 30 µg groups.
- SPRs for the H5N1 AD groups (50.0 % - 75.8%) were higher than those observed for the H5N1 non-AD (30.0%- 41.7%) and Control groups (32.6%). The >70% SPR threshold was only maintained in the H5N1 7.5AD and H5N1 30AD groups.
- SCFs >2.5 were maintained in all groups but were markedly higher in the H5N1 AD groups (7.9-15) compared to H5N1 non-AD (3.3-4.9) and Control (3.6) groups.

The HI antibody titres against A/Vietnam/1194/2004 were measured at D180 only in the H5N1 3.8, H5N1 3.8AD and control groups. The GMT for group H5N1 3.8AD (192.8) was higher than those for the H5N1 3.8 (27.5) and Control groups (7.8). The SCR for group H5N1 3.8AD (78.9%) was higher than those for the H5N1 3.8 (51.4%) and Control (6.5%) groups. Thus the >40% SCR threshold was exceeded in the H5N1 3.8AD and H5N1 3.8 groups. The SPR for group H5N1 3.8AD (84.6%) was higher than those for the H5N1 3.8 (51.4%) and Control (6.5%) groups. Thus the >70% SPR threshold was only exceeded in the H5N1 3.8AD group. The SCF threshold was exceeded in the H5N1 3.8 (4.9) and H5N1 3.8AD (21.6) groups but not in the Control group (1.5).Neutralising antibody titres were measured at D180 against A/Indonesia/05/2005 in the H5N1 3.8AD, H5N1 3.8 and Control groups.The GMT observed for the H5N1 3.8AD (1422.2) group was higher than that observed for the H5N1 3.8 (502.3) and Control (751.3) groups. The SCRs for groups H5N1 3.8 and H5N1 3.8AD were 78.4%-82.9% and were lower than the SCR observed in the Control group (95.7%).

The results from this boosting phase supported the conclusions of study 012 in supporting the administration of a single dose of IN vaccine to subjects who previously received one or two doses of VT vaccine.

H5N1-010

This open label study compared administration of two single or two double doses on D0 and on D21 to subjects aged 61 years and above. Double doses were given as two injections of the licensed vaccine *i.e*. one injection into each arm. The comparative groups received single or double doses of non-adjuvanted vaccine of the same HA content. Randomisation was 3:1 for adjuvanted:non-adjuvanted vaccine regardless of the HA dose.

The study planned to enrol 480 subjects aged 61 years and above (no upper age limit). At randomisation subjects in each group were stratified by age group: 61-65 years, 66-70 years and

>70 years with the allocation ratio 1:1:1. The number of subjects was low in each of the age strata above 71 years of age. The study actually enrolled 437 subjects 61-89 years of age.
All subjects not previously vaccinated with an influenza vaccine for the 2006-2007 season received Fluarix (a split virion, inactivated seasonal influenza vaccine) at least 3 weeks before D0 in order to help standardise any effect of prior seasonal influenza vaccination on responses to H5N1 vaccine.

Prior to vaccination, 151/395 (38.2%) subjects were seropositive for HI antibody against A/Vietnam/1194/2004 but only 8/395 (2%) subjects were seropositive against A/Indonesia/5/2005. Pre-vaccination GMTs were low (8.8-11.3 and 5.0-5.2 against respective strains).

The GMTs against A/Vietnam increased significantly in the adjuvanted groups at D21 (50.0-69.4) and at D42 (126.8-237.3) but there were only small increments in the non-adjuvanted groups. At D42 the GMT was significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

The GMTs against A/Indonesia increased significantly compared to Day 0 after each vaccination dose only in the adjuvanted groups. At D42 the GMT and the seropositivity rate were significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

Based on GMTs a clear adjuvant effect was demonstrated at D42 for HI responses in the single injection and double injection groups against A/Vietnam and A/Indonesia. There was also a dose effect between the two adjuvanted groups at D42 for HI responses to both strains. In contrast there was no significant dose effect between the two non-adjuvanted groups. By D180 the GMT values had decreased compared to Day 42 but were higher in the adjuvanted vaccine groups although the difference was notable only for antibody against A/Vietnam. In addition, the GMT for HI against A/Vietnam was higher in the group that had received a double dose of vaccine at each of D0 and D21 although the 95% CI overlapped.

The SCR against A/Vietnam was >30% in the two adjuvanted vaccine groups at D21 (45.4% and 52.4%) and increased significantly again at D42 (72.4% and 88.3%) with an advantage in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group. The 30% SCR threshold was not reached in the non-adjuvanted groups. Against A/Indonesia the threshold was reached only in the group that received 7.5 µg HA + AS03 and only at D42. A higher response against A/Vietnam/194/2004 was also observed in the adjuvanted groups at Day 180. The CHMP criteria for SCR was met in the 3.8/AS and 7.5/AS groups at D180. In contrast there was no dose effect between the two non-adjuvanted groups.

Since 38% of subjects in this older population were seropositive against A/Vietnam at D0 the SCRs were analysed according to baseline serostatus. The SCR was >30% in the adjuvanted vaccine groups at D21 (44.4% and 55.8%) regardless of the pre-vaccination immune status. The SCR increased significantly further (to reach 73.3% and 94.6%) at D42 for subjects in the adjuvanted vaccine groups who were seronegative to A/Vietnam before vaccination and was significantly higher in the group that received the double dose. In the non-adjuvanted groups the 30% threshold was only reached by initially seropositive subjects in the double dose group at D42.

SCFs exceeded 2.0 against A/Vietnam in three of the four groups at D21 and by all groups at D42. Values were higher in the adjuvanted vaccine groups and significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group. The threshold was only reached against A/Indonesia in the adjuvanted groups at D42 and again there was an advantage for the higher HA dose. When analysed according to initial serostatus to A/Vietnam, the threshold was reached by all groups at D42 except in the initially seropositive subset that received non-adjuvanted 3.8 µg HA.

As for SCR, higher responses were observed against A/Vietnam/1194/2004 in the adjuvanted groups. The CHMP criteria for SCF was still met in the 3.8/AS and 7.5/AS groups at D180. In contrast there was no dose effect between the two non-adjuvanted groups.

SPRs were >60% against A/Vietnam at D21 in both adjuvanted groups (61.2% and 62.1%) with further significant increases at D42 (83.6% and 95.9%). The threshold was not met in the non-adjuvanted groups. The SPRs against A/Indonesia were low at D21 in the adjuvanted groups (3.3% - 9.0%) and increased to 23% - 41% at D42.

In the initially seropositive subset there were significant increases in SPRs at D21 in the adjuvanted groups and the double dose non-adjuvanted group (85.5%, 82.7% and 68.8%, respectively). In the single dose non-adjuvanted group the rate reached 42.9%. There were only modest increments between D21 and D42 in these groups. In the initially seronegative subset the D21 SPRs were 14.3%-50.5%. At D42 the threshold was reached in the two adjuvanted vaccine groups (73.3% and 94.6%) and the rate was significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

At Day 180, the criterion for SPR for A/Vietnam/1194/2004 was met for the 7.5/AS group (69.5% compared to 52.9% in the single dose group). The criterion was not met in the non-adjuvanted vaccine groups.

Neutralising antibody titres were measured at D0 and D42 against A/Indonesia/5/2005 only and in a subset of subjects from the adjuvanted groups. In this older population a high proportion of subjects were already seropositive for NA to A/Indonesia before vaccination (65.5% and 58.5%). Nevertheless at D42 the rates had increased to 94.3% and 100%). The D0 GMTs were similar and increased significantly at D42 as shown below. The 7.5 µg HA + AS03 group showed a higher GMT and greater percentage with titres of 1:40 and 1:80 compared to the 3.8 µg HA + AS03 group. The NA response against A/Indonesia/5/2005 observed six months after the primary vaccination series paralleled the HI responses in the adjuvanted groups.

Overall the study showed a trend of increased seropositivity with age against A/Vietnam/1194/2004, especially for subjects aged above 80 years where about 60% of subjects were seropositive by HI at baseline in each treatment group, noting that the denominators were small. In contrast the pre-vaccination seropositivity rates for HI against A/Indonesia/05/2005 were negligible across the different groups and no effect of age was evident. There was also a trend to lower immune responses as age increased and those subjects aged > 80 years who were seronegative before vaccination required tow double doses to reach the CHMP criteria. However, numbers are very small.

The study demonstrated overall that 3.8 µg HA + AS03 administered at D0 and again at D21 elicited HI antibody responses directed against homologous virus at D42 that met the three CHMP criteria applicable to subjects aged > 60 years and also met the criteria applicable to subjects aged from 18-60 years. In addition, all three criteria were met at D42 regardless of baseline serostatus and two were met at D21 in the subset that was seronegative at baseline (the exception was the SPR). However, the data obtained at D42 indicated a numerical advantage for administration of two doses at D0 and another two doses at D21 when compared to the recommended regimen. This overall advantage for double doses was mainly driven by results in the previously seronegative sub-population.

The additional data on HI and NA at D180 from H5N1-010 showed a continued advantage for adjuvanted versus non-adjuvanted vaccine and a numerical advantage for a double dose of adjuvanted vaccine versus a single dose based on application of the CHMP criteria to the HI data and on comparison of NA data generated in a subset. However, the SCR and SCF criteria were still met in both adjuvanted dose groups and the only appreciable difference was that the double dose group still met (just) the SPR criterion while the single dose group did not.

H5N1-009(-022/-023)
This open label study conducted in Spain provided immunogenicity and safety data of Pandemrix (H5N1) administered as a two-dose primary series (0, 21 days) to children aged 3-9 years. The study was divided into three parts as shown below:

Subjects from each group were enrolled sequentially into the two age strata (6-9 years and then 3-5 years) with the ratio 1:1. Prior exposure to seasonal influenza vaccine was not an exclusion criterion but subjects were expected not to receive seasonal influenza vaccine during the planned duration of the study (to Month 24).

- 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.

	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

The study enrolled 405 subjects of which 388 completed 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). Increments in seropositivity rates followed the GMTs for the AS03 vaccine group but in the control group the seropositivity rates against A/Vietnam/1194/2004 and A/Indonesia/05/2005 strains were zero at all time points.

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 Half HA/Half 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 Half HA/Half 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 Half HA/Half AS03 group were seropositive for NA at D42. In the control group, the seropositivity rates for NA against the vaccine strain on Days 21 and 42 were within the same range (78.6% - 80.0%).

On Day 21 there were no significant differences between the Half HA/Half AS03 and control groups or between the age strata within each group for NA SCRs against the vaccine strain (range 65.1% - 67.4% for Half HA/Half AS03 group and 42.9% - 71.4% for control group). 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. Thus seropositivity rates were 0.0% to 2.4%. 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.

In the AS03-adjuvanted vaccine group:
On Day 42 the SCRs and SPRs against the vaccine strain had 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 had increased to 68.9% and 76.2% in respective age groups. The ≥70% threshold for the lower bound of the 95% CI for seroprotection 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.
The 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
The 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.

In the control group, the seropositivity rates against A/Vietnam/1194/2004 and A/Indonesia/05/2005 were zero at all time points except for one subject who was seropositive after the first *Fluarix* dose. All corresponding GMTs were low or below the cut-off value.

In the AS03 vaccine group:
By 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 Fluarix 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 the three formulations 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. NA was not assessed against A/Indonesia.

Immunogenicity data 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. 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 A/Vietnam the SPRs 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. 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%.

NA was assessed against A/Vietnam at Month 6 in Part A of the study (i.e. half adult dose versus Fluarix). In the AS03 vaccine group the NA GMTs dropped to a similar degree in both age strata so that, 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%.

Additionally, NA against the heterologous A/Indonesia strain was measured up to 12 months in the Part A of the study (i.e. half adult dose versus Fluarix). NA titres of at least 1/80 in the 3-5 years age group were observed in 97.8% at Day 42, 89.6% at Month 6 and 87.2% at Month 12, Corresponding rates in the 6-9 years age group were 97.6% at Day 42, 90.0% at Month 6 and 82.9% at Month 12.

In Parts A, B and C of study 009 (-22/023) in children aged 3-9 years the D42 HI immune response parameters (SCR, SPR, SCF) did not clearly distinguish any one of the three formulations tested. However, the administration of a higher HA dose and, especially, the full adult dose, demonstrated advantages in terms of several HI and NA immune parameters. In particular, use of the adult dose gave improved HI responses to the heterologous strain and much higher NA GMTs.

At Month 6 the HI data showed a clear advantage for the full adult dose in terms of persistence of vaccine-homologous and especially vaccine-heterologous HI immune responses.

However, the NA data from Part A of the study against A/Vietnam and A/Indonesia showed that all in this dose group still had titres of at least 1:80 against A/Vietnam at 6 months and >80% against A/Indonesia at Month 12. These results were contrary to the HI data. On the basis of the D42 HI data and the Month 6 and 12 NA data, taken together with the relative safety profile of the three dose groups (see below) the CHMP considered that the SPC should recommend that half the adult dose (i.e. two doses of 0.25 ml) should be administered to children aged from 6 months to 9 years until such time that data in children with the H1N1v vaccine become available.

Study with a preliminary version of Pandemrix A(H1N1)v

An abridged report on the data from study H1N1-021 was submitted during the Rolling Review of the data for Pandemrix A(H1N1)v. This observer-blinded study is ongoing in three centres in Germany to evaluate the safety and immunogenicity of a two-dose schedule of the A/California/7/2009 (H1N1)v-like candidate vaccine adjuvanted with AS03 in adults aged 18 to 60 years. The study compares the AS03-adjuvanted vaccine to a non adjuvanted vaccine containing 15µg HA from the same strain.

Subjects were randomised (1:1) to one of the two study groups and stratified by age: between 18 and 40 years inclusive, above 41 to 50 years inclusive and above 51 to 60 years inclusive (ratio 2:1:1). The data were reported after administration of the first dose of study vaccine i.e. blood samples taken at 21 days after the first dose.

At the time the clinical material was produced, the antigen bulk was formulated based on HPLC measurements prior to availability of the official SRD reagents. Subsequently, it was determined that the actual HA content of one vaccine dose was 5.25 µg instead of 3.75 µg (i.e. an increase of 40%); likewise, the non adjuvanted dose was 21 µg.

The study enrolled 130 subjects and they all received the first dose of vaccine. Before the vaccination, the percentage of seropositive subjects was higher in younger age stratum (44.6% in the 18-40 years group and 29% in 51-60 years). The proportion of subjects seropositive before vaccination did not differ between group A (H1N1 AS03 adjuvanted vaccine) and group B (H1N1 plain vaccine).

Seropositive rates against A/California/7/2009 H1N1 per age strata before the vaccination

Age strata	Number seropositive subjects per age strata	Percentage of seropositive subjects in the study
18-40 years	29	44.6%
41-60 years	23	35.4%
41-50 years	14	41.1%
51-60 years	9	29%

At Day 21 the HI SCR observed in the H1N1 +AS03 group was 98.4%. SCF and SPR were 41.4 and 98.4%, respectively. In the H1N1 group, the SCR was 95.5%, the SCF was 41.4 and the SPR was 97.0%. The CHMP criteria were met in both age strata (18-40 years and 41-60 years) with no appreciable differences between the age strata.

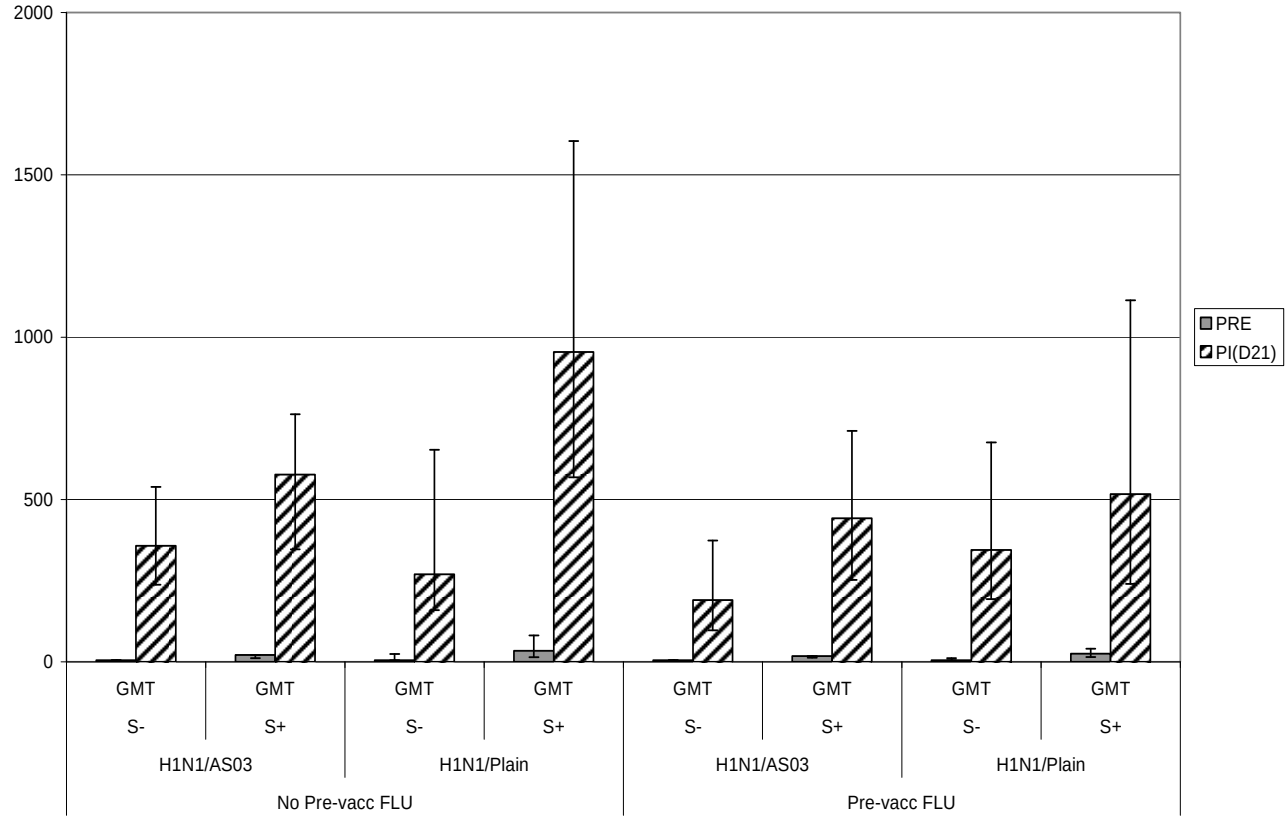
The HI immune responses observed at Day 21 were comparable between treatment groups, which demonstrated the antigen-sparing capacity of the $AS03_A$-adjuvanted vaccine.

Summary of HI antibody results by age at day 21

		≥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
Group H1N1 + AS03$_A$ Overall																
PRE	64	40.6	28.5	53.6	8.6	7.1	10.6	10.9	4.5	21.2	-	-	-	-	-	-
PI(D21)	62	100	94.2	100	359.9	278.2	465.5	98.4	91.3	100	98.4	91.3	100	41.4	31.0	55.2
18-40 years stratum																
PRE	33	39.4	22.9	57.9	8.7	6.4	11.9	15.2	5.1	31.9	-	-	-	-	-	-
PI(D21)	31	100	88.8	100	437.6	323.7	591.6	100	88.8	100	100	88.8	100	49.5	33.2	73.9
41-60 years stratum																
PRE	31	41.9	24.5	60.9	8.6	6.5	11.3	6.5	0.8	21.4						
PI(D21)	31	100	88.8	100	295.9	193.7	452.1	96.8	83.3	99.9	96.8	83.3	99.9	34.6	22.6	53.0
Group H1N1 Overall																
PRE	66	39.4	27.6	52.2	10.0	7.6	13.2	15.2	7.5	26.1	-	-	-	-	-	-
PI(D21)	66	100	94.6	100	414.0	305.9	560.3	97.0	89.5	99.6	95.5	87.3	99.1	41.4	30.0	57.1
18-40 years stratum																
PRE	32	50.0	31.9	68.1	15.1	9.1	24.9	28.1	13.7	46.7	-	-	-	-	-	-
PI(D21)	32	100	89.1	100	580.7	359.6	937.8	96.9	83.8	99.9	93.8	79.2	99.2	38.5	22.5	65.9
41-60 years stratum																
PRE	34	29.4	15.1	47.5	6.8	5.5	8.4	2.9	0.1	15.3	-	-	-	-	-	-
PI(D21)	34	100	89.7	100	301.0	208.4	434.8	97.1	84.7	99.9	97.1	84.7	99.9	44.3	29.9	65.7

There was no impact of prior seasonal vaccination or baseline serostatus on the HI GMTs as can be seen in the figure below.

Overall GMTs against A/California/7/2009(H1N1)v antibodies by previous seasonal vaccination history and pre-vaccination status



While the preliminary results from this study, which did not use final formulation vaccine, need to be viewed with some caution the responses to a single dose of unadjuvanted vaccine are very comparable

with those now reported from several other companies with similar products. The comparison between the two vaccine groups at D21 demonstrates the antigen-sparing effect of the AS03 adjuvant.

The contrast between the post-dose 1 results of this study and all the data obtained with the H5N1 mock-up vaccine is stark but is in line with observations made by other manufacturers. It is clear that the response to a single dose of A(H1N1)v vaccine is very different and markedly higher than was ever observed with the corresponding H5N1 constructs.

This phenomenon is observed regardless of prior vaccination and suggests that there is some natural priming with respect to the pandemic strain as a result of natural exposure to cross-reacting antigens at least in adults. Very early data reported from the US with a different vaccine suggest that the same situation may apply to adolescents although it remains possible for this vaccine two doses are needed for children aged < 11-12 years.

The CHMP considered that it was important to include these preliminary data in the SPC to indicate that a single dose may be sufficient in adults. Confirmatory data from ongoing studies with final formulation pandemic vaccine are awaited. For now, results after a single dose in adults cannot be extrapolated to children. Definitive data are needed from ongoing studies to establish if a single dose could be sufficient in adolescents and in younger children.

Clinical safety

This section will first describe the safety data available before approval of the core dossier application and then the additional safety data from studies reviewed after first approval.

In general all studies involved recording of solicited symptoms during the 7-day follow-up period after each dose together with any analgesics and/or antipyretics taken. Unsolicited symptoms occurring during a 21-day follow-up period after the first vaccination and 30 days after the second one were also recorded in the CRF.

- Patient exposure

Overall, 4,002 healthy subjects (minimum age 18 years) were exposed to H5N1 AS03 adjuvanted vaccine in studies 007 and 008 i.e. total across all doses. More than 3800 of these subjects received an HA dose ≥15 µg i.e. at least 4-fold the HA dose in the intended marketed formulation. Another 961 subjects aged 18-60 years received at least one dose of Third series 3.8 µg/AS03 vaccine in study 002 and were included in the safety evaluation. Additional numbers have been exposed in studies reported after first approval of the core dossier as detailed below.

- Adverse events

H5N1-007

The incidence of symptoms, and in particular local symptoms, was higher in the groups vaccinated with adjuvanted formulations. No significant effect of the antigen dose or consistent trend by dose was observed on the overall incidence of symptoms among the adjuvanted vaccines.

Solicited AEs (any severity) within 7 days after each dose and overall

		General symptoms					Local symptoms				
					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H5N1/30	50	25	50.0	35.5	64.5	50	28	56.0	41.3	70.0
	H5N1/15	50	27	54.0	39.3	68.2	50	20	40.0	26.4	54.8
	H5N1/7.5	50	31	62.0	47.2	75.3	50	17	34.0	21.2	48.8
	H5N1/3.8	50	24	48.0	33.7	62.6	50	18	36.0	22.9	50.8
	H5N1/30/AS03	49	40	81.6	68.0	91.2	49	46	93.9	83.1	98.7
	H5N1/15/AS03	50	41	82.0	68.6	91.4	50	46	92.0	80.8	97.8
	H5N1/7.5/AS03	50	32	64.0	49.2	77.1	50	44	88.0	75.7	95.5
	H5N1/3.8/AS03	51	29	56.9	42.2	70.7	51	46	90.2	78.6	96.7
Dose 2	H5N1/30	50	21	42.0	28.2	56.8	50	23	46.0	31.8	60.7
	H5N1/15	50	19	38.0	24.7	52.8	50	14	28.0	16.2	42.5
	H5N1/7.5	50	14	28.0	16.2	42.5	50	14	28.0	16.2	42.5
	H5N1/3.8	50	13	26.0	14.6	40.3	50	16	32.0	19.5	46.7
	H5N1/30/AS03	49	26	53.1	38.3	67.5	49	39	79.6	65.7	89.8
	H5N1/15/AS03	50	36	72.0	57.5	83.8	50	40	80.0	66.3	90.0
	H5N1/7.5/AS03	50	27	54.0	39.3	68.2	50	41	82.0	68.6	91.4
	H5N1/3.8/AS03	51	30	58.8	44.2	72.4	51	42	82.4	69.1	91.6
Overall/ dose	H5N1/30	100	46	46.0	36.0	56.3	100	51	51.0	40.8	61.1
	H5N1/15	100	46	46.0	36.0	56.3	100	34	34.0	24.8	44.2
	H5N1/7.5	100	45	45.0	35.0	55.3	100	31	31.0	22.1	41.0
	H5N1/3.8	100	37	37.0	27.6	47.2	100	34	34.0	24.8	44.2
	H5N1/30/AS03	98	66	67.3	57.1	76.5	98	85	86.7	78.4	92.7
	H5N1/15/AS03	100	77	77.0	67.5	84.8	100	86	86.0	77.6	92.1
	H5N1/7.5/AS03	100	59	59.0	48.7	68.7	100	85	85.0	76.5	91.4
	H5N1/3.8/AS03	102	59	57.8	47.7	67.6	102	88	86.3	78.0	92.3
Overall/ subject	H5N1/30	50	32	64.0	49.2	77.1	50	38	76.0	61.8	86.9
	H5N1/15	50	32	64.0	49.2	77.1	50	24	48.0	33.7	62.6
	H5N1/7.5	50	32	64.0	49.2	77.1	50	24	48.0	33.7	62.6
	H5N1/3.8	50	27	54.0	39.3	68.2	50	24	48.0	33.7	62.6
	H5N1/30/AS03	49	41	83.7	70.3	92.7	49	47	95.9	86.0	99.5
	H5N1/15/AS03	50	45	90.0	78.2	96.7	50	48	96.0	86.3	99.5
	H5N1/7.5/AS03	50	39	78.0	64.0	88.5	50	48	96.0	86.3	99.5
	H5N1/3.8/AS03	51	38	74.5	60.4	85.7	51	48	94.1	83.8	98.8

In contrast, the incidences of severe symptoms were low and variable across groups with no obvious dose trends. However, the highest rates were seen with one or more of the adjuvanted formulations.

Solicited severe AEs within 7 days overall by subject

		General symptoms					Local symptoms				
					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL
Overall/ subject	H5N1/30	50	1	2.0	0.1	10.6	50	0	0.0	0.0	7.1
	H5N1/15	50	2	4.0	0.5	13.7	50	1	2.0	0.1	10.6
	H5N1/7.5	50	1	2.0	0.1	10.6	50	1	2.0	0.1	10.6
	H5N1/3.8	50	2	4.0	0.5	13.7	50	0	0.0	0.0	7.1
	H5N1/30/AS03	49	0	0.0	0.0	7.3	49	3	6.1	1.3	16.9
	H5N1/15/AS03	50	7	14.0	5.8	26.7	50	10	20.0	10.0	33.7
	H5N1/7.5/AS03	50	2	4.0	0.5	13.7	50	8	16.0	7.2	29.1
	H5N1/3.8/AS03	51	6	11.8	4.4	23.9	51	3	5.9	1.2	16.2

Pain at the injection site was the most frequently reported local symptom in all groups (e.g. 86% in the 3.8 µg/AS03 group). The incidence was significantly higher in groups given adjuvanted vaccines (86-92% after dose 1 and 69-80% after dose 2 compared to 28-50% and 22-40% after respective doses in the groups given non-adjuvanted vaccines). There was also a trend for higher incidences of swelling and redness in groups with adjuvanted vaccines and the rate of induration was significantly higher in adjuvanted groups. However, severe swelling, redness and induration were all reported at low rates.

The most frequently reported general symptoms were fatigue and headache. For all of the solicited general symptoms there was at least a trend for higher incidence in groups that received adjuvanted vaccines. For example, myalgia reported as being vaccine-related was reported for 10-20% in the non-adjuvanted vaccine groups but 36-44.9% with adjuvanted vaccines. Fever was reported with a very low incidence in all groups and no fever above 39°C was reported.

Lymphadenopathy followed administration of 7.5 µg HA (3 cases), 15 µg HA (3 cases) and 30 µg HA (1 case) adjuvanted vaccines. Six of these 7 cases were considered to be related to vaccination. No reports of local lymph node swelling were of grade 3 severity and all subjects recovered without sequelae.

H5N1-008

The highest incidence of any severe symptom after vaccination with 15 µg/AS03 vaccine (16.3%) was reported by subjects aged 18 to 60 years after the first dose. After the first injection, severe symptoms were reported more frequently in subjects aged 18-60 years than in those > 60 years but after the second injection there was little difference between the age strata. Severe symptoms were reported with a significantly lower incidence in subjects vaccinated with Fluarix and placebo.

Among solicited local symptoms pain was the most frequently reported AE in both treatment groups and age strata but was reported with a significantly higher incidence in subjects vaccinated with 15 µg/AS03 than in subjects vaccinated with Fluarix or placebo. Pain was predominantly reported by subjects aged between 18 and 60 years.

In the 15 µg/AS03 group general symptoms were reported more frequently in those aged 18-60 years than in those aged > 60 years. The most common symptoms were fatigue, headache and myalgia in both treatment groups and age strata.

Solicited and unsolicited symptoms reported during the 7-days post-vaccination (Total vaccinated cohort)

		General symptoms					Local symptoms				
					95% CI					95% CI	
	Group	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	H5N1 18-60	3341	2285	68.4	66.8	70.0	3342	3007	90.0	88.9	91.0
	H5N1 >60	403	169	41.9	37.1	46.9	403	281	69.7	65.0	74.2
	Fluarix 18-60	1123	560	49.9	46.9	52.8	1123	808	72.0	69.2	74.6
	Fluarix >60	133	39	29.3	21.8	37.8	133	57	42.9	34.3	51.7
Dose 2	H5N1 18-60	3246	1766	54.4	52.7	56.1	3247	2590	79.8	78.3	81.1
	H5N1 >60	395	157	39.7	34.9	44.8	395	242	61.3	56.3	66.1
	Placebo 18-60	1102	297	27.0	24.4	29.7	1102	256	23.2	20.8	25.8
	Placebo >60	132	32	24.2	17.2	32.5	132	25	18.9	12.6	26.7
Overall/subject	H5N1 18-60	3342	2569	76.9	75.4	78.3	3343	3107	92.9	92.0	93.8
	H5N1 >60	403	225	55.8	50.8	60.7	403	316	78.4	74.1	82.3
	Fluarix/Placebo 18-60	1123	651	58.0	55.0	60.9	1123	833	74.2	71.5	76.7
	Fluarix/Placebo >60	133	47	35.3	27.3	44.1	133	63	47.4	38.7	56.2

In both vaccine groups subjects aged 18 - 60 years more frequently reported unsolicited symptoms than those aged > 60 years. The most common symptoms were injection site pruritus and warmth, influenza like illness and related symptoms and gastrointestinal symptoms (diarrhoea, nausea). There were 95 AE reports coded as the MedDRA preferred terms lymphadenopathy, lymph node pain or lymphadenitis, of which 84/95 occurred in the 15µg/AS03 group. These subjects were more likely than others to report other general symptoms.

Based on the MAH's assessment from D51 to D180 there were 16 subjects in the 15µg/AS03 group and three in the Fluarix group who reported 17 and 3 unsolicited symptoms, respectively, classified as new onset chronic diseases (NOCD). There was no clear disease pattern identified.

Summary of new onset chronic diseases (GSK assessment) reported (Total vaccinated cohort)

	Group				
	HN AS03		Fluarix	All	
	s18	s61	s18	s18	s61
N with at least one unsolicited symptom reported	9	7	3	12	7
N doses followed by at least one unsolicited symptom	9	7	3	12	7
N unsolicited symptoms classified by MEDDRA Term*	9	7	3	12	7
N unsolicited symptoms reported	10	7	3	13	7

HN AS03 = H5N1 15µg HA + AS03, Fluarix = Fluarix/ (Placebo at the 2nd dose)
s18 = 18-60 years, s61 = 61-120 years
* Symptoms reported by a subject after a given dose and classified by the same Preferred Term are counted once

Also, 64 subjects in the 15µg/AS03 group and 14 in the Fluarix group reported 75 and 17 unsolicited symptoms, respectively, classified as medically significant conditions.

Summary of medically significant conditions (GSK assessment) reported (Total vaccinated cohort)

	Group					
	HN AS03		Fluarix		All	
	s18	s61	s18	s61	s18	s61
N with at least one unsolicited symptom reported	56	8	11	3	67	11
N doses followed by at least one unsolicited symptom	56	8	11	3	67	11
N unsolicited symptoms classified by MEDDRA	65	9	14	3	79	12
Number of unsolicited symptoms reported	66	9	14	3	80	12

H5N1-002

There were no consistent differences in AEs reported in this study with final formulation vaccine compared to those reported with the 3.8 µg/AS03 vaccine used in study 007.

The next table shows the incidence of solicited local symptoms over the 7-day follow-up period after vaccination overall by subject. Subjects in the adjuvanted groups frequently reported pain, swelling and redness with generally similar rates across the four groups. Rates were much lower in the non-adjuvanted vaccine groups in which no grade 3 local symptoms were reported.

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

		H5N1_AX					H5N1_AY					H5N1_BX				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/subject																
Ecchymosis (mm)	All	238	14	5.9	3.3	9.7	237	15	6.3	3.6	10.2	240	14	5.8	3.2	9.6
	> 50 mm	238	0	0.0	0.0	1.5	237	2	0.8	0.1	3.0	240	0	0.0	0.0	1.5
Induration (mm)	All	238	57	23.9	18.7	29.9	237	55	23.2	18.0	29.1	240	54	22.5	17.4	28.3
	> 50 mm	238	5	2.1	0.7	4.8	237	4	1.7	0.5	4.3	240	2	0.8	0.1	3.0
Pain	All	238	210	88.2	83.4	92.0	237	199	84.0	78.7	88.4	240	208	86.7	81.7	90.7
	Grade 3	238	12	5.0	2.6	8.6	237	12	5.1	2.6	8.7	240	11	4.6	2.3	8.1
Redness (mm)	All	238	88	37.0	30.8	43.4	237	79	33.3	27.4	39.7	240	77	32.1	26.2	38.4
	> 50 mm	238	6	2.5	0.9	5.4	237	9	3.8	1.8	7.1	240	3	1.3	0.3	3.6
Swelling (mm)	All	238	95	39.9	33.6	46.4	237	80	33.8	27.8	40.2	240	86	35.8	29.8	42.3
	> 50 mm	238	8	3.4	1.5	6.5	237	5	2.1	0.7	4.9	240	10	4.2	2.0	7.5

		H5N1_BY					H5N1_AD					H5N1_BD				
					95 % CI					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Overall/subject																
Ecchymosis (mm)	All	239	24	10.0	6.5	14.6	122	4	3.3	0.9	8.2	123	6	4.9	1.8	10.3
	> 50 mm	239	1	0.4	0.0	2.3	122	0	0.0	0.0	3.0	123	0	0.0	0.0	3.0
Induration (mm)	All	239	80	33.5	27.5	39.8	122	3	2.5	0.5	7.0	123	8	6.5	2.8	12.4
	> 50 mm	239	6	2.5	0.9	5.4	122	0	0.0	0.0	3.0	123	0	0.0	0.0	3.0
Pain	All	239	213	89.1	84.5	92.8	122	26	21.3	14.4	29.6	123	36	29.3	21.4	38.1
	Grade 3	239	14	5.9	3.2	9.6	122	0	0.0	0.0	3.0	123	0	0.0	0.0	3.0
Redness (mm)	All	239	77	32.2	26.3	38.5	122	27	22.1	15.1	30.5	123	21	17.1	10.9	24.9
	> 50 mm	239	1	0.4	0.0	2.3	122	0	0.0	0.0	3.0	123	0	0.0	0.0	3.0
Swelling (mm)	All	239	104	43.5	37.1	50.1	122	8	6.6	2.9	12.5	123	15	12.2	7.0	19.3
	> 50 mm	239	14	5.9	3.2	9.6	122	0	0.0	0.0	3.0	123	0	0.0	0.0	3.0

For solicited general symptoms myalgia and fatigue were reported frequently by subjects in the adjuvanted vaccine groups (myalgia in > 60% in adjuvanted groups but 20-30% in non-adjuvanted; fatigue in 50-60% compared to 30-40%).

Unsolicited symptoms were reported by 383 subjects with rates across all six groups in the range 28-35%. The most frequently reported unsolicited symptoms tended to be associated with likely intercurrent illnesses affecting the respiratory and gastrointestinal tracts and so were very varied in nature.

H5N1-012

The incidence of all and Grade 3 (severe) solicited and unsolicited symptoms reported during the 7-day post-vaccination period did not differ significantly between groups after the first and second priming doses or the Month 6 booster. In addition, there does not appear to be any consistent pattern for higher or lower rates of symptoms with sequential doses or between VT and IN booster doses. Similar findings applied for all and Grade 3 symptoms considered causally related to vaccine. Pain at

the injection site was the most frequently reported solicited symptom in all groups (80.7 % to 89.4 % overall per dose; Grade 3 symptoms 2.6% to 7.8 % overall per dose).
The most commonly reported solicited general adverse event (AEs) following the booster dose (i.e. dose 2 or 3) were myalgia (36.1% - 46.8% after the last primary dose and 49.1% - 62.1% after the booster dose), headache (27.3% - 40.3% and 38.6 % - 48.3 %) and fatigue (34.4 % - 43.8 % and 40.4 % - 51.7 %). No significant difference in the incidence of grade 3 solicited general symptoms was observed between the primary and booster doses.

H5N1-015
The incidences of all and Grade 3, considered related and unrelated solicited and unsolicited symptoms reported during the 7-day post-vaccination period did not differ significantly between the nine groups (i.e. eight previously primed with adjuvanted or non-adjuvanted vaccine and the Control group) after the first dose or between the five groups that received a second dose. The majority of local and general symptoms were considered to be related to vaccination in all study groups.Rates for local symptoms (very predominantly due to the incidence of injection site pain) were higher than for general symptoms.Pain at injection site was the most frequently reported solicited symptom. While there was no significant difference between the groups the rates in the groups primed with non-adjuvanted vaccine and the Control group ranged from 77.8 % to 89.9 % overall per dose compared to 88.9 % to 97.2 % in the groups primed with adjuvanted vaccine. Grade 3 pain occurred in 0.0 % to 3.0 % overall per dose and in 0.0 % to 2.8 % in respective priming groups.

The additional information from studies H5N1-012 and -015 did not raise any new issues for the safety profile of AS03-adjuvanted vaccine containing either A/Vietnam or A/Indonesia.

No consistent pattern for higher or lower rates of symptoms with sequential doses or between VT and IN booster doses could be observed. Similar findings applied for all and Grade 3 symptoms considered causally related to vaccine. In these studies pain at the injection site was the most frequently reported solicited symptom in all groups. The most commonly reported solicited general AEs following booster doses also showed a similar pattern to that described previously after the first and second priming doses with A/Vietnam vaccine.

In this study the numbers of unsolicited AEs reported were higher in the groups primed with non-adjuvanted vaccine compared to those primed with adjuvanted vaccine. The highest numbers of reports came from the Control group. A review of the detailed data suggested that much of the difference might reflect higher rates of reporting headache in the groups primed with non-adjuvanted vaccine and the Control group. In answers to list of questions the MAH justified that the observation made reflected an imbalanced number of vaccine administrations between groups and the duration of the respective follow-up periods. The CHMP considered that the data should not be interpreted as indicating high rates of reporting headache in the groups primed with non-adjuvanted vaccine and in the Control group.

H5N1-010
The incidence of symptoms, and especially local symptoms, was higher in groups that received adjuvanted vaccine compared to those given non-adjuvanted vaccine. There were also more local solicited symptoms causally related to vaccination in the adjuvanted groups than the non-adjuvanted groups following each dose and overall. Subjects in the non-adjuvanted groups reported more general than local symptoms whereas the reverse reporting pattern applied in the two adjuvanted vaccine groups. However, there were few Grade 3 local and general solicited symptoms reported and no significant difference in reporting of grade 3 symptoms was observed between groups.

Rates of reporting local symptoms of pain, redness and swelling were significantly higher in the 3.8 µg HA + AS03 group than in the 3.8 µg HA alone group. Pain and redness also occurred at a significantly higher rate in the group given 7.5 µg HA + AS03 compared to the group that received 7.5 µg HA alone. Between the adjuvanted groups the effect of dose of HA on rates of local symptoms was not consistent although slightly higher rates of pain and redness were seen in the double dose group.

Up to D51 there were no Grade 3 local solicited symptoms reported in the non-adjuvanted groups and there were only three subjects with grade 3 local solicited symptoms in the adjuvanted groups (all were in the 7.5 µg HA + AS03 group; 2 with Grade 3 pain, 1 with grade 3 redness).

Pain at the injection site was the most frequently reported local symptom in the adjuvanted vaccine groups after each administration, followed by redness, swelling, induration and ecchymosis. However, there was no consistent increase in the incidence of local solicited symptoms of any type or grade between Dose 1 and Dose 2. Furthermore, it was noted that:

- Fatigue was the most frequently reported general symptom in the adjuvanted vaccine groups (12.9% to 17.3% compared to 7-8% in the non-adjuvanted vaccine groups) but rates of Grade 3 fatigue were < 2%.
- Headache was reported in 10.8% to 14.4% compared to 2-7% in respective groups but the rates for Grade 3 headache were < 1%.
- Myalgia was also more frequently reported in the adjuvanted vaccine groups (8.6% to 11.5% compared to 4-5%) but rates of Grade 3 myalgia were < 1.5%.
- Rates of other general symptoms, including fever, were low but usually higher in the adjuvanted vaccine groups.
- In general, the results of the biochemical analysis were within the normal range except that up to 28.2% showed elevated blood urea nitrogen values.

Overall, there were no new concerns or unexpected findings in the safety data obtained from this older population. As expected from previous studies in younger adults the incidence of symptoms (local in particular) was higher in the adjuvanted vaccine groups than in the non-adjuvanted vaccine groups. The effect of dose was not detectable. There were no new concerns or unexpected findings in the safety data obtained from this older population up to D180.

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.

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. The incidence of AEs with causal relationship to the vaccination in the subjects aged 6-9 years was 94.1% in the Half HA/Half AS03 group compared with 83.3% in the control subjects. However, rates were comparable among subjects aged 3-5 years (66.7% and 61.1%).

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 but very few had Grade 3 pain.

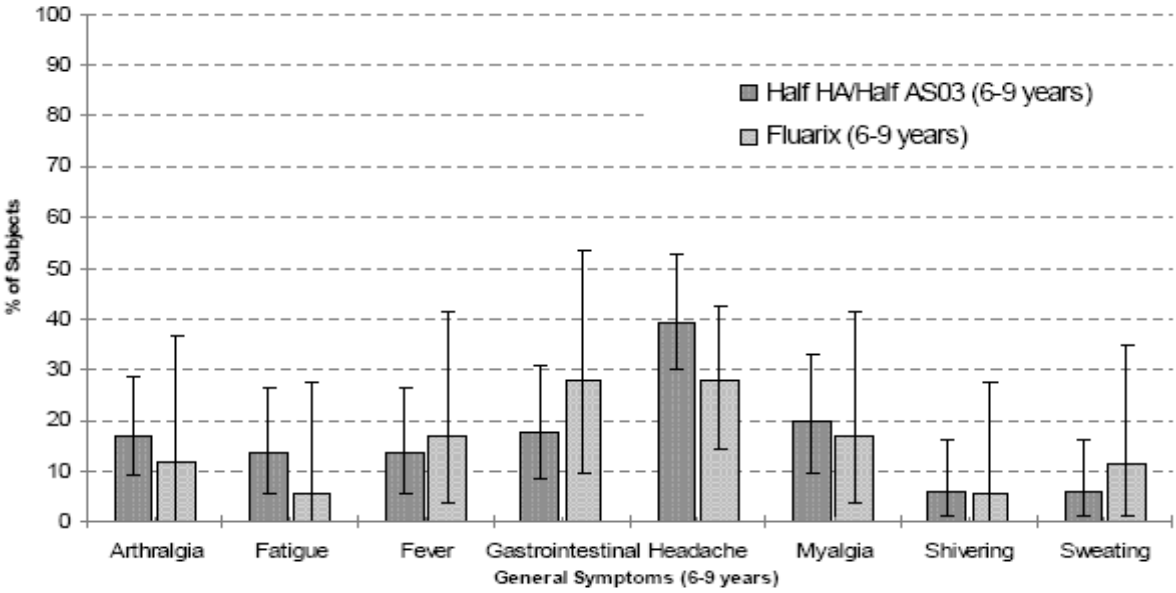
Rates of solicited general symptoms per subject as shown below were not markedly different between vaccine groups in the **6-9 years** age stratum. The rate of any fever (> 37.5°C) after dose 1 of AS03 vaccine was 5.9% but no subject had Grade 3 fever (> 39°C) and no subject in the Fluarix group had 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.

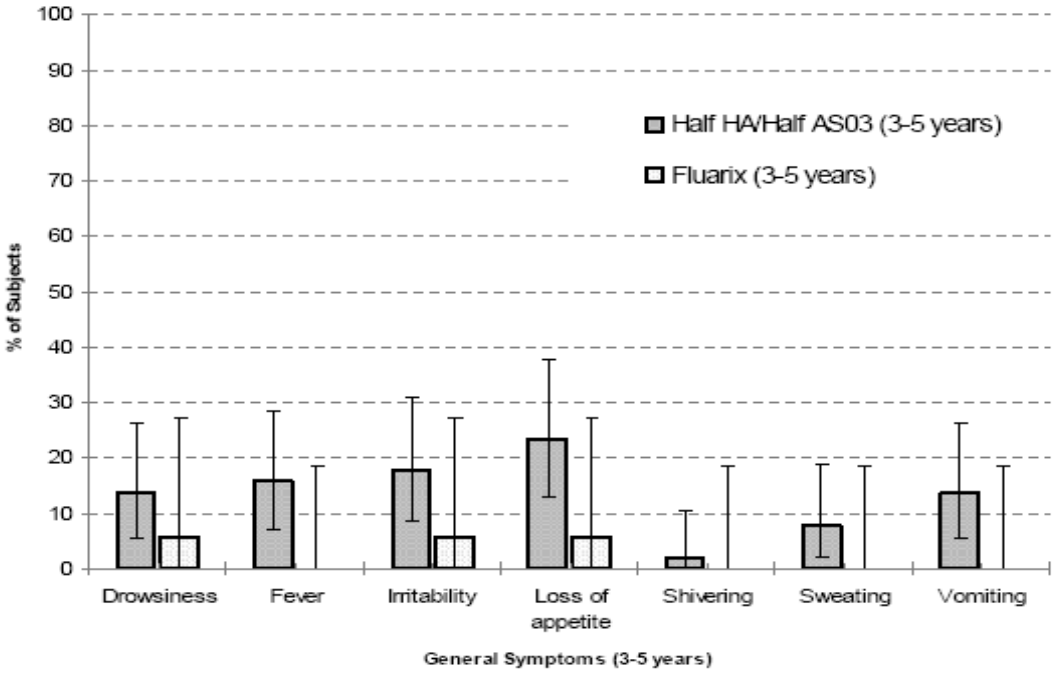
In the **3-5 years** age stratum rates of solicited general symptoms per subject were higher than in the control group. The rate of any fever after dose 1 of AS03 vaccine was 9.8% but 3.9% had Grade 3 fever (> 39°C). The corresponding rates after the second dose were 6% and zero. No subjects in the Fluarix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

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) – for children aged 6-9 years



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) – for children aged 3-5 years



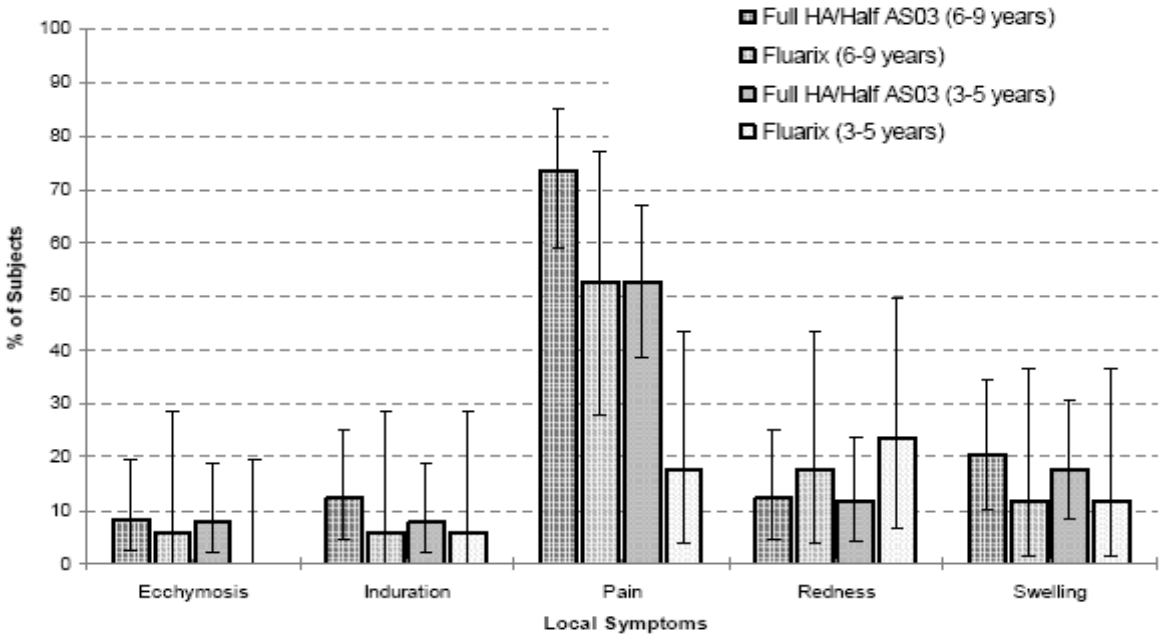
Phase B

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.

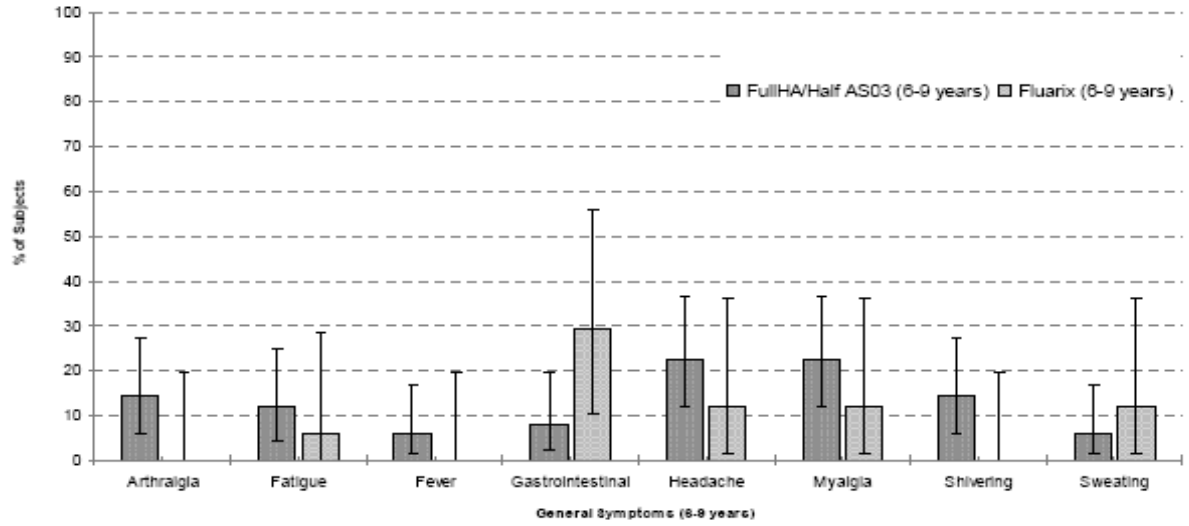
Solicited local symptoms per subject (see graph below) did not show marked differences between AS03 and control except for pain at the injection site.

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.

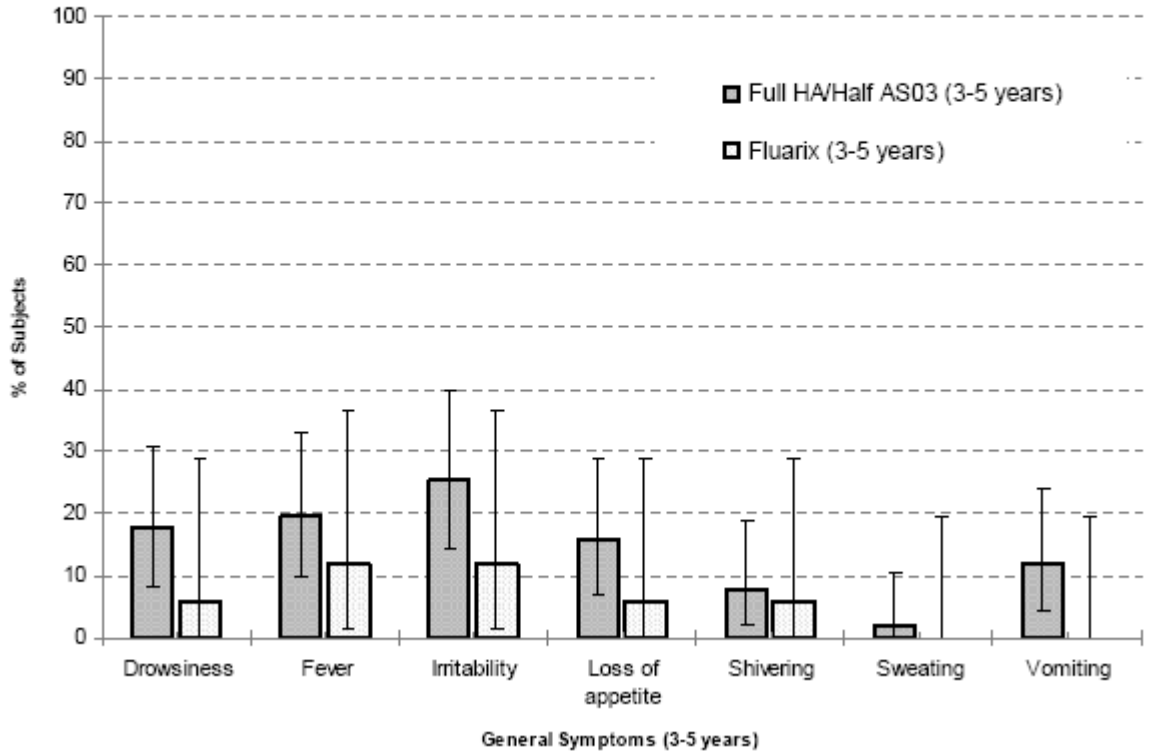
Overall incidence per subject of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort; Phase B) – for children aged 6-9 years



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%.

Overall incidence per subject of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort; Phase B) – for children aged 3-5 years



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.

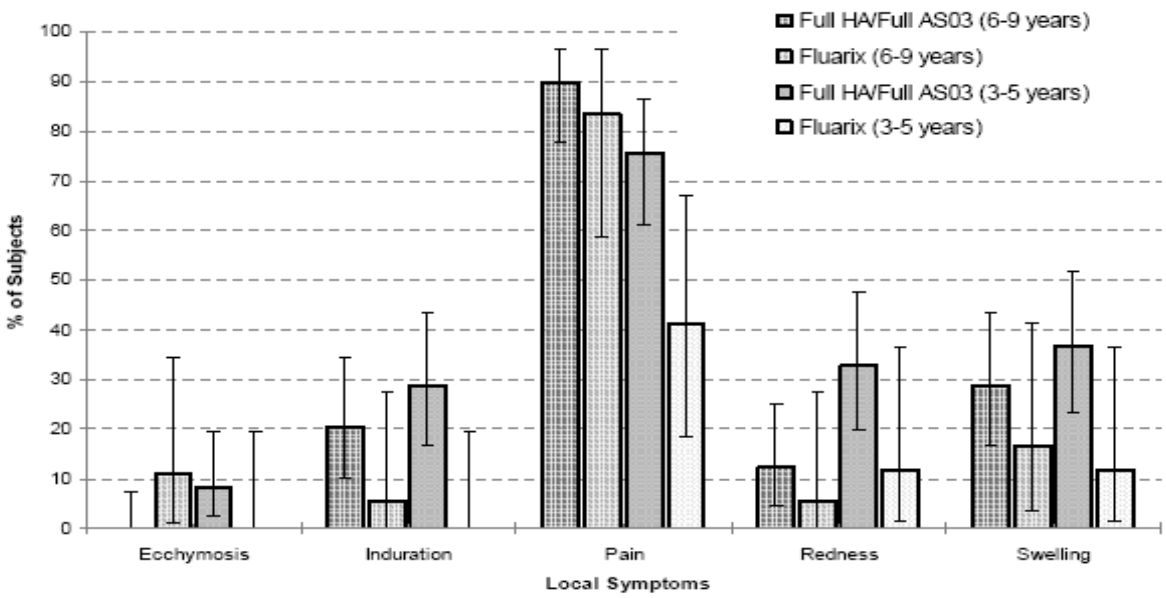
Phase C

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.

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.

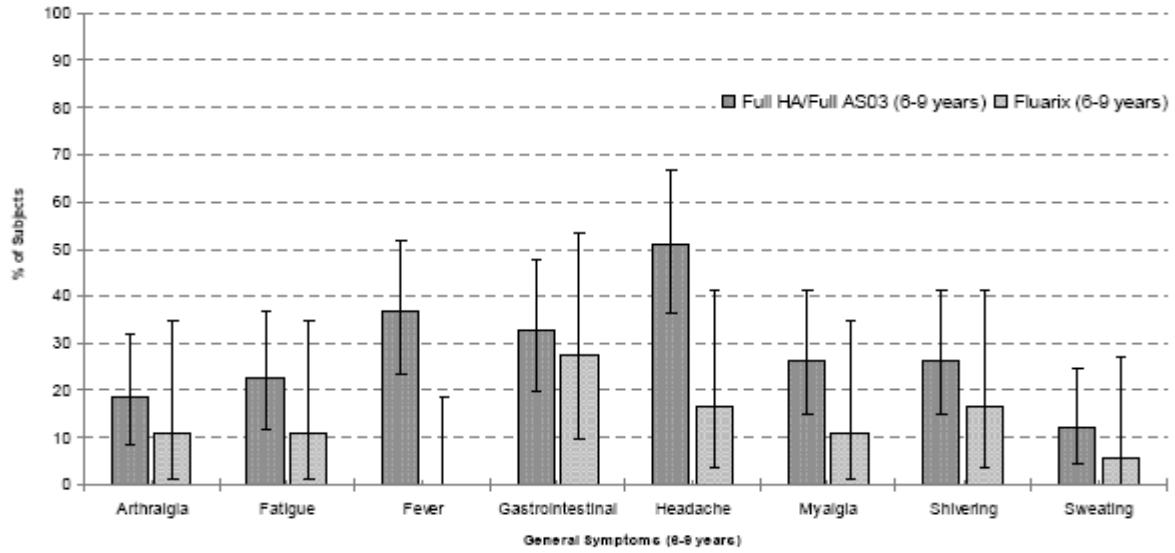
Overall incidence per subject of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period (Total Vaccinated cohort; Phase C)



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).

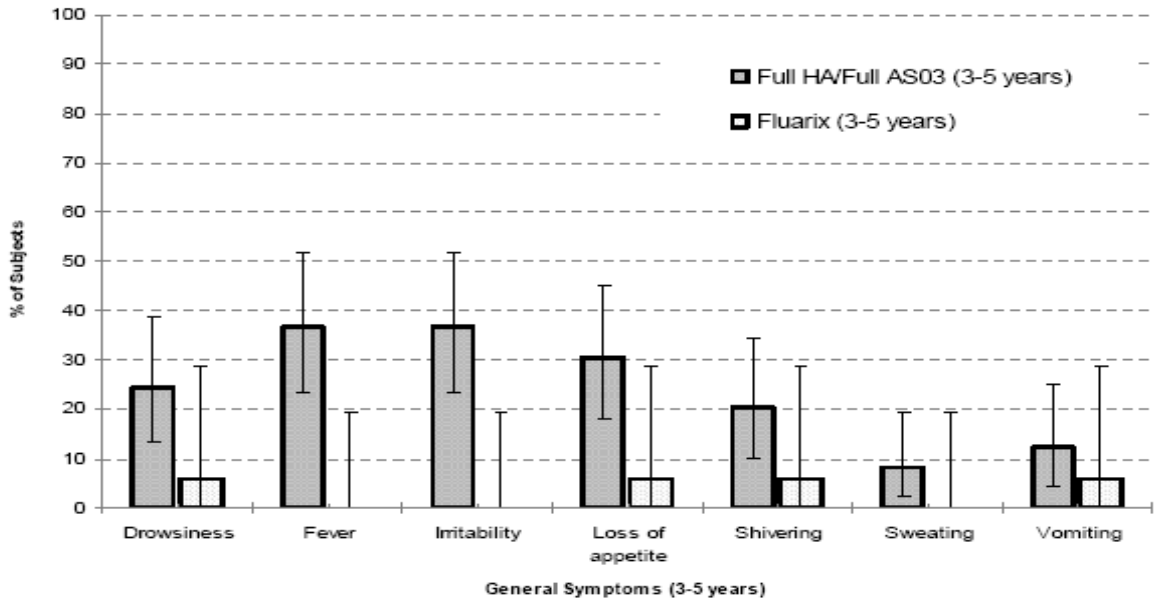
Among **6-9** year-olds rates of general solicited symptoms were higher with AS03 vaccine and the incidence of fever, headache, myalgia, shivering and sweating tended to be higher after Dose 2. Rates of fever after dose 1 were zero in the Fluarix group and 12.2% in the AS03 group (1/6 of these subjects [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.

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%.

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. There were very few Grade 3 unsolicited AEs and unsolicited AEs assessed as causally related to the vaccination were infrequent. 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.

In study H5N1 009 (-022/023), the differences between H5N1/AS03 and control vaccines for general and local symptoms and unsolicited AEs were most marked in Phase C when the adult dose was administered.

As expected from the adult studies, the data indicated higher rates in the AS03 groups for local symptoms, which mainly concerned pain although rates of other symptoms were also usually higher. However, as in adults, the rates of Grade 3 pain have generally been low and were 6-10% with the full adult dose. In Phase A there was a higher rate of fever in the AS03 group in the younger age cohort only. In Phase B general symptoms occurred more often in the AS03 group in both age strata. The most common symptoms in the 6-9 years age stratum were headache and myalgia whereas in the 3-5 years age stratum the most common were irritability and fever (but rates of Grade 3 symptoms were ≤ 2%).

In Phase C solicited general symptoms (the most common being headache and fever in the 6-9 year-olds, and fever and irritability in the 3-5 year-olds) were much more frequently observed in the AS03 group when compared with the control group. The incidence of Grade 3 solicited symptoms was low except for a higher incidence of Grade 3 fever (10-14% overall per subject in the two age strata) and Grade 3 loss of appetite (only 3-5 year-olds) in the AS03 group.

When comparing the age strata, a higher incidence of unsolicited AEs was observed in the subjects aged 3-5 years irrespective of vaccine group. In Phase C, the occurrence of unsolicited AEs in the 6-9 year-olds was higher in the AS03 group than in the control group, while there was no difference in the incidence of unsolicited AEs between the vaccine groups in the 3-5 year-olds.

The additional safety data collected up to Month 6 raised no new concerns.

H1N1-021
Only safety data after the first dose of vaccine have been provided. The incidences of local and systemic reactions to Pandemrix A(H1N1)v were very similar to those reported with the mock-up vaccine H5N1. There was no case of fever after the first dose. The incidence of grade 3 symptoms (unsolicited and solicited) was low: 4.7%.

- Serious adverse event/deaths/other significant events

In **study H5N1-007** there were no deaths or non-fatal SAEs up to D51. From D51 to D180 seven subjects reported a SAE, ranging from 0-2 per dose group but none was considered to be related to vaccination.

In **study H5N1-008** there were 11/3802 (0.3%) subjects in the 15µg/AS03 vaccine group and 6/1269 (0.5%) in the Fluarix/placebo group who reported SAEs. All SAEs were considered as not related to vaccination by the investigator and all resolved. There were no deaths.
Between D51 and D180 3.8% of those aged > 60 years in the 15µg/AS03 group reported a SAE compared to 3.9% in this age group from the Fluarix group. Rates in subjects aged 18-60 years were 0.8% and 0.9% in the two vaccine groups. There was no discernible pattern in SAEs observed. In the 15µg/AS03 vaccine group none of the SAEs seemed likely to be in any way related to vaccination based on nature or date of onset.

In **study H5N1-002** there were seven subjects who reported SAEs during the study. Review of these SAEs indicates that none was related to vaccine. One subject died but this was unrelated to vaccine.

In study **H5N1-012** six subjects reported seven SAEs up to the data lock point of which six were are resolved and one was fatal. Non-fatal SAEs included concussion, uterine neoplasm, aggravation of cervico-brachial syndrome, cerebral infarction and hemiparesis and uterine polyp requiring surgery. No SAEs were considered to be related to vaccination and one was reported during the 30-day follow-up post-vaccination period (after the second primary dose).

In study **H5N1-015** eight subjects (2 in adjuvanted groups, 3 in non-adjuvanted groups and 3 in control group) reported 9 SAEs between Day 0 and Day 180. There were no deaths. None of these reported SAEs were assessed by the investigator as causally related to the vaccination.

In study **H5N1-010**, there were 5 SAEs reported by 4 subjects up to the initial D51 data lock point. These were clearly intercurrent illnesses unrelated to vaccination, none was fatal and all were resolved. SAEs were reported between Day 52 and Day 180. During this period 13 subjects reported a total of 13 SAEs up to the data lock point. Of these SAEs; two were unresolved, six were resolved and five were fatal. The five fatalities concerned a cerebrovascular accident (2), congestive cardiac failure (2) and ventricular fibrillation. Overall (from D0 onwards) 18 SAEs were reported by 16 subjects in this study. There were eight non-fatal adverse events during the extended safety follow-up period. None of these SAEs were assessed by the investigators as related to the vaccination.

In study **H5N1-009 (-022/-23),** no SAEs or deaths have been reported in phases A and B. In Phase C 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.

There were two cases of auto-immune hepatitis (AIH) reported (in one of these the diagnosis was not confirmed) across the studies preformed with AS03-adjuvanted H5N1 vaccines, including HA manufactured in Dresden as for Pandemrix and in Quebec in a version of the vaccine that is not yet approved. The full review of the cases of possible AIH suggested that in each instance this was likely an underlying disorder present before immunisation. There was no evidence that vaccination exacerbated the AIH in these patients.

Subsequently there was a full review of other cases of hepatic events reported so far from all of the studies conducted with AS03-adjuvanted H5N1 and seasonal influenza vaccines. There is currently no evidence to indicate these cases were AIH and alternative causes for the hepatic events existed. Therefore, there is currently no evidence to suggest that AS03-adjuvanted vaccines are causally associated with development of AIH or other autoimmune disorders. However, the MAH and the CHMP will keep these issues under close review during the post-marketing period.

- Safety related to drug-drug interactions and other interactions

There are no data on co-administration of Pandemrix with other vaccines.

- Discontinuation due to adverse events

There were no discontinuations due to AEs in study 007.

In 008 three subjects who received 15µg/AS03 vaccine dropped out due to SAEs assessed as not related to vaccination. In addition, 22 subjects reported non serious AEs that led to premature discontinuation from the study. Of these 21 were from the 15µg/AS03 group (9 by day 21) and there was only one withdrawal from the Fluarix group (by Day 42). After review the MAH concluded that there was an excess of AEs associated with withdrawal in the adjuvanted vaccine group but no pattern of AEs associated with withdrawals could be discerned.
In study 002 the only early discontinuation was due to the death that was unrelated to vaccine.

- Post marketing experience

There is no post-marketing experience at present.

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 (V3.04) 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.

Risk Management Plan

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

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

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

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

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

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

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

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

Summary of the risk management plan

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

Identified/Potential safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk		
None	N/A	• N/A
Important potential risk		
Anaphylaxis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	• Contraindication for history of anaphylactic reaction to any constituent of the vaccine in the proposed labelling • Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components Section 4.8 Post-marketing surveillance *From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse reactions have been reported:* *<u>Uncommon</u>:* *Generalised skin reactions including urticaria* *<u>Rare</u>:* *Neuralgia, convulsions, transient thrombocytopenia.* *Allergic reactions, in rare cases leading to shock, have been reported.* *<u>Very rare</u>:* *Vasculitis with transient renal involvement.* *Neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.*
Autoimmune hepatitis	• Enhanced pharmacovigilance	
Bell's palsy	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Convulsion	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Demyelinating disorders	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Encephalitis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Guillain-Barré syndrome	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study • Study to establish a case-series in France, with possibility for case-control analysis, if needed	
Increased concentrations of hepatic enzymes	• Enhanced pharmacovigilance	
Neuritis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Vasculitis	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	
Vaccination failure	• Enhanced pharmacovigilance • Incidence will be estimated in participants of the post-authorisation safety study	NA
Important missing information		
Vaccine effectiveness	• GSK Biologicals will support ECDC vaccine effectiveness project • GSK Biologicals will obtain results from the UK HPA project	SPC section 4.2 *There is currently very limited clinical experience with an investigational formulation of Pandemrix (H1N1) containing a higher amount of antigen (see section 5.1) in healthy adults aged 18-60 years and no clinical*

Identified/Potential safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		experience in the elderly, in children or in adolescents.
Data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy. • Spontaneously reported by patients and HCPs • Enrolled/observed during post-authorisation safety study • Observed during clinical trials • Reported via Pregnancy Register	SPC section 4.6 *There are currently no data available on the use of Pandemrix in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.* *Animal studies with Pandemrix do not indicate reproductive toxicity (see section 5.3).* *The use of Pandemrix may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.* *Pandemrix may be used in lactacting women.*
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)	• SPC section 4.2 *"…no clinical experience in the elderly, in children or in adolescents."*
Data in subjects with compensated underlying conditions; No data in subjects with severe underlying medical conditions and immunocompromised	• Routine pharmacovigilance • Post-authorisation cohort study: individuals will be included based on national recommendations, underlying medical conditions will be documented for *post hoc* analyses	SPC section 4.4 *Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient*
Medication errors/misidentification of vaccine	• Review spontaneous reports of medication errors • Review of percentage of spontaneous adverse event reports that contain the vaccine brand name and batch number	• Use and handling section of SPC provide detailed instructions for mixing vaccine • Labelling of vials enables distinction between antigen vial and adjuvant vial • Additional stand-alone instructional materials (pictogram and video) to demonstrate proper mixing • Provision of stickers in each vaccine package that include vaccine brand name and batch number to be affixed to healthcare records
Contamination with multi-dose vials	• Review of spontaneous reports of injection site infection, injection site abscess, injection site cellulitis	• Use and handling section of SPC provide detailed instructions for mixing and administration of vaccine with instructions to discard vaccine for any variation in appearance and to replace needle used for withdrawal of vaccine with a needle suitable for intramuscular injection. • Shelf-life section of SPC states, "After mixing, the vaccine should be used within

Identified/Potential safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		24 h." • Vaccine contains thiomersal as a preservative. • Additional stand-alone instructional materials (pictogram and video) to demonstrate proper mixing and administration.

2.6 Product Information

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

2.7 Overall conclusions, risk/benefit assessment and recommendation

Clinical Context

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

Current estimates for the attack rate associated with the influenza A(H1N1)v virus over the first wave of infection vary from approximately 10-30 % in different geographical areas. There are no established criteria for classifying pandemics in terms of severity. The perceived severity can vary with geographical area, with sequential pandemic waves and in accordance with several other factors. Descriptions of severity based on factors such as rates of hospitalisation may be misleading due to different thresholds for this between countries and age groups.

The development of Pandemrix 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). The core dossier procedure allows the insertion of the pandemic strain A(H1N1)v into the authorised mock-up vaccine as a strain change variation procedure.

This principle is based on the extrapolation of the extensive clinical safety and immunogenicity data obtained with the mock-up vaccine (containing H5N1 strains) to the same vaccine construct using the current influenza A(H1N1)v pandemic strain. That is, on an expectation that insertion of the influenza A(H1N1)v strain into the mock-up vaccine construct would result in a vaccine similarly or even more immunogenic than the H5N1 mock-up version and with a similar safety profile when used in a comparable population (i.e. in terms of immunological naivety, health status and age group).

The specific commitments that accompany the strain change variation include collection of data from ongoing and planned clinical studies, which will provide safety and immunogenicity data. These data will be submitted and reviewed on a rolling basis and updates to the Clinical Particulars in the SPC will be made as necessary.

The MAH reported preliminary clinical data following administration of a single dose of AS03-adjuvanted A(H1N1)v vaccine (with a slightly higher HA content than will be included in Pandemrix) to healthy adults aged from 18-60 years before the strain change variation was approved. These data indicated that in contrast to the H5N1 mock-up vaccine a single dose of A(H1N1)v vaccine might be sufficient in this population. These preliminary data were in keeping with results reported concurrently

by several other manufacturers worldwide with a variety of A(H1N1)v vaccine constructs and in different populations. The CHMP considered that these data were potentially very important and they were taken into consideration when drafting the SPC. The SPC will be updated as soon as confirmatory data on responses to a single dose of Pandemrix A(H1N1)v become available. In addition, data obtained from different age groups will be added as appropriate.

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 in the mock-up licence can be considered supportive for this pandemic strain change licence. Supporting quality data required specifically for the strain change have been provided and satisfactorily demonstrate the quality of the vaccine.

Non-clinical pharmacology and toxicology

At time of the strain variation all non-clinical data with Pandemrix was generated with vaccine constructs that included influenza A (H5N1) strains.

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically using ferret challenge models. Of animals receiving adjuvanted vaccine 87% and 96% were protected against the lethal homologous or heterologous challenge, respectively. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant only control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity, local tolerance, embryo-foetal and postnatal toxicity (up to the end of the lactation period).

As no administration around implantation phase of the embryos was performed, the use of AS03-adjuvanted vaccine in early pregnancy was not studied. The MAH agreed to conduct a study in which the vaccine will be given to pregnant animals during early pregnancy. Animal studies did not indicate harmful effects with respect to fertility, pregnancy or embryofetal development. This is reflected in the SPC.

Clinical

While it was expected that the insertion of the influenza A(H1N1)v strain into the mock-up vaccine construct of Pandemrix would not have a substantial effect on immune responses the preliminary data from study H1N1-021 have indicated that a single dose might be sufficient to elicit immune responses considered to be potentially protective at least in healthy adults aged 18-60 years. These findings contrasted with the consistent data from the H5N1 studies that indicated the need for two doses in all age groups tested so far. The difference most likely relates to a considerable degree of priming of the immune systems of subjects to one or more antigens in the A(H1N1)v vaccine as a result of past natural exposure to cross-reacting viruses and/or seasonal influenza vaccines containing strains that elicited cross-reacting antibody to the final pandemic strain.

Further data will be available shortly in different age groups that may confirm the initial findings and indicate whether a single dose might also be sufficient in the elderly and in children and adolescents. Meanwhile it is stated that two doses are preferred in adults aged 18-60 years although a single dose may be sufficient. It is also stated that two doses are currently recommended for the elderly and for children aged from 6 months to 17 years. If the apparently satisfactory responses in adults aged 18-60 years reflect natural priming and/or previous seasonal vaccination it may be that the elderly are also

well-primed although their immune responses could also be subject to effects of immunosenescence so a single dose might not be enough.

The data available with the H5N1 mock-up vaccine in children are currently limited to the age group 3-9 years. These data are insufficient to determine whether children should receive the adult dose or less then (e.g. half) the adult dose to achieve optimal immune responses. However, even the half adult dose of H5N1 vaccine appeared to elicit satisfactory immune responses (with the caveat that even less is known about the correlation between antibody levels and protection in children than in adults) although there were some advantages in terms of antibody to drifted variants with the adult dose. Therefore, and taking into account also the differences in reactogenicity between the adult and half adult dose in this age group, the SPC states that if vaccination is considered to be necessary then two vaccinations with the half adult dose may be sufficient.

In the absence of specific data and based mainly on experience with seasonal influenza vaccines the SPC suggests that the adult dose may be considered for children and adolescents aged 10-17 years for whom vaccination is thought to be necessary. In children aged 6 months up to 3 years it is suggested that the recommendations made for 3-9 year-olds may be appropriate. Due to the lack of experience in the use of influenza vaccines in children aged < 6 months there is no dose recommendation made at present. Specific data will be obtained in this age group at a later date.

There are no clinical data available with this vaccine in pregnant women.
Non-clinical studies with regard to female fertility, embryo-foetal and postnatal toxicity (up to the end of the lactation period) were conducted in rats with the Pandemrix mock-up vaccine containing the AS03 adjuvant. There was no cause for concern identified in this study despite no data are available on administration around the implantation phase of the embryos.
Serological studies exploring the immunogenicity suggest that antibody response to influenza vaccine is similar in pregnant women and non-pregnant women. Therefore it is expected that Pandemrix will be adequately immunogenic in pregnant women. Although currently available safety data are very limited, non-clinical data with the current vaccines/adjuvants and experience from other types of vaccines (both non-adjuvanted and adjuvanted) do not raise concerns with respect to use during pregnancy.
Furthermore, vaccine safety in pregnant women and effectiveness will be closely monitored, as part of the RMP. Observational studies using established pregnancy registries are planned.

There are insufficient safety data at present to evaluate the A(H1N1)v vaccine but the expectation is that the safety profile will be similar to that described for the H5N1 mock-up vaccine. The safety database observed with the H5N1 constructs has been reflected in the Summary of Product Characteristics. Adverse reactions that might be specific to the influenza A(H1N1)v strain can only be evaluated during post-approval usage. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities are adequate and appropriate.

Data from ongoing and planned clinical trials as specified in the specific obligations for Pandemrix A(H1N1)v will be reviewed on an ongoing basis. These studies will provide safety, immunogenicity and effectiveness data for the influenza A(H1N1)v vaccine. The SPC will be updated accordingly as the CHMP considers necessary.

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

- User consultation

Further to the approval of the initial MAA, the MAH submitted results of user testing which were assessed within variation II-06 adopted on 10 July 2009.

Risk-benefit assessment

Benefits

The real benefits of Pandemrix A(H1N1)v can only be assessed by its use during a pandemic. At present the benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination with the mock-up version of Pandemrix (i.e. containing H5N1 strains) plus the limited data available from administration of a single dose of A(H1N1)v vaccine to healthy adults aged 18-60 years.

After two doses administered 21 days apart the H5N1 vaccine has been shown to be suitably immunogenic in the populations in which it has been tested. There are no data on the use of the mock-up vaccine in subjects aged 10-17 years or subjects aged < 3 years. Based on data in children aged 3-9 years it would be expected that the adult dose would be immunogenic in children aged 10-17 years but it may be that half the adult dose could be sufficient. The data in children aged 3-9 years suggest that half the adult dose may be sufficient for those aged from 6 months to 9 years. The dose recommendations will be updated as soon as data on use of Pandemrix A(H1N1)v vaccine in various age groups become available from the ongoing clinical studies.

The additional data with Pandemrix A(H1N1)v suggest that adults aged 18-60 years may require only a single dose to achieve immediate levels of potentially protective antibody. These data are insufficient to predict whether a similar consideration will apply to the elderly and to subjects aged < 18 years for the time being.

Based on the data with H5N1 vaccine and the available data with A(H1N1)v vaccine the expected benefit of Pandemrix is to provide some protection against clinically-apparent infection due to A(H1N1)v.

Risks

The mock-up H5N1 vaccine was commonly or very commonly associated with a range of local and systemic adverse reactions but these were not often of severe intensity. The current safety database with H5N1 vaccine is considered to be sufficient to describe adverse reactions that occur uncommonly and to give an indication of any rare events in the population it has been tested. There are some adverse reactions known to be very rarely associated with influenza vaccines and it is currently not possible to predict if higher rates might be observed with Pandemrix A(H1N1)v compared with, for example, seasonal influenza vaccines.

On the basis of a reasonable assumption that the safety of the A(H1N1)v vaccine should be comparable to that of the mock-up vaccine the anticipated safety profile would not preclude the use of the vaccine as currently described in the SPC. However, it remains possible that the data generated with mock-up H5N1 vaccine cannot entirely predict the safety profile of Pandemrix A(H1N1)v since there remains a possibility of adverse reactions associated with the pandemic influenza strain. The specific commitments include collection of safety, immunogenicity and effectiveness data from the ongoing and planned clinical studies.

Balance

Based on all the quality safety and efficacy data that supported approval of Pandemrix H5N1 mock-up vaccine together with quality and very preliminary clinical data specific to the pandemic influenza A(H1N1)v strain it is considered that in the current pandemic situation the benefits outweigh the risks that may be associated with the use of the vaccine in accordance with the SPC.

Recommendation

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