



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Pandemic influenza vaccine

Proprietary Product Name: Arepanrix H5N1

Sponsor: GSK Australia Pty Ltd

**March 2011**

**TGA** Health Safety  
Regulation

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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## I. Introduction to Product Submission

### Submission Details

<i>Type of Submission</i>	New Biological Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	1 February 2011
<i>Active ingredient(s):</i>	Pandemic influenza vaccine, split virion, AS03-adjuvanted
<i>Product Name(s):</i>	Arepanrix H5N1
<i>Sponsor's Name and Address:</i>	GSK Australia Pty Ltd Level 4, 436 Johnston Street, Abbotsford Victoria 3067
<i>Dose form(s):</i>	Vaccine suspension for injection; 2.5 mL vial with adjuvant emulsion 2.5 mL vial
<i>Strength(s):</i>	3.75 µg HA antigen + AS03 adjuvant (0.5 mL total)
<i>Container(s):</i>	Presented as 2 separate glass vials containing antigen suspension and AS03 adjuvant. Contents from the 2 vials are mixed at the time of administration.
<i>Pack size(s):</i>	50 doses per carton
<i>Approved Therapeutic use:</i>	Prophylaxis of influenza in an officially declared pandemic situation. Arepanrix H5N1 should be used in accordance with official recommendations.
<i>Route(s) of administration:</i>	Intramuscular (IM)
<i>Dosage:</i>	Two doses given 21 days apart by intramuscular route in adults 18 years and older.
<i>ARTG Number (s)</i>	166254

### Product Background

The sponsor already has an approved pandemic influenza A H5N1 mock-up vaccine (Pandemrix) derived from A/Vietnam/1194/2004 (Clade 1) virus and manufactured in Dresden (3.75µg HA-ASO3 adjuvanted<sup>1</sup>). Arepanrix H5N1 vaccine was developed to further extend the manufacturing capacities for pandemic/prepandemic vaccines (it is also referred to as Q-Pan). The current Australian application is therefore to register a new vaccine due to manufacture at a new site. At present, as a comparator for the new product, the sponsor has used Pandemrix derived from A/Indonesia/05/2005 strain of H5N1 (Clade 2). This is referred to as D-Pan. Arepanrix H5N1 is prepared from an A/Indonesia/05/2005 strain of H5N1 antigen and it is manufactured in its facilities located in Quebec (referred to as Q-Pan H5N1 vaccine or Q-Pan). The amount of antigen and the amount of AS03 adjuvant contained in Q-Pan and D-Pan vaccine are identical (3.75 µg antigen per dose). The manufacturing process used to produce the Q-Pan and D-Pan H5N1 antigens differs to some extent, yet both antigens are formaldehyde inactivated sodium deoxycholate split-virions.

<sup>1</sup> AS03 (Adjuvant System 03) is an oil in water adjuvant composed of the biodegradable oils squalene and  $\alpha$ -tocopherol (vitamin E), and polysorbate 80 (surfactant).

The clinical development of Q-Pan vaccine took benefit from the development of the D-Pan vaccine. In particular, the choice of the antigen dose was based on a dose-range study performed with D-Pan, that is, Study D-Pan-H5N1-007.

Pandemrix (H5N1), the D-Pan H5N1 vaccine, was granted registration by the TGA in June 2008. It is registered for the following indication:

*“Prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official recommendations.”*

Arepanrix H5N1 vaccine, the Q-Pan H5N1 vaccine, has not been approved by any regulatory agency to date. Of note, on 13 October 2009, Health Canada authorised the use of Arepanrix H1N1 for active immunization against influenza strain in an officially declared pandemic situation. Both Pandemrix and Arepanrix have also been updated to H1N1 in Europe.

Four mock-up pandemic influenza vaccines are currently registered in Australia to various sponsors and range from conventional egg-grown inactivated split virion, adjuvanted and unadjuvanted to Vero cell based whole virion products.

### **Regulatory Status**

A similar product to Arepanrix H5N1 vaccine, Pandemrix H5N1 vaccine, was licensed in the EU in May 2008. This similar AS03 adjuvanted H5N1 vaccine is currently licensed in the EU through three different Marketing Authorisation Applications (MAAs):

- One for pandemic use, that is, Pandemrix (A/Vietnam/1194/04 strain), licensed as a mock-up vaccine
- Two for prepandemic uses, that is, Prepandrix (A/Indonesia/05/2005 strain) and Duplicate License (A/Vietnam/1194/04 strain).

Arepanrix H5N1 is currently under evaluation in EU (submitted 6 August 2009) and Canada (submitted 25 February 2009).

### **Product Information**

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

## **II. Quality Findings**

### **Drug Substance (active ingredient)**

#### **Structure**

The drug substance is an H5N1 avian influenza haemagglutinin similar to other H5N1 vaccines

#### **Manufacture**

HA antigen manufactured analogous to method used for seasonal influenza vaccines.

#### **Physical and Chemical Properties**

Similar to those for seasonal influenza vaccines

#### **Specifications**

The proposed specifications are justified and appropriate validation data have been submitted in support of the test procedures.

#### **Stability**

Stability data have been generated under real time conditions to establish a shelf life of 18 months.

## Drug Product Formulation(s)

The proposed vaccine is analogous to the seasonal influenza vaccines. The vaccine consists of two components, an immunogen suspension and an adjuvant emulsion. These are mixed in a 10 dose presentation prior to administration.

## Manufacture

The product is manufactured by propagating the H5N1 vaccine strain in eggs, harvesting the allantoic fluid, concentrating, splitting, inactivating and fractionating the HA antigen [method analogous to the manufacture of the seasonal influenza vaccines]. The adjuvant consists of  $\alpha$ -tocopherol and squalene. The mixed vaccine is an oil-in-water emulsion where the H5N1 HA is in the aqueous phase. The antigen suspension and adjuvant emulsion are sterilised by membrane filtration and filled aseptically into 10-dose vials.

## Specifications

The proposed specifications are justified and appropriate validation data have been submitted in support of the test procedures.

## Stability

Proposed shelf life of Pandemrix H5N1 is 18 months at 2-8°C. The shelf life of the adjuvant suspension in the 10-dose vials is 36 month at 2-8 °C.

## Bioavailability

Not relevant for this product.

## Quality Summary and Conclusions

### Issues of concern

The Pharmaceutical subcommittee (PSC) was concerned about:

- Multidose vial presentation. Australian Drug Evaluation Committee (ADEC now called Advisory Committee on Prescription Medicines (ACPM)) has recommended that multidose vaccines should not be used but they are widely used for pandemic vaccines
- The bioburden levels of the intermediates are higher than TGA would prefer.

The application went back for further consideration at a later PSC meeting in November 2010 (for the outcomes of this meeting see below under *VI. Overall Conclusion and Risk/Benefit Assessment*).

## III. Nonclinical Findings

### Introduction

The Arepanrix H1N1 submission was supported by *nonclinical data* mainly for vaccine derived from the H5N1 A/Indonesia/05/2005 strain, manufactured at the GSK Quebec site. Nonclinical H5N1/AS03 vaccine data were submitted in a previous submission for a pandemic influenza vaccine manufactured at the GSK Dresden site. Nonclinical data in this submission were also used to support registration of Pandemrix H5N1. Arepanrix and Pandemrix are also referred to as Q-Pan and D-Pan, respectively.

### Submission quality

The submission contained nonclinical vaccine immunogenicity, viral challenge, safety pharmacology, acute (local tolerance) and repeat-dose toxicity, reproductive and

developmental toxicity and adjuvant genotoxicity studies (Good Laboratory Practice (GLP) compliant). A series of studies on the mode of action of AS03 adjuvant were also submitted in summary form. Overall, the nonclinical studies met the general requirements of the relevant European Medicines Agency (EMA) vaccine, pandemic influenza vaccine and adjuvant nonclinical guidelines<sup>2</sup>.

## Pharmacology

Immunogenicity studies were conducted in naïve animals, to model exposure to a pandemic influenza strain to which humans have no prior exposure.

Two immunogenicity studies in un-primed mice tested the antibody response to two consecutive IM doses of split H5N1/AS03 vaccine. Strong antibody responses were detected by both ELISA and haemagglutination inhibition (HI) to adjuvanted vaccine over a wide range of HA doses (0.04–5 µg), whereas responses to unadjuvanted vaccine were weak/undetectable. The geometric mean HI titer in both studies was >1000 at the lowest HA dose of 0.04 µg (2x the human dose, adjusted for body surface area).

**Table 1.**

HA antigen doses in nonclinical immunogenicity/viral challenge studies				
Study	HA antigen doses (µg)	HA antigen doses (µg/kg)*	HA antigen doses (µg/m <sup>2</sup> )**	Animal/human dose multiples (µg/m <sup>2</sup> )
Mouse immunogenicity (x2)	0.04, 0.2, 1, 5	2, 10, 50, 250	6, 30, 150, 750	2, 12, 60, 300
Ferret homologous challenge	1.9, 3.8, 7.5	1.9, 3.8, 7.5	19, 38, 75	7, 15, 30
Ferret heterologous challenge	0.2, 0.6, 1.5, 3.8	0.2, 0.6, 1.5, 3.8	2, 6, 15, 38	0.8, 2, 6, 15
Humans	3.75	0.075	2.5	---
* Bodyweights: Mouse 20 g, rat 220 g, ferret 1 kg (body surface area 0.1 m <sup>2</sup> ), rabbit 2 kg, human 50 kg.				
**Body surface area conversion factors: mouse 3, rat 6, ferret 10, rabbit 11, human 33.				

## Protective efficacy studies in ferrets

A new lethal challenge study in naïve ferrets tested the protective efficacy of 2 consecutive IM doses of split H5N1 vaccine (1.9, 3.8 and 7.5 µg HA) adjuvanted with full or half dose AS03 (AS03/2). The adjuvanted vaccine induced functional antibody titers against the parent virus at all HA doses, and against three H5N1 drift variants, whereas responses were much lower without adjuvant. Antibody responses were generally higher for AS03 than AS03/2. AS03 alone was not immunogenic.

Upon challenge with homologous wild-type virus, ferrets in the antigen and adjuvant control groups developed high fever, showed major bodyweight losses, most shed virus in the throat (7/12) and lungs (10/12), and 8/12 were euthanized/died, with diffuse dark red areas evident in the lungs. In the adjuvanted groups, temperature increases and bodyweight losses were mild or absent, few shed virus in the throat (2/36) and lungs (4/36), and 0/36 ferrets died.

A second new lethal challenge study in naïve ferrets tested the protective efficacy of 2 consecutive IM doses of split H5N1 vaccine (3.75 µg HA + AS03; 0.24, 0.6, 1.5, 3.75 µg HA + AS03/2). The vaccine adjuvanted with AS03 or AS03/2 induced functional antibody titers against the parent virus, whereas responses were much lower without adjuvant. Upon lethal

<sup>2</sup> <http://www.tga.gov.au/docs/html/euguidead.htm>,  
[http://www.tga.gov.au/docs/html/euguide/euad\\_nonc.htm#nonclinicalgeneral](http://www.tga.gov.au/docs/html/euguide/euad_nonc.htm#nonclinicalgeneral)

challenge with A/Hong Kong/156/97 (H5N1), most ferrets administered the highest dose (HD) of the study were protected against major bodyweight losses, virus shedding in the throat and lung, and death. Less protection was provided at lower antigen/ adjuvant doses (0.24, 0.6 or 1.5 µg HA + AS03/2) but protection in terms of survival was still superior to the unadjuvanted vaccine. The lowest dose of 0.24 µg HA is 0.8x the proposed human dose, adjusted for body surface area.

In summary, the naïve mouse and ferret studies demonstrated strong enzyme-linked immunosorbent assay (ELISA) and functional antibody responses to split H5N1 antigen adjuvanted with AS03. Antibody responses were low to undetectable in the absence of AS03 adjuvant. Cell-mediated responses were not investigated. Protection against lethal homologous and heterologous H5N1 challenge was demonstrated in ferrets, although doses were generally high in relation to the proposed human dose. In general, vaccine with half dose AS03 was less effective than the full dose. A wider dose range of AS03 was not investigated in the current submission.

### **Mechanisms of action of AS03 adjuvant**

Arepanrix H5N1 vaccine contains AS03 adjuvant for the dual purposes of inducing a strong immune response in naive subjects, and antigen sparing in a pandemic.

AS03 is an oil in water adjuvant composed of the biodegradable oils squalene and  $\alpha$ -tocopherol (Vitamin E), and polysorbate 80 (surfactant). Squalene occurs naturally in plants, animals and humans, and is an intermediate metabolite in the synthesis of cholesterol in humans. It is the main component by weight of MF59 adjuvant (Novartis) in the seasonal trivalent influenza vaccine Fluad, currently marketed in Europe, and Focetria, a pandemic H1N1 influenza vaccine approved by the EMA in 2009.

A series of studies investigated the mode of actions of AS03 adjuvant. There was no detectable physico-chemical interaction between antigen and adjuvant upon mixing suggesting direct action.

Overall, the AS03 adjuvant primarily acts as an immunostimulant, with transient effects on multiple co-stimulatory and pro-inflammatory cytokines. Although AS03 does not act as an antigen depot, its action requires the antigen and adjuvant to be in proximity upon injection.

The safety of the AS03 adjuvant formulated with split influenza vaccines was investigated in safety pharmacology, repeat-dose and reproductive toxicity, local tolerance and genotoxicity studies (below).

### **Safety pharmacology**

A safety pharmacology study in which anaesthetised rats were administered a split H3N2/AS03 (Quebec) vaccine intravenously (IV) showed no treatment related respiratory or cardiovascular effects for at least 120 min post dose. Central nervous system (CNS) and other system-toxicities were not investigated in safety pharmacology studies, but were adequately investigated in repeat dose toxicity studies.

### **Pharmacokinetics**

No vaccine pharmacokinetic studies were submitted, and they were not required according to the relevant EMA vaccine, pandemic influenza vaccine guidelines. The biodistribution of the adjuvant and antigen was evaluated in mice (see above).

### **Relative exposure**

The adjuvant is the main component in the vaccine by weight (excluding water).

Animal:human exposure ratios to the adjuvant were adequate in all toxicity studies. The full



human dose of adjuvant was administered in rabbit toxicity studies, resulting in an exposure multiple of a minimum of 8x, adjusted for body surface area. Exposure ratios for the HA antigen were also adequate (following table).

**Table 2.**

HA antigen exposure multiples in nonclinical toxicity studies				
Study (report no.)	HA antigen dose ( $\mu\text{g}$ )	HA antigen dose ( $\mu\text{g}/\text{kg}$ )*	HA antigen dose ( $\mu\text{g}/\text{m}^2$ )**	Animal/human HA exposure multiple ( $\mu\text{g}/\text{m}^2$ )
Rat safety pharmacology (GVB 0016/072148)	7.5	34	205	82
Rabbit repeat dose toxicity (1990/956)***	30	15	165	66
Rabbit repeat dose toxicity (GPS 1536-06194)	15	7.5	82.5	32
Rabbit repeat dose toxicity (2990/356)	60, 30	30, 15	330, 165	132, 66
Rabbit repeat dose toxicity (V 8550)	3.8	1.9	20.9	8
Rat repro + devel. toxicity (GVB0007/063710)***	6	27	164	66
Rat repro + devel. toxicity (GBV/0009/064374)	9	41	245	98
Rat repro + devel. toxicity (153-08129)	1.5	6.8	40.9	16
Humans	3.75	0.075	2.5	---
*Bodyweights: Mouse 20 g, rat 220 g, ferret 1 kg (body surface area $0.1 \text{ m}^2$ ), rabbit 2 kg, human 50 kg.				
**Body surface area conversion factors: mouse 3, rat 6, ferret 10, rabbit 11, human 33.				
***Previous submission.				

## Toxicology

Four repeat dose toxicity IM studies were conducted in rabbits. The earliest study tested H5N1/AS03 (Dresden) vaccine, the second study tested H3N2 (Dresden or Quebec) vaccine priming and H3N2 (Quebec) vaccine boosting, and the third and fourth studies tested H5N1/AS03 (Quebec) vaccine (30 and  $3.75 \mu\text{g}$  HA), respectively. A total of three or four consecutive IM doses, or two priming and two boosting doses were administered, followed by a 28 day recovery period. All four toxicity studies were accompanied by measurements of antibody responses, conducted by the Sponsor, which showed seroconversion in all rabbits. Low levels of antibodies were detected in a few control rabbits in two studies (and in a rat reproductive toxicity study), with the cause unknown, but the incidences and levels were not sufficient to compromise the studies.

Clinical signs were limited to minimal oedema and/or erythema at vaccine injection sites, transient increases in body temperature and slight decreases in food consumption and weight in a few rabbits. Dermal Draize scores were generally zero.

Collectively the studies demonstrated an acute inflammatory response to the vaccine or adjuvant, with transient increases in serum globulins, fibrinogen, total WBC, neutrophils and platelets. Slight increases in creatinine kinase reflected slight muscle degeneration as a consequence of injection. The relative increased spleen and lymph node weights, microscopically evident as spleen and lymphoid hyperplasia, reflected the inflammatory and immune responses. The spleen and lymph changes had partially reversed after 28 days recovery.

Microscopic examination of vaccine injection sites showed inflammation, with inflammatory cell infiltrates, fasciitis, perivascular and perineural inflammation, fibrosis, and cellulitis. Injection site inflammation was generally graded as slight/mild. After 28 days recovery the injection site inflammation had partially resolved, and was generally graded as slight or minimal. Comparison of vaccine, adjuvant only, antigen only and PBS control groups showed that the incidence and severity of the inflammation was largely or entirely due to the adjuvant, with some dose-dependency (full versus half dose). The injection procedure and the antigen occasionally made a minor contribution to the inflammation. Overall the studies indicated that the adjuvanted vaccine did not induce excessive or irreversible changes at the injection sites.

Microscopic findings were confined to the injection sites, lymph nodes and spleen, with 2 exceptions. Microscopy in rabbits in study 2990/356, three days after the third dose, revealed an increased severity of inflammatory cell foci in the liver of females given “FluQIV60/AS03/2”, and to a lesser extent “FluQIV60” or “FluQPAN30/ AS03” vaccines, and an increased incidence of minimal inflammatory cell foci in the heart of females given (FluQIV60” or “FluQPAN30/AS03” vaccines (see Main report for vaccine compositions). The minimal inflammatory cell foci were occasionally seen as a background finding in rabbits. The liver and heart findings were not evident microscopically 28 days after the last dose, indicating full reversibility. These findings were not correlated with any changes in clinical chemistry or haematology, and the investigators considered it unclear whether they were treatment related.

Relatively high incidences of inflammatory cells in the heart of males (very slight in 2 males and slight in 1 male), but not females, 3 days after the last dose of “FluQ-Pan3.8/AS03” vaccine, were observed in study V8550, but the incidence *cf.* controls was not statistically significant, and the investigators considered it unlikely to be treatment-related. The exposure margins are sufficiently high to mitigate concerns regarding the liver and heart findings, should they be treatment-related.

The sponsor commented that Gram’s stain demonstrated gram-positive ovoid microorganisms in brain and kidney of affected animals and that these findings are consistent with a natural background infection by *Encephalitozoon cuniculi*, which is spread horizontally through contaminated urine. The presence of encephalitis implies that the rabbits were infected at least three months prior to necropsy. Hence, the background incidence of inflammation and/or possible early stage *E. Cuniculi* infection observed makes these findings difficult to definitively ascribe to treatment. The sponsor commented that Study V8550 was conducted to verify the consistency of the microscopic findings observed in Study 2990/356; the incidences of liver or heart microscopic inflammation findings did not differ significantly from control animals in this second study.

### *Squalene*

Many older adults, regardless of their vaccination history, have low titers of naturally occurring antibodies that react with squalene (del Giudice *et al.*, 2006<sup>3</sup>). Squalene was implicated in the so-called Gulf War Syndrome, although it was not a component in vaccines administered to veterans. In a review of this implication, the WHO Global Advisory Committee on Vaccine Safety (6-7 June 2006) concluded that “... fears of squalene in

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<sup>3</sup> Del Giudice G *et al.* (2006). Vaccines with the MF59 adjuvant do not stimulate antibody responses against squalene. *Clin. Vaccine Immunol.* 13(9): 1010-1013.

vaccine-inducing pathological anti-squalene antibodies are unfounded”, but recommended careful post-market follow-up to detect any vaccine-related adverse events in other age groups.

### **Local tolerance**

Two single-dose local IM tolerance studies were conducted in rabbits. The first study tested H3N2 vaccine (15 µg HA) with the human dose of AS03, and the second study tested H5N1/AS03 (Quebec) (30 µg HA) vaccine. The injection site observations of minimal or mild injection site inflammation associated with the adjuvant were consistent with histological findings in the repeat-dose toxicity studies.

There were no studies of perivenous or intra-arterial local tolerance. The Product information has a precaution against intravascular or intradermal injection.

### **Genotoxicity**

Previously submitted *in vitro* and *in vivo* genotoxicity studies with AS03 adjuvant were negative. The assessment of genotoxicity was consistent with the EMEA guideline for new adjuvants.

### **Carcinogenicity studies**

Carcinogenicity studies were not required for Arepanrix H1N1 vaccine. This is consistent with EMEA vaccine, pandemic influenza vaccine and adjuvant guidelines.

### **Reproductive and developmental toxicity**

Three reproductive and developmental IM toxicity studies were conducted in female rats, using FluLaval and Fluarix seasonal trivalent vaccines, and H5N1/AS03 vaccine manufactured in Dresden or Quebec. The studies were accompanied by measurements of antibody responses in dams, fetuses and pups.

The studies showed no significant effects on female mating performance or fertility nor on embryofetal or postnatal development. Vaccine antigen-specific antibodies were detected in dams, fetuses and pups, with postnatal increases in pups suggesting antibody transfer in milk.

Fertility studies were not conducted in male animals, but no histological effects on the male reproductive organs were detected in the repeat-dose toxicity studies in rabbits.

The proposed Australian pregnancy category of B2 is appropriate.

### **Nonclinical Summary and Conclusions**

1. Immunogenicity studies in naive mice showed that two consecutive IM doses (0.04, 0.2, 1, 5 µg HA) of split H5N1/AS03 vaccine elicited substantial antibody responses (ELISA, HI) at all HA doses, whereas unadjuvanted vaccine responses were low or undetectable.
2. In a new lethal challenge study, naïve ferrets administered two consecutive IM doses of split H5N1/AS03 vaccine (1.9, 3.8 and 7.5 µg HA) developed functional antibody titers against the vaccine parent virus, and cross-neutralising antibodies against 3 H5N1 drift variants. Vaccine with half-dose AS03 (AS03/2) was less effective. After challenge with homologous wild-type virus, vaccinated ferrets were protected from high fever, viral shedding in throat and lungs, major bodyweight losses and mortality at all HA doses. The unadjuvanted vaccine elicited a weak immune response and provided minimal protection. The adjuvant alone had no immunological or protective effect.

In a second lethal challenge study, ferrets administered two consecutive IM doses of split A/Indonesia/5/05 (H5N1) vaccine (3.75 µg HA + AS03 or AS03/2) developed functional antibody titers against the parent virus, and were cross-protected against A/Hong Kong/156/97 (H5N1). Less protection was provided at lower antigen/adjuvant doses (0.24, 0.6 or 1.5 µg HA + AS03/2), but protection was still superior to the unadjuvanted vaccine. Similar results were reported in previous ferret efficacy studies submitted for a previous pandemic vaccine application.

3. AS03 adjuvant is composed of the biodegradable oils squalene and  $\alpha$ -tocopherol, and polysorbate 80. A series of studies investigated the mode of action of AS03. There were no physico-chemical interactions between antigen and adjuvant upon mixing, IM injection, or uptake into the draining lymph node. In mice the adjuvant acted as an immunostimulant, increasing the proliferation of antigen-expressing T cells, and expression of co-stimulatory molecules and pro-inflammatory cytokines by antigen presenting cells in the draining lymph node.
4. A safety pharmacology study in which anaesthetised rats were IV administered a split H3N2/AS03 vaccine showed no respiratory or cardiovascular effects.
5. Collectively the nonclinical repeat dose toxicity studies demonstrated a transient inflammatory response, with increases in serum globulins, fibrinogen, total WBC, neutrophils and platelets. Increased relative spleen and lymph node weights reflected the inflammatory and immune responses. Microscopy showed mild injection site inflammation, with inflammatory cell infiltrates, fasciitis, perivascular and perineural inflammation, and fibrosis. Local inflammation was caused mainly by the adjuvant, and partially, but not fully resolved after 28 days recovery.
6. Two single-dose local tolerance studies in rabbits with H3N2/AS03 H5N1 (Quebec) vaccines showed slight injection site inflammation, consistent with that observed in the repeat-dose toxicity studies.
7. Previously submitted *in vitro* and *in vivo* genotoxicity studies with AS03 adjuvant were negative.
8. Three reproductive and developmental toxicity studies were conducted in female rats, using FluLaval and Fluarix seasonal trivalent vaccines, and H5N1/AS03 (Dresden, Quebec) vaccines. The studies showed no significant effects on female mating performance, fertility, nor on embryofetal or postnatal development. Vaccine antigen-specific antibodies were detected in dams, fetuses and pups, with postnatal increases indicating transfer in milk.
9. In summary, the nonclinical data for Arepanrix H5N1 vaccine are consistent with EMEA nonclinical guideline requirements for pandemic vaccines and adjuvants, and are sufficient to support registration.

## RECOMMENDATIONS

The immunogenicity of the vaccine and its protective efficacy were demonstrated in animals. The capacity of the adjuvant to increase antibody responses was demonstrated in several species.

The major effect observed in toxicity studies was a transient inflammatory response due to the adjuvant. Injection site inflammation, which was mild, partially resolved over a 28 day recovery period.

Nonclinical data are sufficient to support registration of Arepanrix H5N1 vaccine, at a dose of 3.75 µg HA in adults.

The mechanistic studies of AS03 adjuvant were submitted in summary form. The Sponsor is requested to provide original study reports, if available. The sponsor has indicated that a ferret H1N1 challenge study with Arepanrix H1N1 vaccine is in progress. The report for this study should be submitted upon completion.

## IV. Clinical Findings

### Introduction

#### Content of the current submission

Five studies (Table 1) are completed, including two pivotal studies with Q-Pan vaccine (Q-Pan-001 and Q-Pan-002) and three supportive studies with D-Pan vaccine (H5N1-007, H5N1-008 and H5N1-002). An overview of these five completed studies is presented in Table 3 below.

**Table 3:** Overview of studies with AS03-adjuvanted formulations of the pandemic/pre-pandemic vaccine

Study	Primary Objective(s)	Population/ age of subjects	Study vaccines	N safety	N immuno
<b>Pivotal studies</b>					
Q-Pan-001	Immunogenicity Reactogenicity/safety	Unprimed population 18-64 years	Monovalent split virus (H5N1) 3.8µg HA* – Quebec sourcing, A/Indo strain + full or half dose AS03	303	290
			Monovalent split virus (H5N1) 3.8µg HA* –Dresden sourcing, A/Indo strain + full or half dose AS03	299	283
			Monovalent split virus (H5N1) 3.8µg HA* – Quebec sourcing No adjuvant	78	75
Q-Pan-002	Immunogenicity Reactogenicity/safety	Unprimed population ≥18 years	Monovalent split virus (H5N1) 3.8µg HA* – Quebec sourcing, A/Indo strain – 3 lots +full AS03 dose– 3lots	3422	1967
			Placebo (saline)	1139	116
<b>Supportive studies</b>					
<b>Immunogenicity</b>					
H5N1-007	Immunogenicity Reactogenicity/safety	Unprimed population 18-60 years	Monovalent split vaccine (H5N1), 30 µg, 15 µg, 7.5 µg or 3.8 µg HA* - Dresden sourcing, A/Vietnam strain with or without AS03 2-dose schedule 21 days apart	400	394
<b>Safety</b>					
H5N1-008	Reactogenicity/safety	Unprimed population > 18 years	Monovalent split vaccine (H5N1) 15 µg HA with AS03 Fluarix (first dose), placebo (second dose) 2-dose schedule 21 days apart	3802 1269	455 154
H5N1-002	Immunogenicity Reactogenicity/safety	Unprimed population 18-60 years	Monovalent split virus (H5N1) 3.8 µg HA – 2 lots + full AS03 – 2 lots	961	933
			Monovalent split virus (H5N1) 3.8 µg HA – 2 lots + diluent	245	236

N safety = Total vaccinated cohort; N immuno = ATP\* cohort for immunogenicity  
 \*: As the vaccine doses were expressed using only one digit throughout the clinical documentation, 3.75 µg HA was rounded up to 3.8 µg HA in the Clinical Overview, Clinical Summaries and clinical study reports

A list of ongoing and planned studies for Q-Pan H5N1 vaccine was submitted.

### GCP aspect

The five studies included in this submission were conducted by experienced investigators and monitored by appropriately trained GSK Clinical Research Associates. Each clinical trial was performed in compliance with the Good Clinical Practice (GCP) Guidelines in operation at the time of the initiation of the study. All study protocols underwent Ethics Review Board appraisal. Studies were performed in accordance with the provisions of the Declaration of Helsinki and its amendments.

### Pharmacokinetics

As mentioned in the “Note for Guidance on Clinical Evaluation of New Vaccines (CPMP/EWP/463/97), pharmacokinetic studies are generally not required for injectable vaccines as the kinetic properties of vaccines do not provide information useful for

establishing adequate dosing recommendations. Pharmacokinetic studies were therefore not conducted.

## Drug Interactions

No new studies were submitted.

## Pharmacodynamics

Pharmacodynamic evaluations were performed. Clinical studies were designed to evaluate the characteristics of the immune response, such as the level of specific antibodies produced and the persistence of antibody titres. These findings are discussed under *Efficacy* below.

## Efficacy

### Introduction

Immunogenicity assessment

In the absence of the actual pandemic strain circulation, no efficacy data can be generated for a pandemic vaccine. The efficacy of an influenza vaccine indicated for pandemic/prepandemic use can only be evaluated in large post marketing studies after the pandemic onset. The potential for efficacy can be estimated, however, based on immunogenicity. The immunogenicity data obtained during the vaccine development are discussed from the following aspects:

- Immunogenicity against the vaccine strain
- Cross-reactive immunity against drift strains
- Persistence of the immune response

In the submitted clinical trials, three immunogenicity endpoints (SPR, SCR, and SCF) were defined as follows:

**SPR:** seroprotection rate which is defined as the proportion of participants achieving seroprotection

**SCR:** seroconversion rate which is defined as the proportion of participants achieving either seroconversion or a significant increase in antibody titre.

**SCF or GMFI:** geometric mean fold increase which is defined as the ratio of the post-vaccination geometric mean titre (GMT) divided by the pre-vaccination antibody geometric mean titre (GMT).

These endpoints are consistent with the EMEA guideline (CPMP/BWP/214/96) relating to evaluation of seasonal influenza vaccines. The criteria for the effective immunogenicity response defined in CPMP/BWP/214/96 are based on HI assay (see Table 4 below). It is noted that both HI assay and MN assay were conducted in the two pivotal studies. No target criteria based on MN assay for effective immunogenicity response are defined in any of the regulatory guidelines relating to influenza vaccines.

1. The correlates of protection for pandemic influenza or any other non-circulating virus are currently not known. In the absence of such information, the EMEA guidance document for pandemic vaccines (CPMP/VEG/4717/03<sup>4</sup>) states that the tested pandemic vaccines should at least be able to elicit sufficient immunological responses to meet all three criteria for the three immunogenicity endpoints defined in the Committee for Proprietary Medicinal Products (CPMP) guideline for seasonal influenza vaccines (CPMP/BWP/214/96)<sup>5</sup>.

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<sup>4</sup> [www.ema.europa.eu/docs/en\\_GB/...guideline/2009/.../WC500003882.pdf](http://www.ema.europa.eu/docs/en_GB/...guideline/2009/.../WC500003882.pdf)

<sup>5</sup> EMEA (12 March 1997). Committee for Proprietary Medicinal Products (CPMP). Note for guidance on

**Table 4:** Committee for Medicinal Products for Human Use (CHMP) criteria for the three immunogenicity endpoints (CPMP/BWP/214/96)

Based on HI assay	CHMP criteria	
	18 – 60 years	> 60 Years
1. SPR: Protective titres that is, $\geq 1:40$	> 70%	> 60%
2. SCR: seroconversion* or Significant increase#	> 40%	> 30%
3. GMFI or SCF: Fold increase in GMT	> 2.5	> 2.0
* Subjects with antibody titre increase from < 1:10 (lower limit of detection) pre-vaccination to $\geq 1:40$ post - vaccination.		
# Subjects with antibody titre $\geq 1:10$ pre-vaccination (that is, seropositive at baseline) and showed at least 4 fold increase post-vaccination.		

In the FDA guideline [Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines and the FDA guideline for seasonal influenza vaccine<sup>6</sup>], only two immunogenicity endpoints, SPR and SCR, are defined, and the FDA's Center for Biologics Evaluation and Research (CBER) criteria for the effective immunogenicity response are also based on HI assay (Table 5 below). There is no corresponding CBER criterion regarding the fold increase in GMT (SCF or GMFI).

**Table 5:** CBER criteria for the two immunogenicity endpoints

Based on HI assay	CBER criteria	
	18 – 64 years	> 64 Years
1. The lower bound of the two-sided 95% CI for SPR:	> 70%	> 60%
2. The lower bound of the two-sided 95% CI for SCR	> 40%	> 30%

In the two pivotal studies submitted in this application (Q-Pan-H5N1-001 and Q-Pan-H5N1-002), the immune response was also characterized by testing sera for virus neutralizing antibodies. In addition, in order to evaluate whether the candidate Q-Pan vaccine was able to induce some cross-reactive immunity against an avian influenza strain heterologous to the vaccine strain, the humoral response both in terms of HI and neutralising antibodies was also characterized against the A/Vietnam/1194/2004 (H5N1) strain in the two studies, and against two additional heterologous Clade 2 strains for a subset of subjects in Q-Pan-H5N1-001 (neutralising antibodies only).

#### *Selection of the antigen dose*

Since a comprehensive antigen dosing study has been performed with D-Pan H5N1 (Study H5N1-007 for Pandemrix application), no antigen dosing study was repeated with the Q-Pan H5N1.

harmonisation of requirements for influenza vaccines. (CPMP/BWP/214/96)

<sup>6</sup>[www.bcg-usa.com/regulatory/docs/2006/FDA20063B.pdf](http://www.bcg-usa.com/regulatory/docs/2006/FDA20063B.pdf) and

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm>

Study D-Pan-H5N1-007 was submitted and evaluated in previous applications relating to the registration of Pandemrix H5N1 vaccine (D-Pan H5N1). Study D-Pan-H5N1-007 was a dose response study, and the study demonstrated that when combined with AS03, an antigen content of 3.75 µg per dose was appropriate to induce homologous HI responses that met all three Committee for Medicinal Products for Human Use (CHMP) criteria.

The first Q-Pan study (Q-Pan-h5n1-001) was performed using the vaccine containing 3.75 µg of antigen. To confirm that the results obtained earlier with D-Pan H5N1 could be extrapolated to Q-Pan H5N1, the equivalence of D-Pan H5N1 and Q-Pan H5N1 when both were adjuvanted with AS03, was assessed as one of the secondary objectives in Q-Pan-H5N1001.

### **Study Q-Pan-H5N1-001**

#### **Study objectives and design**

The study was designed as a randomized, observer-blind, multi-centered, active-controlled trial. The primary objective of the study was to demonstrate the adjuvant activity of AS03 by comparing the immunogenicity of Q-Pan H5N1 antigen at the 3.75 µg dose level with AS03 at two different strengths (full and half) versus that of Q-Pan H5N1 antigen alone (without AS03) at the 3.75 µg dose level. The aim of the study was also to assess the safety of Q-Pan H5N1 at the 3.75 µg dose level with full and half strength AS03 in terms of solicited local and general reactogenicity events, unsolicited adverse events (AEs), and serious adverse events (SAEs) in comparison to Q-Pan H5N1 antigen alone.

The secondary objectives include to:

- describe the immunogenicity of Q-Pan H5N1 antigen at the 3.75 µg dose level with full and half strength AS03 in terms of SCR, SPR and SCF (or GMFI) against the homologous virus
- assess the equivalence of Q-Pan H5N1 and D-Pan H5N1 vaccines based on vaccine homologous virus HI GMTs.
- describe the comparative safety of Q-Pan H5N1 and D-Pan H5N1 vaccines
- further describe immunogenicity of selected vaccine regimens in terms of vaccine homologous
- determine virus microneutralization (MN) titers and both HI and MN titers against one or more H5N1 drift variant virus strains (cross-reactivity).

#### **Study vaccines**

The study vaccine, Q-Pan H5N1 vaccine, and the comparator, D-Pan H5N1 vaccine are described in the *Introduction* to this AusPAR document.

#### **Study methods**

The study was a randomized, observer-blind, multi-centered, active-controlled five-arm trial. Subjects were to be randomized in a 1:2:2:2:2 ratio to the following groups:

**Group A:** Quebec-manufactured antigen without adjuvant, (N ≈ 75), or

**Group B:** Quebec-manufactured antigen with full strength adjuvant, (N ≈ 150), or

**Group C:** Quebec-manufactured antigen with half strength AS03, (N ≈ 150), or

**Group D:** Dresden-manufactured antigen with full strength AS03, (N ≈ 150), or

**Group E:** Dresden-manufactured antigen with half strength AS03, (N ≈ 150)



Treatment comprised two doses of test articles on study Days 0 and 21; the total duration of the study was approximately 6 months for each subject, from enrolment through the last study follow-up.

All vaccines were to be administered IM on Days 0 and 21. Randomization was to be stratified by site and age (18 to 40 years and 41 to 64 years); no attempt was to be made to equalize enrolment into the two age strata within a given treatment group, but total treatment assignments was to be limited such that no more than 60% of subjects fell into one age stratum.

### **Study subjects**

Healthy adults 18 to 64 years of age were eligible to enrol to the study. A total of 680 subjects were actually enrolled and vaccinated, including 78 subjects in Group A (vaccine without adjuvant) and 152, 151, 151, and 148 subjects in Groups B, C, D, and E, respectively (vaccine with adjuvant). The demographic profile of the 5 groups of subjects was comparable with respect to mean age, gender and racial distribution. The mean age ranged from 18 to 64 years, there were slightly more female subjects in the study than male subjects, and the population was ethnically predominantly Caucasian.

A total of 673 subjects contributed to the Day 42 primary analysis, including 76 subjects in Group A (vaccine without adjuvant) and 150, 151, 151, and 145 subjects in Groups B, C, D, and E, respectively (vaccine with adjuvant). A total of 662 subjects completed the 182 day follow-up.

### **Immunogenicity assessments**

All immunogenicity assessments were performed by GSK Biologicals laboratories or in a validated laboratory designated by GSK Biologicals using standardized validated procedures with adequate controls.

### **Effect of adjuvant dose**

Study Q-Pan-H5N1-001 evaluated two different doses (full and half) of AS03 adjuvant in comparison to non-adjuvanted formulation. The primary objective of demonstrating the adjuvant activity of AS03 for the Quebec-manufactured vaccine was evaluated by a test of the superiority of the antigen plus adjuvant formulation versus the antigen alone. Differences in SCR and adjusted GMT ratios were calculated between groups. In order to claim superiority, the lower limit of the 95% Confidence Interval (CI) of the SCR difference was to be > 15%, and the lower limit of the adjusted GMT ratio was to be > 2.

The table below (Table 6) summarises the results of the pair wise comparisons between the three Q-Pan recipients groups, that is, formulated with full, half or no AS03 adjuvant. The immune responses against the vaccine strain (A/Indonesia/05/2005) and a heterologous strain (A/Vietnam/1194/2004) were assessed.

**Table 6:** Effect of adjuvant dose: comparison of SCR and GMT ratios at Day 42 (Study Q-Pan-H5N1-001)

Antibody	Groups compared	Difference in SCR			Adjusted GMT ratios		
		%	95% CI		%	95% CI	
			LL	UL		LL	UL
A/Indonesia/05/2005	Q-Pan AS03 full dose versus Q-Pan No AS03	79.89	69.36	87.27	43.40	29.93	62.94
	Q-Pan AS03 half dose versus Q-Pan No AS03	72.39	61.04	80.80	29.96	20.68	43.41
	Q-Pan AS03 full dose versus Q-Pan AS03 half dose	7.50	1.97	13.84	1.45	1.07	1.97
A/Vietnam/1194/2004	Q-Pan AS03 full dose versus Q-Pan No AS03	60.47	51.45	68.30	6.98	4.84	10.07
	Q-Pan AS03 half dose versus Q-Pan No AS03	57.57	48.57	65.52	5.83	4.04	8.84
	Q-Pan AS03 full dose versus Q-Pan AS03 half dose	2.90	-8.35	14.08	1.20	0.89	1.62

The results showed that both full- and half dose AS03 formulations were superior to the non-adjuvanted formulation, for all criteria set (SCR and GMT) and for the response obtained against both A/Indonesia (vaccine strain) and A/Vietnam (heterologous strain). However, no statistical significance difference was found when comparing the full dose AS03 to the half-dose AS03 formulation.

The choice of the adjuvant dose included in the final formulation of the Q-Pan vaccine, that is, full dose AS03, is nevertheless supported by the post-hoc analysis of the immunogenicity in two age strata (18-40 and 41-64 years old).

**Table 7:** Seropositivity rates and GMTs for A/Indonesia/5/05 antibodies, by age group (ATP-I)

Antibody	Group	Sub-group	Timing	N	≥ 10 1/DIL						≥ 40 1/DIL						GMT	
					n	%	95% CI		n	%	95% CI		value	95% CI				
							LL	UL			LL	UL		LL	UL			
A/Indonesia/5/05	Full AS03	18-40	PRE	155	0	0.0	0.0	2.4	0	0.0	0.0	2.4	5.0	5.0	5.0	5.0		
			PI(D21)	155	86	55.5	47.3	63.5	65	41.9	34.1	50.1	21.3	16.9	27.0	27.0		
			PII(D42)	155	150	96.8	92.6	98.9	149	96.1	91.8	98.6	586.6	483.2	712.1	712.1		
		41-64	PRE	129	1	0.8	0.0	4.2	0	0.0	0.0	2.8	5.0	5.0	5.1	5.1		
			PI(D21)	129	83	64.3	55.4	72.6	59	45.7	36.9	54.7	25.3	19.6	32.6	32.6		
			PII(D42)	129	127	98.4	94.5	99.8	126	97.7	93.4	99.5	364.1	299.2	443.1	443.1		
	Half AS03	18-40	PRE	161	0	0.0	0.0	2.3	0	0.0	0.0	2.3	5.0	5.0	5.0	5.0		
			PI(D21)	160	82	51.3	43.2	59.2	66	41.3	33.5	49.3	19.2	15.3	24.2	24.2		
			PII(D42)	160	149	93.1	88.0	96.5	149	93.1	88.0	96.5	484.0	386.2	606.5	606.5		
		41-64	PRE	128	1	0.8	0.0	4.3	0	0.0	0.0	2.8	5.0	5.0	5.1	5.1		
			PI(D21)	128	70	54.7	45.7	63.5	48	37.5	29.1	46.5	17.2	13.7	21.6	21.6		
			PII(D42)	128	119	93.0	87.1	96.7	113	88.3	81.4	93.3	209.7	160.4	274.2	274.2		

Full AS03 = Q-Pan and D-Pan with full strength AS03

Half AS03 = Q-Pan and D-Pan with half strength AS03

18-40 = 18-40 years

41-64 = 41-64 years

PRE = Blood sample taken before vaccination

PI(D21) = Blood sample taken 21 days after the first vaccination

PII(D42) = Blood sample taken 21 days after the second vaccination

Seroprotection = FLU A/IND/05 AB antibody titre ≥ 40 1/DIL

GMT = geometric mean antibody titer calculated on all subjects

N = number of subjects with available results

n/% = number/percentage of subjects with titer within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

The results obtained for the older age stratum are not as positive as for younger adults as a drop of 14% in homologous SCR is observed when halving the AS03 dose in the older age group (versus 4% in the younger age group). Similarly, halving the AS03 dose in 41-64 age strata led to an almost two-fold reduction in homologous GMTs. These results show that while the half dose adjuvant induced adequate immunogenicity in younger adults it led to a discernable decrease in immune response in adults 41-64 years of age. Accordingly, the vaccine with full-dose adjuvant is considered as better choice to ensure that a strong immune response is induced by vaccination in the whole adult range.

### Immunogenicity post-Dose II

The primary immunogenicity endpoints were the Day 42 HI antibody responses (SCF, SCR and SPR) against vaccine-homologous virus in subjects receiving two doses of the vaccine. The According-To-Protocol cohort for Immunogenicity analysis (ATP-I) included all evaluable subjects (that is, those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom a complete set of data concerning immunogenicity endpoint measures required for the primary endpoints were available.

A total of 648 subjects were included in the ATP-I cohort, the primary cohort for immunogenicity analysis. This included 75 subjects in Group A and 144, 146, 140, and 143 subjects in Groups B, C, D, and E, respectively. Subsets of 50 subjects per treatment group were randomly designated before any testing or analysis for additional evaluation of microneutralization titers (MN titers). Subjects within this subset of 50 per treatment group who were also evaluable in the ATP-I cohort contributed to the analysis of MN titers.

### HI responses at Day 42

The HI responses against vaccine strain H5N1 A/Indonesia/05/2005 at 21 days after the first (Day 21) and the second dose (Day 42) of Q-Pan H5N1 and D-Pan H5N1 vaccines is presented in the table below (Table 8). This is based on ATP immunogenicity cohort (ATP-I cohort).

**Table 8:** HI responses against vaccine strain H5N1 A/Indonesia/05/2005 of the Q-Pan and D-Pan vaccines (H5N1) in Study Q-Pan-001 (ATP-I cohort)

Study (Age vaccination)	Time-point	Strain	Manuf. site†	HA (µg / dose)	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	144	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	-	75	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	5.0	5.0	5.1	-	-	-	-	-	-	0.0	0.0	2.6
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	5.0	5.0	5.1	-	-	-	-	-	-	0.0	0.0	2.5
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	144	22.5	17.8	28.6	4.5	3.6	5.7	41.7	33.5	50.2	41.7	33.5	50.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	19.9	15.7	25.3	4.0	3.1	5.1	41.1	33.0	49.5	41.1	33.0	49.5
		H5N1 Indonesia	Quebec	3.8	-	75	6.1	5.2	7.1	1.2	1.0	1.4	6.7	2.2	14.9	6.7	2.2	14.9
		H5N1 Indonesia	Dresden	3.8	AS03	140	23.5	18.3	30.3	4.7	3.6	6.0	45.7	37.3	54.3	45.7	37.3	54.3
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	16.8	13.5	20.9	3.3	2.7	4.1	38.0	30.0	46.5	38.0	30.0	46.5
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	144	464.7	383.4	563.4	92.9	76.7	112.7	97.2	93.0	99.2	97.2	93.0	99.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	320.7	246.9	416.6	64.1	49.4	83.3	89.7	83.6	94.1	89.7	83.6	94.1
		H5N1 Indonesia	Quebec	3.8	-	75	10.5	8.2	13.5	2.1	1.6	2.7	17.3	9.6	27.8	17.3	9.6	27.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	480.3	390.5	590.7	95.3	77.3	117.5	96.4	91.9	98.8	96.4	91.9	98.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	347.7	272.0	444.5	69.0	54.0	88.3	92.3	86.6	96.1	92.3	86.6	96.1

SCF: seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq 1:40$ , or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

SPR: seroprotection rate (i.e. proportion of subjects with HI titre  $\geq 1:40$ )

† Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

**Table 9:** CHMP criteria: homologous HI antibody responses at Day 42 (Study Q-Pan-001)

Study/ Groups	Vaccine strain/ Age group	SCR			SPR			SCF		
		%	95% CI		%	95% CI		%	95% CI	
			LL	UL		LL	UL		LL	UL
Q-Pan-001	A/Indonesia/05/2005									
Q-Pan full AS03	18-64	97.2	93.0	99.2	97.2	93.0	99.2	92.9	76.7	112.7
Q-Pan half AS03		89.7	83.6	94.1	89.7	83.6	94.1	64.1	49.4	83.3
Q-Pan no AS03		17.3	9.6	27.8	17.3	9.6	27.8	2.1	1.6	2.7
D-Pan full AS03		96.4	91.9	98.8	96.4	91.9	98.8	95.3	77.3	117.5
D-Pan half AS03		92.3	86.6	96.1	92.3	86.6	96.1	69.0	54.0	88.3

**SCR:** After two doses of the vaccines, the SCR were 97.2% and 89.7% for the Q-Pan vaccine (full and half adjuvant dose, respectively), and 96.4% and 92.3% for the D-Pan vaccine (full and half adjuvant dose, respectively), SCR obtained with the non-adjuvanted group was 17.3%. Therefore the CHMP criterion for SCR (> 40%) was largely fulfilled by all adjuvanted groups, while not reached by the non-adjuvanted formulation. High levels of SCR were already observed after one vaccine dose: all adjuvanted groups, except one (D-Pan with half dose adjuvant) reached the required threshold at Day 21.

**SPR:** As the majority of subjects were initially seronegative to the vaccine strain, SPR values were in most groups identical to SCRs values. All of the adjuvanted treatment groups fulfilled the CHMP criterion for SPR.

**SCF (GMFI):** SCF were 92.9 and 95.3 for Q-Pan and D-Pan (full adjuvant dose) recipients, respectively. Slightly lower values are attained by half-adjuvant dose groups, that is, 64.1 and 69.0 for Q-Pan and D-Pan groups, respectively. However, the CHMP threshold value of 2.5 is far exceeded, and this criterion is already fulfilled after the first vaccine dose in all adjuvanted vaccine groups.

### Homologous neutralizing antibody response

As no seroprotection threshold has been established for the MN assay, a simple four fold increase (vaccine response) in MN titre at post-vaccination is used to evaluate whether vaccinated individuals have responded against the vaccine strain. Neutralizing antibody responses against vaccine strain (H5N1 A/Indonesia/05/2005) in terms of GMTs, vaccine response (VR or SCR) and the percentage of subjects with serum neutralization titres (SNT)  $\geq 1:28$ ,  $\geq 1:40$  and  $\geq 1:80$  are presented in the two tables below (Tables 10 and 11).

**Table 10:** Neutralizing antibody responses (GMT, titre  $\geq 1:28$ , vaccine response) against vaccine strain H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine (ATP-I, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA ( $\mu\text{g}$ per dose)	AS03	N	GMT			$\geq 1:28$			Vaccine Response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	47	22.3	17.4	28.5	27.7	15.6	42.6	-	-	-
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	31.8	23.0	43.8	40.4	26.4	55.7	-	-	-
		H5N1 Indonesia	Quebec	3.8	-	49	25.7	19.9	33.1	36.7	23.4	51.7	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03	48	23.7	18.3	30.8	31.3	18.7	46.3	-	-	-
	Post I (D21)	H5N1 Indonesia	Dresden	3.8	AS03/2	50	25.7	19.6	33.7	34.0	21.2	48.8	-	-	-
		H5N1 Indonesia	Quebec	3.8	AS03	47	199.0	148.9	266.1	100	92.5	100	76.6	62.0	87.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	240.1	191.4	301.3	96.0	86.3	99.5	68.1	52.9	80.9
		H5N1 Indonesia	Quebec	3.8	-	49	78.6	57.7	107.1	81.6	68.0	91.2	42.9	28.8	57.8
	Post II (D42)	H5N1 Indonesia	Dresden	3.8	AS03	49	260.5	208.1	326.0	100	92.7	100	79.2	65.0	89.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	248.7	202.0	306.3	100	92.7	100	71.4	56.7	83.4
		H5N1 Indonesia	Quebec	3.8	AS03	47	1566.8	1227.3	2000.2	100	92.5	100	97.9	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	1242.1	902.2	1710.0	100	92.6	100	91.3	79.2	97.6
		H5N1 Indonesia	Quebec	3.8	-	49	183.8	138.4	244.2	93.9	83.1	98.7	73.5	58.9	85.1
		H5N1 Indonesia	Dresden	3.8	AS03	49	1497.2	1192.0	1880.5	100	92.7	100	95.8	85.7	99.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	1352.8	1075.5	1701.6	100	92.9	100	96.0	86.3	99.5

N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Vaccine response defined as antibody titer  $\geq 4$ -fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

**Table 11:** Neutralizing antibody responses (titre  $\geq 1:40 \geq 1:80$ ) against strain vaccine H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine (ATP-I cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA ( $\mu\text{g}$ per dose)	AS03	N	$\geq 1:40$			$\geq 1:80$		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	47	21.3	10.7	35.7	12.8	4.8	25.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	36.2	22.7	51.5	23.4	12.3	38.0
		H5N1 Indonesia	Quebec	3.8	-	49	28.6	16.6	43.3	16.3	7.3	29.7
		H5N1 Indonesia	Dresden	3.8	AS03	48	22.9	12.0	37.3	14.6	6.1	27.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	26.0	14.6	40.3	20.0	10.0	33.7
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	93.6	82.5	98.7	80.9	66.7	90.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	96.0	86.3	99.5	96.0	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	75.5	61.1	86.7	53.1	38.3	67.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	98.0	89.1	99.9	93.9	83.1	98.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	98.0	89.1	99.9	95.9	86.0	99.5
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	100	92.5	100	100	92.5	100
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	100	92.6	100	100	92.6	100
		H5N1 Indonesia	Quebec	3.8	-	49	91.8	80.4	97.7	81.6	68.0	91.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	100	92.7	100	100	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	100	92.9	100	100	92.9	100

N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

High levels of baseline seropositivity were observed in 27.7-40.4% of subjects. After two vaccine doses, all subjects from the adjuvanted groups were seropositive (100%). Moreover, all subjects displayed MN titres  $\geq 1/80$ . In terms of GMTs, very high values were obtained in the adjuvanted groups, reaching 1529.0 and 1497.2 for the full-adjuvanted Q-Pan and D-Pan groups, respectively. Slightly lower titres are observed for the half-adjuvanted formulations, but with overlapping 95% CIs (1242.1 and 1352.8 for Q-Pan and D-Pan vaccine recipients, respectively), while titres of 183.8 only are reached by non-adjuvanted vaccine recipients.

### Cross-reactive immunity

In Study Q-Pan-H5N1-001, the capacity of Q-Pan vaccine to induce cross-reactive immunity was assessed by evaluating heterologous HI and neutralising antibody responses. The cross-reactivity was assessed against one variant belonging to the Clade 1 group (A/Vietnam, HI titer) and two variants belonging to the Clade 2 group (A/Turkey and A/Anhui, MN titer only).

### HI responses

The HI responses of Q-Pan vaccine were measured against the A/Vietnam/1194/2004 strain. A/Indonesia/05/2005 (H5N1) represents Clade 2, sub-Clade 1, and it was the first pandemic vaccine prototype strain released by the WHO in May 2006 whereas A/Vietnam/1194/2004 (H5N1) belongs to Clade 1. The HI responses against heterologous H5N1 strain A/Vietnam/1194/2004 in the ATP-I cohort are presented in the table below.

**Table 12:** HI responses (Day 42) against heterologous strain H5N1 A/Vietnam/1194/2004 of the Q-Pan and D-Pan vaccine (ATP-I cohort, Q-Pan-001)

Study (Age of vaccination)	Time-point	Strain	Manuf. site†	HA (µg /dose)	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	144	6.3	5.0	5.6	-	-	-	-	-	-	2.1	0.4	6.0
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	5.3	5.0	5.6	-	-	-	-	-	-	1.4	0.2	4.9
		H5N1 Indonesia	Quebec	3.8	-	75	5.4	5.0	5.8	-	-	-	-	-	-	0.0	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	5.5	5.1	5.9	-	-	-	-	-	-	2.1	0.4	6.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	5.4	5.1	5.7	-	-	-	-	-	-	1.4	0.2	5.0
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	144	9.9	8.4	11.7	1.9	1.6	2.2	13.2	8.1	19.8	15.3	9.8	22.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	8.5	7.3	10.0	1.6	1.4	1.9	9.6	5.3	15.6	12.3	7.5	18.8
		H5N1 Indonesia	Quebec	3.8	-	75	5.8	5.1	6.6	1.1	1.0	1.2	1.3	0.0	7.2	4.0	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	9.1	7.6	10.8	1.7	1.4	1.9	12.1	7.2	18.7	15.0	9.5	22.0
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	8.9	7.6	10.3	1.6	1.4	1.9	10.6	6.0	16.8	14.8	9.4	21.7
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	144	39.9	32.2	49.5	7.6	6.1	9.4	61.8	53.3	69.8	63.9	55.5	71.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	33.4	26.6	41.9	6.3	5.0	7.9	58.9	50.5	67.0	60.3	51.9	68.3
		H5N1 Indonesia	Quebec	3.8	-	75	5.8	5.1	6.5	1.1	1.0	1.2	1.3	0.0	7.2	4.0	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	33.3	26.0	42.7	6.1	4.7	7.8	56.4	47.8	64.8	59.3	50.7	67.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	30.6	24.3	38.5	5.7	4.5	7.1	53.5	45.0	61.9	56.3	47.8	64.6

At Day 42, a significant increase in GMTs against the heterologous strain is observed in all four adjuvanted groups, whereas virtually no effect on the heterologous titres is observed in the non-adjuvanted group. SCF, SCF, and SPR increased significantly following vaccination with all adjuvanted formulations, reaching levels ranging from 53.5% to 61.8% for SCR, 5.7 to 7.6 for SCF, and 56.3% to 63.9% for SPR. Results obtained in the non-adjuvanted group remained close to baseline for these parameters. The SCFs, SCRs, and SPRs obtained in the groups vaccinated either with D-Pan or Q-Pan vaccines showed widely overlapping 95% CIs.

When compared to the homologous HI responses, the HI responses to the heterologous strain were lower, but these results are indicative of the induction of a cross-reactive immune response against heterologous strains following immunisation with the Q-Pan vaccine.

### Heterologous neutralising antibodies response

Neutralizing antibody responses against heterologous H5N1 strain A/Vietnam/1194/2004 in the ATP-I cohort were assessed in a subset group of people (n = 50) in this study, and the results are presented in the two tables below.

**Table 13:** Neutralizing antibody responses (GMT, titre  $\geq$  1:28 and vaccine response) against strain H5N1 A/Vietnam/1194/2004 of the Q-Pan and D-Pan vaccine (ATP-I cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site†	HA (µg per dose)	AS03	N	GMT			$\geq$ 1:28			Vaccine response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	47	57.0	41.3	78.6	70.2	55.1	82.7	-	-	-
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	82.3	59.0	114.7	80.4	66.1	90.6	-	-	-
		H5N1 Indonesia	Quebec	3.8	-	49	55.7	38.7	80.2	67.3	52.5	80.1	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03	49	51.3	34.6	76.2	55.1	40.2	69.3	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	59.6	44.2	80.5	72.0	57.5	83.8	-	-	-
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	250.9	203.6	309.2	100	92.5	100	44.7	30.2	59.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	260.9	205.1	331.9	96.0	86.3	99.5	30.4	17.7	45.8
		H5N1 Indonesia	Quebec	3.8	-	49	145.2	108.0	195.3	91.8	80.4	97.7	34.7	21.7	49.6
		H5N1 Indonesia	Dresden	3.8	AS03	49	201.9	151.9	268.4	98.0	89.1	99.9	49.0	34.4	63.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	215.0	174.3	265.3	100	92.7	100	40.8	27.0	55.8
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	264.8	216.7	323.6	100	92.5	100	53.2	38.1	67.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	327.1	269.8	396.6	100	92.5	100	45.5	30.4	61.2
		H5N1 Indonesia	Quebec	3.8	-	49	143.9	111.2	186.2	98.0	89.1	99.9	30.6	18.3	45.4
		H5N1 Indonesia	Dresden	3.8	AS03	49	319.2	261.6	389.4	100	92.7	100	67.3	52.5	80.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	254.0	213.0	302.9	100	92.9	100	42.0	28.2	56.8

**Table 13:** Neutralizing antibody responses (titre  $\geq 1:40 \geq 1:80$ ) against strain H5N1 A/Vietnam/1194/2004 of the Q-Pan and D-Pan vaccine (ATP-I cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site†	HA ( $\mu\text{g}$ per dose)	AS03	N	$\geq 1:40$			$\geq 1:80$		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	47	61.7	46.4	75.5	51.1	36.1	65.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	71.7	56.5	84.0	58.7	43.2	73.0
		H5N1 Indonesia	Quebec	3.8	-	49	67.1	42.2	71.2	32.7	19.9	47.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	55.1	40.2	69.3	42.9	28.8	57.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	66.0	51.2	78.8	48.0	33.7	62.8
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	97.9	88.7	99.9	95.7	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	96.0	86.3	99.5	96.0	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	91.8	80.4	97.7	77.6	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	93.9	83.1	98.7	85.7	72.8	94.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	98.0	89.1	99.9	89.8	77.8	96.6
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	100	92.5	100	95.7	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	100	92.5	100	97.9	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	-	49	89.8	77.8	96.6	77.6	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	100	92.7	100	100	92.7	100
H5N1 Indonesia		Dresden	3.8	AS03/2	50	100	92.9	100	94.0	83.5	98.7	

Neutralizing antibody responses to the drift-variant A/Vietnam/1194/04 were of smaller magnitude in terms of both vaccine response rates and GMTs, but overall demonstrated a similar pattern. Higher GMTs against A/Vietnam/1194/04 and an increased proportion of subjects seropositive for such antibodies at baseline were noted. A 4-fold increase in serum neutralising antibody titres was obtained in 44.7% of subjects at Day 21 and in 53.2% of subjects at Day 42.

The results of MN titers against two other Clade 2 viruses, A/Anhui/1/05 and A/turkey/Turkey/1/05, are presented in the two tables below. The result showed that Q-Pan H5N1 vaccine could induce neutralizing responses against these agents in a reasonable percentage of the vaccinated subjects.

**Table 15:** Neutralizing antibody responses (GMT, titre  $\geq 1:28$  and vaccine response) against strains H5N1 A/Anhui/05 and A/Turkey/05 of Q-Pan H5N1 vaccine (ATP-I cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	GMT			$\geq 1:28$			Vaccine Response		
					Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	A/Anhui/05	H5N1 3.8 $\mu\text{g}$ (Quebec) Indonesia + full AS03	Pre	143	14.0	14.0	14.0	0.0	0.0	2.5	-	-	-
			Post II (D42)	142	91.3	78.4	106.4	95.1	90.1	98.0	78.9	71.2	85.3
	A/Turkey/05	H5N1 3.8 $\mu\text{g}$ (Quebec) Indonesia + full AS03	Pre	143	25.6	21.9	29.9	35.7	27.8	44.1	-	-	-
			Post II (D42)	143	594.4	523.6	674.7	100.0	97.5	100.0	88.8	82.5	93.5

**Table 15:** Neutralizing antibody responses (titre  $\geq 1:40 \geq 1:80$ ) against strains H5N1 A/Anhui/05 and A/Turkey/05 of Q-Pan H5N1 vaccine (ATP-I cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	$\geq 1:40$			$\geq 1:80$		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-001 18-64 yrs	A/Anhui/05	H5N1 3.8 $\mu\text{g}$ (Quebec) Indonesia + full AS03	Pre	143	0.0	0.0	2.5	0.0	0.0	2.5
			Post II (D42)	142	80.3	72.8	86.5	60.6	52.0	68.7
	A/Turkey/05	H5N1 3.8 $\mu\text{g}$ (Quebec) Indonesia + full AS03	Pre	143	25.2	18.3	33.1	15.4	9.9	22.4
			Post II (D42)	143	98.6	95.0	99.8	98.6	95.0	99.8

### Persistence of immune response

The persistence of the immune responses at Day 182 following the vaccination with the Q-Pan vaccine was assessed by measuring the HI and neutralising antibodies.

### HI antibody responses

Analysis of the immunogenicity by HI titers was performed on the ATP-I cohort (n = 648 subjects). The key HI antibody response parameters at Day 182 are summarized in the table below (Table 17).

**Table 17:** Key A/Indonesia/5/05 HI Antibody Response Parameters (GMT, SCF, SCR, SPR) at Day 182

Study (Age vaccination)	Time-point	Strain	Manuf. site†	HA (µg / dose)	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	141	27.8	22.8	33.8	5.6	4.6	6.8	54.6	46.0	63.0	54.6	48.0	63.0
		H5N1 Indonesia	Quebec	3.8	AS03/2	145	22.6	18.4	27.9	4.6	3.7	5.6	45.5	37.2	54.0	45.5	37.2	54.0
		H5N1 Indonesia	Quebec	3.8		74	6.6	5.1	6.2	1.1	1.0	1.2	2.7	0.3	9.4	2.7	0.3	9.4
		H5N1 Indonesia	Dresden	3.8	AS03	138	26.1	20.7	32.8	5.2	4.1	6.5	48.6	40.0	57.2	49.3	40.7	57.9
		H5N1 Indonesia	Dresden	3.8	AS03/2	138	22.6	18.3	28.0	4.6	3.6	5.6	44.9	36.5	53.6	45.7	37.2	54.3

While HI responses at Day 182 were not as high as at Day 42, the HI responses remained notably elevated relative to baseline in those treatment groups that had received adjuvanted vaccines. At Day 182, the treatment groups receiving vaccine with full-strength adjuvant continued to meet the SCR criterion outlined in both CHMP and CBER guidance.

No treatment group continued to fulfil the SPR criterion required by CHMP or CBER at Day 182. However, SPR at Day 182 remained approximately 50% among adjuvanted vaccine recipients, and substantially higher in the recipients of adjuvanted vaccines as opposed to those who received no adjuvant. Likewise, GMTs and SCFs at Day 182 remained notably higher in the adjuvanted vaccine groups (full and half-strength) relative to the unadjuvanted group.

#### Homologous neutralising antibody persistence (MN titers)

The neutralising antibody responses against homologous virus (A/Indonesia/5/05) at Days 21, 42, and 182 is presented in Table 18, and the GMTs at pre-vaccination, Days 21, 42, and 182 post first dose of the vaccine are summarized in Table 19.

**Table 18:** Vaccine response rates for A/Indonesia//5/05 neutralising antibody at Days 21, 42, and 182

Vaccine Response Rates for A/Indonesia/5/05 Neutralizing Antibody at Days 21, 42, and 182			
Treatment Group	% of Vaccine Responders Day 21 (95% CI)	% of Vaccine Responders Day 42 (95% CI)	% of Vaccine Responders Day 182 (95% CI)
A (Q000AS03)	42.9 (28.8, 57.8)	73.5 (58.9, 85.1)	53.1 (38.3, 67.5)
B (Q100AS03)	76.6 (62.0, 87.7)	97.9 (88.7, 99.9)	91.5 (79.6, 97.6)
C (Q50AS03)	68.1 (52.9, 80.9)	91.3 (79.2, 97.6)	78.3 (63.6, 89.1)
D (D100AS03)	79.2 (65.0, 89.5)	95.8 (85.7, 99.5)	87.5 (74.8, 95.3)
E (D50AS03)	71.4 (56.7, 83.4)	96.0 (86.3, 99.5)	87.5 (74.8, 95.3)

For all groups, the vaccine response rates (VRRs) at Day 182 were lower than that at Day 42, but were still higher than the VRRs at Day 21.

**Table 19:** A/Indonesia//5/05 neutralising antibody GMTs at pre-vaccination, and Days 21, 42, and 182



A/Indonesia/5/05 Neutralizing Antibody GMTs Pre-vaccination and at Days 21, 42, and 182 Post First Dose				
Treatment Group	GMT Value PRE (95% CI)	GMT Value Day 21 (95% CI)	GMT Value Day 42 (95% CI)	GMT Value Day 182 (95% CI)
A (Q000AS03)	25.7 (19.9, 33.1)	78.6 (57.7, 107.1)	183.8 (138.4, 244.2)	108.9 (81.9, 144.7)
B (Q100AS03)	22.3 (17.4, 28.5)	199.0 (148.9, 266.1)	1566.8 (1227.3, 2000.2)	414.0 (346.2, 495.1)
C (Q50AS03)	31.8 (23.0, 43.8)	240.1 (191.4, 301.3)	1242.1 (902.2, 1710.0)	417.1 (335.0, 519.3)
D (D100AS03)	23.7 (18.3, 30.8)	280.5 (208.1, 326.0)	1497.2 (1192.0, 1880.5)	456.2 (387.4, 537.3)
E (D50AS03)	25.7 (19.6, 33.7)	248.7 (202.0, 306.3)	1352.8 (1075.5, 1701.6)	450.1 (384.7, 526.5)

The GMTs at Day 182 persisted at levels above the pre-vaccination values in all groups, and the Day 182 GMTs in the adjuvanted vaccine groups were approximately 4-fold higher than that in non-adjuvanted group (Group A).

### The persistence of the heterologous HI response

In Q-Pan-H5N1-001, the persistence of the heterologous HI antibody response was assessed against the A/Vietnam strain. A substantial decline in the anti-A/Vietnam HI response at Day 182 was observed. Similarly to the homologous response, levels of GMTs declined at Day 182 to approximately those observed after the first vaccination, that is, Day 21. However, values are still above those observed in the non-adjuvanted vaccine group. Seroprotection rates retained by adjuvanted vaccine recipients were between 10.6% and 13.1%, versus 1.4% in the non-adjuvanted group, showing again an advantage of the adjuvanted formulations.

### Immunogenic equivalence between Q-Pan and D-Pan vaccine

A secondary objective of Q-Pan-H5N1-001 was to assess the equivalence of the vaccine antigen manufactured in Quebec (Q-Pan) and the antigen manufactured in Dresden (D-Pan), both administered with AS03. For this analysis, subjects in the Q-Pan groups with full and half dose AS03 were pooled together to form the Q-Pan with adjuvant group. Similarly, D-Pan groups with full and half dose AS03 were pooled to form the D-Pan with adjuvant group. The analysis of the equivalence of the Quebec and Dresden sources of antigen was to be performed by analysis of variance on the  $\log_{10}$  transformed reciprocal HI titers at Day 42, with treatment group as a fixed factor, and age strata and baseline antibody titers as covariates. The analysis was to use data from Groups B, C, D and E. A 95% CI on the Group B plus Group C versus Group D plus Group E mean difference in  $\log_{10}$  reciprocal titers was to be calculated, and the anti-log of these limits used to calculate the CI on the GMT ratio. For the groups to be considered equivalent, the limit of the 95% CI on the ratio was to be between 0.67 and 1.5 (2/3 and 3/2).

The comparison between the Q-Pan and D-Pan vaccine assessed by HI antibody GMT is presented in Table 20. The GMT ratio was 0.94 (95% CI 0.75-1.17) for the homologous response and 1.16 (95% CI 0.92-1.46) for the heterologous anti-Vietnam strain response. The criterion was met for both the homologous and heterologous response since both ratios were within the pre-specified limits of 0.67-1.5. The two vaccines are therefore considered equivalent in terms of the immunogenicity. The demonstrated immunogenic equivalence between Q-Pan and D-Pan vaccines justifies that the results of the dose range study (Study H5N1-007) performed with D-Pan vaccine can also be applied to the Q-Pan vaccine.

**Table 20:** Adjusted GMT ratios for subjects receiving Quebec antigen with full or half dose adjuvant compared with subjects receiving Dresden antigen with full or half dose adjuvant at Day 42

Antibody	Treatment Group				Adjusted GMT ratio (Q-Pan / D-Pan)		
	Q-Pan with adjuvant		D-Pan with adjuvant		Value	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
HI antibody against A/Indonesia/05/2005	290	371.2	282	396.9	0.94	0.75	1.17
HI antibody against A/Vietnam/1194/2004	290	36.6	282	31.6	1.16	0.92	1.46

D-Pan with adjuvant = D-Pan with full dose and half dose AS03

Q-Pan with adjuvant = Q- Pan with full dose and half dose AS03

Adjusted GMT = geometric mean antibody titre adjusted for age strata, baseline titre

N = Number of subjects with both pre- and post-vaccination results available

95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titre - pooled variance); LL = lower limit, UL = upper limit

### Study Q-Pan-H5N1-002

Study Q-Pan-H5N1- 002 was a Phase III, observer-blind, randomized, placebo-controlled, multi-center trial. The study was to evaluate the safety and immunogenicity of a two-dose series of Q-Pan H5N1 vaccine antigen in association with AS03 adjuvant in adults aged  $\geq 18$  years.

### Study objectives

One of the key primary objectives of the study was to demonstrate the immunogenic equivalence of three consecutive lots of H5N1 vaccine antigen manufactured in Quebec combined with 3 consecutive lots of AS03 manufactured in Rixensart. The lot consistency hypothesis was tested on the basis of GMTs (HI response to vaccine-homologous virus), and it was to be addressed in healthy young adults 18-49 years of age. Safety of the Q-Pan H5N1 antigen adjuvanted with AS03 was also assessed as a primary objective.

As the secondary objectives, the immunogenicity of the Q-Pan H5N1 antigen with AS03 was assessed by measuring the post-immunization (Day 42) vaccine-homologous virus HI titers. The immunogenicity was assessed against the CHMP criteria in two age strata: 18 to 60 years of age and  $> 60$  years of age. The persistence of the immunogenicity (at Day 182) was also assessed in terms of vaccine-homologous virus HI and MN titers and MN titers for one or more drift-variant viruses.

### Study vaccines

The study vaccine was Q-Pan H5N1 (Quebec) and the reference or comparator vaccine was the inactive placebo control which was sterile preserved isotonic saline for injection.

### Study design

The study was an eight-arm trial, and enrolled subjects were randomized at a 1:1:1:1 ratio to receive 1 of 4 treatments (three lots of study vaccine and placebo). Within each treatment, the randomization was stratified by age to target age interval ratios of 1.5 (18-30 years): 1.5 (31-49 years): 1 (50-64 years): 1.5 (65-75 years): 0.5 ( $> 75$  years). The resultant groups were as follows:

Group A (18-49 years): Q-Pan H5N1 antigen (lot A) with adjuvant (lot 1), (N  $\approx$  555)

Group B (18-49 years): Q-Pan H5N1 antigen (lot B) with adjuvant (lot 2), (N  $\approx$  555)

Group C (18-49 years): Q-Pan H5N1 antigen (lot C) with adjuvant (lot 3), (N  $\approx$  555)

Group D (18-49 years): Placebo, (N  $\approx$  555)

Group E (50-64 years): Q-Pan H5N1 antigen (lot A, B, or C) with adjuvant (lot 1, 2, or 3), (N ≈ 555; 185 per lot)

Group F (50-64 years): Placebo, (N ≈ 185)

Group G (> 64 years): Q-Pan H5N1 antigen (lot A, B, or C) with adjuvant (lot 1, 2, or 3), (N ≈ 1110; 370 per lot)

Group H (> 64 years): Placebo, (N ≈ 370).

Subjects were to be vaccinated on Days 0 and 21, with one dose of the appropriate test article administered IM in the deltoid of the non-dominant arm on Day 0, and one dose administered in the dominant arm on Day 21.

### Study subjects

It was planned to enrol approximately 4440 healthy adults from three age groups: 18 to 49 years, 50 to 64 years, and > 64 years. The study subjects were to be randomly assigned at a 3:1 ratio to treatment with active study vaccine (Groups A, B, C, E, [555 subjects each group] and G [1110 subjects]) or placebo (Groups D [555 subjects], F [185 subjects], and H [370 subjects]).

Healthy adults 18 years of age or greater were eligible to enrol. A total of 4561 subjects were enrolled and vaccinated, including 3422 subjects in the Q-Pan group and 1139 subjects in the placebo group. The demographic information was similar for the TVC and ATP-I cohort.

A total of 4343 subjects completed the study through the Day 182 analysis, including 3263 subjects in the Q-Pan group and 1080 subjects in the placebo group. A total of 218 subjects withdrew from the study as of Day 182; reasons for study withdrawal included loss to follow-up, withdrawal of consent, migration from the study area, protocol violations, serious or non-serious adverse events, and unspecified other reasons (see Table 21 below).

**Table 21:** Number of subjects entered, completed, and withdrawn and reason for withdrawal (TVC)

	18-64 years			>64 years		
	Q-Pan	Placebo	Total	Q-Pan	Placebo	Total
Number of subjects vaccinated	2304	768	3072	1118	371	1489
Number of subjects completed	2177	720	2897	1086	360	1446
Number of subjects withdrawn	127	48	175	32	11	43
Reasons for withdrawal						
Serious Adverse Event	2	3	5	2	2	4
Non-serious adverse events	2	1	3	1	1	2
Protocol violation	1	0	1	0	1	1
Consent withdrawal (not due to an adverse event)	21	3	24	11	5	16
Migrated/moved from study area	16	1	17	3	2	5
Lost to follow-up (subjects with incomplete vaccination course)	21	13	34	3	0	3
Lost to follow-up (subjects with complete vaccination course)	50	24	74	8	0	8
Others	14	3	17	4	0	4

Vaccinated = number of subjects who were vaccinated in the study  
 Completed = number of subjects who completed Day 182 study visit  
 Withdrawn = number of subjects who did not come for the Day 182 visit

### Study duration

The duration of the study was approximately 1 year (364 days) for each subject, from enrolment through to the last study follow-up. The duration of actual treatment comprises two test article doses at an approximate 21-day interval.

### Statistic consideration

Lot consistency was tested by forming pair-wise ratios of GMT values for A/Indonesia/5/05 reciprocal HI titers induced by the 3 treatment groups representing the three consecutive lots of antigen combined with three consecutive lots of adjuvant. The criterion for success was

that the 2-sided 95% confidence bounds for all three pair-wise ratios were entirely within the interval 0.67 to 1.5. Primary endpoint hypothesis tests were based on data at Day 42, approximately three weeks after the second vaccine dose.

Immunogenicity analyses were performed on the ATP-I cohort. The primary immunogenicity analyses concerned post-immunization SCR and SPR for the A/Indonesia/5/05 in the Q-Pan group. The SPR, SCR and GMFR were calculated and presented according to the CHMP criterion for the 2 age strata (18 to 60 years of age and > 60 years of age).

Vaccine-homologous virus immunogenicity at Day 182 (6 months after the first dose of vaccine) was compared to the same criteria for SCR and SPR as applied at Day 42, but this comparison was used for descriptive purposes only. The immunogenicity results by MN assays were also presented.

### Lot-to-lot consistency

A primary objective of Q-Pan-H5N1-002 was to demonstrate the immunogenic equivalence, based on Day 42 vaccine-homologous virus HI GMTs, of three consecutive lots of H5N1 antigen (manufactured in Quebec) combined with three consecutive lots of AS03 (manufactured in Rixensart, Belgium), in subjects 18 to 49 years of age. The criterion for success was that the 2-sided 95% confidence bounds for all the pair-wise ratios of GMT values were to be entirely within the interval of [0.67; 1.5]. The results of the pair-wise Day 42 GMT ratios of HI antibodies against A/Indonesia/05/2005 are presented in the table below.

**Table 22:** Adjusted GMT ratios of HI antibodies against A/Indonesia/05/2005 at Day 42 for all Q-Pan vaccine lots in subjects 18-49 years of age (ATP cohort for immunogenicity)

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

The lot to lot consistency has been demonstrated as the 2-sided 95% confidence bounds for all the pair-wise ratios of GMT values were within the pre-defined range of [0.67; 1.5].

### Immunogenicity post-Dose II

The post-Dose II immunogenicity was assessed in the ATP-I cohort which consisted of a total of 2083 subjects. The ATP-I cohort included 1967 subjects in the Q-Pan group and 116 subjects in the placebo group. There were a total of 1556 in the age group of 18-60 years old and 527 in the age group of > 60 years old.

### HI responses at post-Dose II (Day 42)

The HI responses against A/Indonesia/05/2005 after the second dose of vaccination with Q-Pan H5N1 vaccine (Day 42) is presented in the table below:

**Table 23:** HI responses against A/Indonesia/05/2005 for Q-Pan H5N1 vaccine at Day 42 (ATP-I)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			SCF			SCR			SPR		
					Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	1488	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	0.2
			Placebo	68	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	5.3
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	1488	258.0	239.7	277.7	51.4	47.8	55.3	91.0	89.4	92.4	91.0	89.4	92.4
			Placebo	68	5.2	4.9	5.5	1.0	1.0	1.1	1.5	0.0	7.9	1.5	0.0	7.9
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	479	5.2	5.0	5.3	-	-	-	-	-	-	0.4	0.1	1.5
			Placebo	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	479	89.0	77.1	102.7	17.2	14.9	19.9	76.4	72.3	80.1	76.8	72.8	80.5
			Placebo	48	5.5	4.6	6.5	1.1	0.9	1.3	2.1	0.1	11.1	2.1	0.1	11.1

After two doses of the Q-Pan vaccine (at Day 42):

- SPR reached 91.0% in adults 18-60 years of age and 76.8% in adult > 60 years of age.
- SCR reached 91.0% in adults 18-60 years of age and 76.4% in adult > 60 years of age.
- SCF reached 51.4% in adults 18-60 years of age and 17.2 in adult > 60 years of age.

The values of SPR, SCR, and SCF obtained at Day 42 after two doses of Q-Pan vaccine comfortably exceed the required threshold for all three CHMP criteria. None of the results after the placebo have met the CHMP criteria.

#### Homologous MN results post-Dose II (Day 42)

Neutralizing antibody responses against vaccine strain (H5N1 A/Indonesia/05/2005) in terms of GMTs, vaccine response and the percentage of subjects with serum neutralization titres  $\geq 1:28$ ,  $\geq 1:40$  and  $\geq 1:80$  are presented in the two tables below.

**Table 24:** Neutralizing antibody responses (GMT, GMFR, titre  $\geq 1:28$ , vaccine response) against vaccine strain of the AS03 adjuvanted Q-Pan H5N1 vaccine (ATP-I, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			GMFR			$\geq 1:28$			Vaccine response		
					Value	95% CI		Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	178	21.2	18.8	23.9	-	-	-	24.2	18.1	31.1	-	-	-
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	178	1529.0	1332.0	1755.1	72.1	58.5	88.9	100	97.9	100	94.4	89.9	97.3
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	56	54.0	42.0	69.3	-	-	-	75.0	63.7	84.2	-	-	-
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	56	619.4	462.7	829.1	11.5	8.1	16.3	98.2	91.8	99.9	80.4	67.6	89.8

N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

GMFR = Geometric mean fold rise

Vaccine response defined as antibody titer  $\geq 4$ -fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

**Table 25:** Neutralizing antibody responses (titre  $\geq 1:40$ ,  $\geq 1:80$ ) against vaccine strain of the AS03 adjuvanted Q-Pan H5N1 vaccine in Q-Pan-H5N1-002 (ATP-I, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	178	18.5	13.9	24.0	11.8	8.0	16.5
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	178	100	98.3	100	100	98.3	100
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	58	62.6	50.7	73.3	44.6	33.3	56.5
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	58	98.2	91.8	99.9	96.4	89.2	99.4

N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

High levels of baseline seropositivity were observed, in 24.2% and 75.0% of subjects aged 18-60 years and >60 years, respectively. After two vaccine doses, all subjects from 18-60 years group were seropositive (100%), and the vaccine response rates (VRRs) were 94.4% and 80.4% in the 18-60 and > 60 age group respectively.

Similar high GMT value was obtained in the 18-60 age group, where all subjects receiving the Q-Pan vaccine had antibody titres above the 1:80 cut-off.

### Cross-reactive immunity (MN titres)

Heterologous neutralising antibody responses against A/Vietnam/1194/2004, a H5N1 drift variant strain, were evaluated in a subset of subjects. Of note, only candidate vaccine recipients were assessed. Results are presented in the two tables below. The HI responses against the drift strains were not assessed in this study.

**Table 26:** Neutralizing antibody responses (GMT, GMFR, titre ≥ 1:28, vaccine response) against H5N1 A/Vietnam/1194/2004 of the AS03 adjuvanted Q-Pan H5N1 vaccine (Q-Pan-H5N1-002, ATP-I cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			GMFR			≥1:28		Vaccine response			
					Value	95% CI		Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	171	27.8	23.9	32.4	-	-	-	37.4	30.2	45.1	-	-	-
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	171	159.8	142.1	179.8	5.7	4.9	6.7	96.5	92.5	98.7	65.5	57.9	72.6
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	54	96.4	72.8	128.0	-	-	-	83.3	72.7	91.0	-	-	-
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	54	216.6	174.1	269.4	2.2	1.7	2.9	96.3	88.8	99.3	24.1	13.5	37.6

N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

GMFR = Geometric mean fold rise

Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

**Table 27:** Neutralizing antibody responses (titre ≥ 1:40, ≥ 1:80) against A/Vietnam/1194/2004 of the AS03 adjuvanted Q-Pan vaccine in Study Q-Pan-H5N1-002 (ATP-I cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	171	31.0	25.2	37.3	18.1	13.4	23.7
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	171	95.9	92.4	98.1	84.2	78.9	88.6
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	54	81.5	70.6	89.6	70.4	58.5	80.4
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	54	96.3	88.8	99.3	92.6	83.8	97.4

At Day 42 with subjects aged 18-60, vaccine response rate (VRR) was 65.5%, the GMTs showed a 5.7 fold increase over baseline titres, and the proportion of subjects reaching the titre of 1/80 showed more than a 4.6- fold increase over baseline.

For adults > 60 years of age, while there was a higher level of baseline seropositivity compared to adults aged 18-60 years, post-Dose II seropositivity rates were similar between the two age groups. A 2.2-fold increase in GMTs is observed after two doses of Q-Pan vaccine, with a VRR of 24.1%. Importantly, the proportion of elderly subjects who reached neutralising titres of  $\geq 1/80$  at Day 42 was higher than in younger adults, that is 92.6% in the older versus 84.2% in the younger age stratum.

### Persistence of immune response (HI)

The persistence of antibody responses at Day 182 has been assessed in Study Q-Pan-H5N1-002 for homologous HI antibodies only. Analysis of immunogenicity was performed on the ATP-I cohort (n = 2083). The key HI antibody response parameters at Day 182 are summarized in Table 26 according to the CBER-mandated age strata and in Table 29 and 30 according to the EMEA/CHMP mandated age strata.

**Table 28:** Key A/Indonesia/5/05 HI Antibody Response Parameters at Day 182 According to CBER-mandated Age Strata. ATP Immunogenicity Cohort

Treatment Group	% of Subjects Seroconverted (95% CI)	% of Subjects with Reciprocal Titer $\geq 40$ (95% CI)
Q-Pan, 18-64 years	61.5 (56.3, 66.5)	61.5 (56.3, 66.5)
Placebo, 18-64 years	2.7 (0.1, 14.2)	2.7 (0.1, 14.2)
Q-Pan, > 64 years	64.8 (54.1, 74.6)	65.9 (55.3, 75.5)
Placebo, > 64 years	0.0 (0.0, 17.6)	0.0 (0.0, 17.6)

**Table 29:** Key A/Indonesia/5/05 HI Antibody Response Parameters at Day 182 According to EMEA/CHMP mandated Age Strata (ATP-I cohort)

Treatment Group	% of Subjects Seroconverted (95% CI)	% of Subjects with Reciprocal Titer $\geq 40$ (95% CI)
Q-Pan, 18-60 years	62.0 (56.8, 67.1)	62.0 (56.8, 67.1)
Placebo, 18-60 years	3.4 (0.1, 17.8)	3.4 (0.1, 17.8)
Q-Pan, > 60 years	62.5 (52.5, 71.8)	63.5 (53.4, 72.7)
Placebo, > 60 years	0.0 (0.0, 12.8)	0.0 (0.0, 12.8)

**Table 30:** HI responses against vaccine strain (H5N1 A/Indonesia/05/2005) of the Q-Pan vaccine up to Day 182 in Q-Pan-H5N1-002 (ATP-I cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			SCF			SCR			SPR		
					Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	1488	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	0.2
			Placebo	88	5.0	5.0	5.0	-	-	-	-	-	-	-	0.0	0.0
		Post II (D42)	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	1488	258.0	239.7	277.7	51.4	47.8	55.3	91.0	89.4	92.4	91.0	89.4	92.4
			Placebo	68	5.2	4.9	5.5	1.0	1.0	1.1	1.5	0.0	7.9	1.5	0.0	7.9
		Post II (D182)	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	353	37.2	31.8	43.6	7.4	6.3	8.7	62.0	56.8	67.1	62.0	56.8	67.1
			Placebo	29	5.7	4.7	6.9	1.1	0.9	1.4	3.4	0.1	17.8	3.4	0.1	17.8
	>60 years	Pre	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	479	5.2	5.0	5.3	-	-	-	-	-	-	0.4	0.1	1.5
			Placebo	48	5.0	5.0	5.0	-	-	-	-	-	-	-	0.0	0.0
		Post II (D42)	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	479	89.0	77.1	102.7	17.2	14.9	19.9	76.4	72.3	80.1	76.8	72.8	80.5
			Placebo	48	5.5	4.6	6.5	1.1	0.9	1.3	2.1	0.1	11.1	2.1	0.1	11.1
		Post II (D182)	Q-Pan H5N1 (3.8 $\mu$ g) Indonesia + AS03	104	39.6	29.9	52.5	7.8	5.9	10.4	62.5	52.5	71.8	63.5	53.4	72.7
			Placebo	27	5.3	4.7	5.8	1.1	0.9	1.2	0.0	0.0	12.8	0.0	0.0	12.8

The results showed that the HI responses (SCR, SPR, GMT, or GMFR) against the vaccine homologous H5N1 virus at Day 182 had clearly declined from Day 42 levels. At Day 182:

**SCR:** the Q-Pan group continued to meet the SCR criterion for the vaccine-homologous strain as outlined in CBER guidance for pandemic influenza vaccines (61.5% for Q-Pan subjects 18 to 64 years of age and 64.8% for Q-Pan subjects > 64 years of age, with the lower

bounds of 95% CI  $\geq$  40 % and 30%, respectively). Similarly, CHMP criteria for SCR were fulfilled in both 18-60 year-old subjects and subjects > 60 years of age at Day 182.

**SPR:** the Q-Pan recipients no longer fulfilled the SPR target set by CBER guidance in either age stratum. Nonetheless, approximately two-thirds of vaccines retained reciprocal HI titers  $\geq$  40 at Day 182. Q-Pan recipients in the 18-60 year old age stratum fell just short of the EMEA criterion for SPR (70%) at Day 182, while Q-Pan recipients > 60 years of age did continue to meet the EMEA target at Day 182.

**SCF:** SCFs at Day 182 declined relative to Day 42, but remained notably higher in the Q-Pan groups and still fulfilled the CHMP criteria.

### **Evaluator's overall conclusions on immunogenicity**

The antigen dose for the Q-Pan H5N1 candidate vaccine was chosen based on a dose range study (H5N1-007) performed with D-Pan H5N1 vaccine, where it was demonstrated that in presence of the AS03 adjuvant, antigen content as low as 3.75  $\mu$ g was sufficient to induce the immune response meeting all three CHMP criteria. The immune responses observed with the Q-Pan H5N1 vaccine were very similar to those obtained with D-Pan H5N1 vaccine, the equivalence between the two vaccines was demonstrated in Q-Pan-H5N1-001. Demonstration of immunogenic equivalence justified the extrapolation of the antigen dose selected with D-Pan vaccine to the Q-Pan vaccine.

Study Q-Pan-H5N1-001 also demonstrated that the immunogenicity of the Q-Pan antigen (3.75  $\mu$ g antigen) with full- or half-strength adjuvant was markedly superior to the Q-Pan antigen without adjuvant, as determined by SCRs and GMTs at Day 42, and the three CHMP criteria were met (and exceeded) after a two-dose vaccination course in all treatment groups receiving adjuvanted vaccine. The reduction of the AS03 adjuvant dose (full to half) had modest effect on vaccine-homologous virus immunogenicity in subjects 18 to 40 years old, but led to a significant reduction in GMT and proportion of subjects attaining reciprocal titers  $\geq$  40 (SPR) among subjects 41-64 years old.

The capacity of the candidate Q-Pan H5N1 vaccine (with full AS03 adjuvant) to induce high immune responses, exceeding the three CHMP criteria, was further confirmed in the larger study, Q-Pan-H5N1-002, where subjects in the age groups of 18-60 years and > 60 years were assessed. The consistency of the immunogenicity between three lots of the candidate Q-Pan H5N1 vaccine was also demonstrated in Q-Pan-H5N1-002.

The capacity of the candidate Q-Pan vaccine to induce cross-reactive immune response against a heterologous strain of A/Vietnam /1194/2004 was assessed in terms of HI antibodies and neutralising antibodies in Q-Pan-H5N1-001. The HI and MN results (at Day 42) showed that comparing to the immune response against the homologous vaccine strain, the immune response against the heterologous strain of A/Vietnam /1194/2004 was lower in magnitude, but was still indicative of its capacity to induce cross-reactive immunity. Q-Pan-H5N1-001 also showed that Q-Pan H5N1 vaccine could induce neutralising antibodies against the two additional draft strains (A/Anhui and A/turkey/Turkey) in a reasonable percentage of the vaccinated subjects. Similar responses against A/Vietnam/1194/2004 strain measured by neutralizing antibodies were also observed in Q-Pan-H5N1002.

The persistence of the immune response up to Day 182 (6 months) was evaluated. The HI results in both studies showed that the immune response at Day 182 declined relative to Day 42, and the SPR values were no longer fulfil the CHMP criteria, although more than 50% of the candidate Q-Pan vaccine (with full AS03 adjuvant) recipients retained reciprocal HI titers  $\geq$  40 (SPR) against the vaccine strain at Day 182 (Table 31).



**Table 31:** HI responses against the vaccine strain and the heterologous strain at Days 21, 42 and 182 following vaccination with the candidate Q-Pan vaccine (Study Q-Pan-H5N1-001)

Days post vaccination	Viral strain against which HI response was measured	HI response		
		SCR (%)	SPR (%)	SCF (x)
Day 21	Vaccine strain (A/Indonesia)	41.7	41.7	4.5
	heterologous strain (A/Vietnam)	13.2	15.3	1.9
Day 42	Vaccine strain (A/Indonesia)	<b>97.2</b> <b>(93.0-99.2)</b>	<b>97.2</b> <b>(93.0-99.2)</b>	<b>92.9</b> <b>(76.7-112.7)</b>
	heterologous strain (A/Vietnam)	61.8	63.9	7.6
Day 182	Vaccine strain (A/Indonesia)	54.6	54.6	5.6
	heterologous strain (A/Vietnam)	9.2	10.6	1.7

Bolded entries indicate primary outcome with 95% confidence intervals

The persistence of HI responses against the drift variant (A/Vietnam/1194/2004) were much lower at Day 182 (Q-Pan-H5N1-001). In addition, the GMTs were lower than the Day 21 values and were only marginally higher than the pre-vaccination values.

## Safety

### Overall Extent of Exposure

The number of doses of the various H5N1 vaccine formulations administered in pivotal studies (Q-Pan-H5N1001 and Q-Pan-H5N1-002) and in supportive studies (D-Pan H5N1-002, -007 and -008) is provided in the table below.

**Table 32:** Overall number of doses of monovalent split virus vaccine (H5N1) administered in the target age group in pivotal study Q-Pan-H5N1-001 and in supportive studies D-Pan-H5N1-002, H5N1-007 and H5N1-008

Study	Age group	Schedule	Number of doses evaluated for reactogenicity												
			H5N1 antigen manufactured in Quebec			H5N1 antigen manufactured in Dresden									
			H5N1 vaccine adjuvanted with AS03		H5N1 vaccine (plain)	H5N1 vaccine adjuvanted with AS03					H5N1 vaccine (plain)				
			3.8µg HA AS03	3.8µg HA AS03/2*	3.8µg HA	3.8µg HA AS03/2*	30µg HA AS03	15µg HA AS03	7.5µg HA AS03	3.8µg HA AS03	30µg HA	15µg HA	7.5µg HA	3.8µg HA	
Q-Pan-001	18-64 yrs	0, 21 days	301	299	155	292	-	-	-	298	-	-	-	-	
Q-Pan-002	≥18 yrs	0, 21 days	6747	-	-	-	-	-	-	-	-	-	-	-	
H5N1-002	18-60 yrs	0, 21 days	-	-	-	-	-	-	-	1907	-	-	-	486	
H5N1-007	18-60 yrs	0, 21 days	-	-	-	-	98	100	100	102	100	100	100	100	
H5N1-008	18-60 yrs	0, 21 days	-	-	-	-	-	6664	-	-	-	-	-	-	
	>60 yrs	0, 21 days	-	-	-	-	-	801	-	-	-	-	-	-	
Total for each HA /AS03 dose			7048	299	155	292	98	7565	100	2307	100	100	100	586	
Total for H5N1 split/ AS03, H5N1 split (plain)			7347			155	10362					886			
Total for H5N1 split /± AS03 for Quebec and Dresden derived H5N1 antigen			7502			11248									
Total for H5N1 split /± AS03			18750												

\*AS03/2: half dose AS03, corresponding to half the adjuvant content as contained in the candidate vaccine formulation

The H5N1 antigen manufacturing source (Quebec or Dresden), the different concentrations of HA per dose and the presence and dose of AS03 as an adjuvant are also mentioned in the table above. In total, 18750 doses of monovalent split virus vaccine (H5N1) have been administered to 7947 subjects in the evaluation of safety, of which 7502 doses in 2685 subjects contained Q-Pan antigen and 11248 doses in 5462 subjects contained D-Pan antigen. Of the 7502 Q-Pan vaccine doses, 7347 doses in 2607 subjects were AS03 adjuvanted. Of the 11248 D-Pan vaccine doses, 10362 doses in 5262 subjects were adjuvanted with AS03.

A total of 7048 doses of the selected formulation of the Q-Pan candidate vaccine (with full AS03) adjuvant) have been evaluated in 2456 subjects in Q-Pan-H5N1-001 and Q-Pan-H5N1-002. In these two pivotal studies, the safety/reactogenicity assessment included recording of solicited local (pain, redness, swelling) and general (fever, fatigue, headache, joint pain, muscle aches, shivering, sweating) AEs during a 7 day period after each vaccination, recording of unsolicited AEs within 21 days after each vaccination and overall (Day 0 - 84), and recording of the medically-attended events (MAE) and SAEs during the entire study period. New onset chronic diseases (NOCD) were also monitored in Q-Pan-H5N1-001. For both studies, each subject experiencing an unsolicited symptom was asked if he/she received medical attention (hospitalization, emergency room visit or an otherwise unscheduled visit to or from medical doctor). MAEs and SAEs were recorded up to Day 182 for Q-Pan-H5N1-001 and up to Day 364 for Q-PanH5N1-002.

### Safety data in Study Q-Pan-H5N1- 001

Safety analysis was performed on all 680 subjects included in the total vaccinated cohort (TVC), the primary cohort for safety analysis. This included 78 subjects in Group A (vaccine without adjuvant) and 152, 151, 151, and 148 subjects in Groups B, C, D, and E, respectively (vaccine with adjuvant). In follow-up through approximately 182 days following the first vaccine dose, overall compliance was good (97.4%). No subjects were lost to follow-up due to AEs or SAEs.

### Solicited adverse events

The number and percentage of doses followed by solicited local or general symptoms in subjects aged 18-64 years old are presented in the two tables below.

**Table 33:** The percentage of doses followed by solicited local symptoms including those of Grade 3 intensity in Study Q-Pan-H5N1-001 (Total vaccinated cohort)

Study (schedule)	N	Intensity	Pain			Redness			Swelling		
			%	95%CI LL	UL	%	95%CI LL	UL	%	95%CI LL	UL
<b>Q-Pan-001 (2 dose schedule at 0, 21 days) in 18 to 64 years old</b>											
H5N1 split Quebec	301	Total	81.7	76.9	85.9	2.3	0.9	4.7	6.0	3.6	9.3
(HA 3.8µg) AS03 full	301	Grade 3	4.0	2.1	6.9	0.0	0.0	1.2	0.0	0.0	1.2
H5N1 split Quebec	299	Total	74.9	69.6	79.7	0.7	0.1	2.4	3.7	1.9	6.5
(HA 3.8µg) AS03 half	299	Grade 3	0.7	0.1	2.4	0.0	0.0	1.2	0.0	0.0	1.2
H5N1 split Quebec	155	Total	14.8	9.6	21.4	0.0	0.0	2.4	0.0	0.0	2.4
(HA 3.8µg)	155	Grade 3	0.6	0.0	3.5	0.0	0.0	2.4	0.0	0.0	2.4
H5N1 split Dresden	298	Total	85.2	80.7	89.1	4.0	2.1	6.9	9.1	6.1	12.9
(HA 3.8µg) AS03 full	298	Grade 3	3.7	1.9	6.5	0.0	0.0	1.2	0.0	0.0	1.2
H5N1 split Dresden	292	Total	72.9	67.5	78.0	2.1	0.8	4.4	3.4	1.7	6.2
(HA 30µg) AS03 half	292	Grade 3	1.0	0.2	3.0	0.0	0.0	1.3	0.0	0.0	1.3

N = number of doses followed by at least one solicited symptom sheet completed;

% = percentage of doses followed by a report of the specified symptom;

95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Grade 3 pain = severe pain that prevents normal activity; Grade 3 redness, swelling = largest surface diameter >100mm

**Table 34:** The percentage of doses followed by solicited general symptoms including those of Grade 3 intensity and those considered to be related to vaccination in Study Q-Pan-H5N1-001 (TVC)

Study (schedule)	N	Relationship to Vaccination/ Intensity	Fatigue			Fever			Headache			Muscle aches			Shivering		
			%	95%CI		%	95%CI		%	95%CI		%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	
<b>Q-Pan-001 (2 dose schedule at 0, 21 days) in 18 to 64 years old</b>																	
H5N1 split Quebec (HA 3.8µg) AS03 full	301	Total	29.2	24.2	34.7	1.7	0.5	3.8	31.2	26.0	36.8	36.5	31.1	42.3	8.3	5.4	12.0
	301	Grade 3	2.7	1.2	5.2	0.0	0.0	1.2	3.7	1.8	6.4	4.0	2.1	6.9	2.0	0.7	4.3
	301	Related	28.9	23.8	34.4	1.7	0.5	3.8	27.2	22.3	32.6	35.5	30.1	41.2	8.3	5.4	12.0
H5N1 split Quebec (HA 3.8µg) AS03 half	299	Total	21.7	17.2	26.9	1.7	0.5	3.9	26.4	21.5	31.8	39.8	24.6	35.3	7.7	4.9	11.3
	299	Grade 3	1.0	0.2	2.9	0.0	0.0	1.2	0.7	0.1	2.4	1.3	0.4	3.4	0.0	0.0	1.2
	299	Related	20.7	16.3	25.8	1.0	0.2	2.9	24.1	19.3	29.3	27.4	22.4	32.9	6.4	3.9	9.7
H5N1 split Quebec (HA 3.8µg)	155	Total	12.9	8.1	19.2	0.0	0.0	2.4	20.6	14.6	27.9	11.0	6.5	17.0	3.2	1.1	7.4
	155	Grade 3	1.3	0.2	4.6	0.0	0.0	2.4	0.6	0.0	3.5	0.6	0.0	3.5	0.0	0.0	2.4
	155	Related	12.3	7.5	18.5	0.0	0.0	2.4	18.8	11.3	23.6	10.3	6.0	16.2	3.2	1.1	7.4
H5N1 split Dresden (HA 3.8µg) AS03 full	298	Total	30.2	25.0	35.8	4.0	2.1	6.9	30.2	25.0	35.8	41.6	36.0	47.4	10.4	7.2	14.4
	298	Grade 3	1.3	0.4	3.4	0.0	0.0	1.2	2.3	0.9	4.8	1.0	0.2	2.9	0.3	0.0	1.9
	298	Related	27.5	22.5	33.0	3.7	1.9	6.5	28.2	23.2	33.7	38.6	33.0	44.4	8.7	5.8	12.5
H5N1 split Dresden (HA 30µg/ AS03 half)	291	Total	32.3	27.0	38.0	3.8	1.9	6.7	28.9	23.7	34.4	30.9	25.7	36.6	6.2	3.7	9.6
	291	Grade 3	0.7	0.1	2.5	0.3	0.0	1.9	1.4	0.4	3.5	2.1	0.8	4.4	1.0	0.2	3.0
	291	Related	31.3	26.0	36.9	3.8	1.9	6.7	27.1	22.1	32.6	30.2	25.0	35.9	6.2	3.7	9.6

N = number of doses followed by at least one solicited symptom sheet completed, % = percentage of doses followed by a report of the specified symptom; 95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit  
Grade 3 = severe (symptom that prevents normal activity); Grade 3 fever = >38°C

The results showed that the incidence of solicited local and general symptoms was higher among subjects receiving adjuvanted vaccine; specifically, symptoms such as pain, muscle aches, and fatigue seemed to increase with the addition of adjuvant. However these symptoms were not generally severe. AS03-adjuvanted Q-Pan and D-Pan vaccines presented a similar reactogenicity profile. Adjuvant reduction had only a modest effect on the rate of local reactogenicity of any intensity, but did tend to reduce Grade 3 local symptoms, especially Grade 3 pain. The effects of reduced adjuvant dose on rates of general solicited symptoms showed similar trends to those seen with local symptoms, but the amplitude of the effects were less pronounced.

## Unsolicited AEs

The most commonly reported unsolicited AEs are summarized in the table below.

**Table 35:** Most frequent unsolicited AEs (>2% incidence in any treatment group), by MedDRA preferred term, from Day 0 through 84 (Total vaccinated cohort)

MedDRA Preferred Term	Group A (Q000AS03) N=78	Group B (Q100AS03) N=152	Group C (Q50AS03) N=151	Group D (D100AS03) N=151	Group E (D50AS03) N=148
At least 1 unsolicited event, n (%)	35 (44.9)	77 (50.7)	71 (47.0)	81 (53.6)	89 (60.1)
Nasopharyngitis, n (%)	6 (7.7)	4 (2.6)	14 (9.3)	9 (6.0)	4 (2.7)
Headache, n (%)	3 (3.8)	4 (2.6)	3 (2.0)	13 (8.6)	12 (8.1)
Nausea, n (%)	3 (3.8)	11 (7.2)	6 (4.0)	7 (4.6)	5 (3.4)
Pharyngolaryngeal pain, n (%)	5 (6.4)	5 (3.3)	4 (2.6)	10 (6.6)	7 (4.7)
Upper respiratory tract infection, n (%)	3 (3.8)	5 (3.3)	2 (1.3)	7 (4.6)	8 (5.4)
Back pain, n (%)	3 (3.8)	3 (2.0)	4 (2.6)	6 (4.0)	4 (2.7)
Diarrhea, n (%)	0	4 (2.6)	4 (2.6)	5 (3.3)	5 (3.4)
Lymphadenopathy, n (%)	0	3 (2.0)	3 (2.0)	7 (4.6)	4 (2.7)
Sinusitis, n (%)	0	5 (3.3)	4 (2.6)	2 (1.3)	2 (1.4)
Cough, n (%)	3 (3.8)	2 (1.3)	2 (1.3)	2 (1.3)	3 (2.0)
Dizziness, n (%)	0	4 (2.6)	2 (1.3)	3 (2.0)	3 (2.0)
Myalgia, n (%)	1 (1.3)	0	2 (1.3)	5 (3.3)	3 (2.0)
Pain in extremity, n (%)	0	2 (1.3)	1 (0.7)	5 (3.3)	2 (1.4)
Neck pain, n (%)	1 (1.3)	1 (0.7)	2 (1.3)	2 (1.3)	4 (2.7)
Anemia, n (%)	0	4 (2.6)	2 (1.3)	0	1 (0.7)
Vomiting, n (%)	0	0	0	4 (2.6)	1 (0.7)
Dyspepsia, n (%)	2 (2.6)	0	2 (1.3)	0	1 (0.7)
Gastroesophageal reflux disease, n (%)	2 (2.6)	0	1 (0.7)	0	0
Depression, n (%)	2 (2.6)	0	0	0	0

There was a relatively low incidence of unsolicited AEs in all treatment groups, with no statistically notable difference between adjuvanted and unadjuvanted vaccine. No unsolicited event was reported by more than 6% of subjects overall or more than 10% of subjects in a treatment group by each MedDRA preferred term. As shown above, unsolicited AE reports of lymphadenopathy occurred in 2-5% of recipients of adjuvanted vaccine. These events were mild and transient.

Unsolicited symptoms requiring a medically attended visit (through Day 182) were reported by 21% of subjects overall, with no substantial difference between treatment groups. Only four subjects overall reported unsolicited symptoms that were Grade 3, vaccine-related, and

resulted in a medically attended visit. These included heat exhaustion, fatigue, muscle strain, and nasal congestion.

The AEs with potential immune-mediated causation were reported by < 3% of subjects overall (through Day 182) and were distributed across all treatment groups. The most frequently reported AE in this category was back pain and was reported in eight subjects overall. No subject with back pain had any other complaints suggestive of a neurologic disorder or a generalized arthropathy. One subject reported a breast mass, which was assessed by the investigator as fulfilling the characteristics of new onset chronic diseases (NOCD) (through Day 182).

#### **Serious Adverse Events (SAEs):**

SAEs reported during the entire study period (up to Day 182) following vaccination with Q-Pan or D-Pan vaccine adjuvanted with AS03 in Q-Pan-H5N1-001 were reported. A total of 15 SAEs were reported in six subjects, all in groups receiving adjuvanted vaccine. SAEs included cholelithiasis, pancreatitis, chest pain, basal cell carcinoma, ovarian cyst, uterine leiomyoma, pulmonary embolism, cervical carcinoma, ascites, clostridial gastroenteritis, hematoma, hydronephrosis, pelvic abscess, pleural effusion and rectal perforation. Eight of these events occurred in a single subject, related to cervical carcinoma and complications of its surgical treatment. There have been no SAEs deemed to be treatment-related. No deaths or vaccine-related SAEs were reported during the study (through Day 182).

#### **Withdrawals due to AEs / SAEs:**

No subject experienced an adverse event that led to premature discontinuation of the study vaccine.

#### **Pregnancies:**

Three pregnancies occurred during the course of the trial, including one subject in Group D, and two subjects in Group E. The subject in Group D is known to have delivered a healthy infant; pregnancy outcome information on the other two subjects is pending.

#### **Safety data in Study Q-Pan-H5N1- 002**

All 4561 subjects were included in the Total Vaccinated Cohort (TVC), the primary cohort for analysis of safety. This included 3422 subjects in the Q-Pan group, and 1139 subjects in the placebo group, respectively. In follow-up through approximately 182 days after the first vaccine dose, the majority of enrolled subjects completed the study through Day 182. Only 14 subjects, 7 in the Q-Pan group and 7 in the placebo group, have been withdrawn due to AEs or SAEs.

#### **Solicited AEs**

The four tables below present the incidences of solicited local and general AEs in subjects aged 18-64 and > 64 years old, respectively. The incidence of solicited local and general AEs was higher among subjects receiving Q-Pan vaccine compared to those receiving placebo. Specifically, symptoms such as injection site pain, muscle aches, headache and fatigue were increased in frequency among subjects receiving the candidate Q-Pan vaccine compared to placebo. However, these symptoms were not generally severe. Safety results, stratified by age strata 18-64 and > 64 years old, show that a slightly lower reactogenicity is observed among elderly subjects.

**Table 36:** The percentage of doses followed by solicited local symptoms including those of Grade 3 intensity in subjects aged 18-64 years old in study Q-Pan-H5N1-002 (Total vaccinated cohort)

Study (schedule)	N	Intensity	Pain			Redness			Swelling		
			%	95%CI		%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL	LL	UL	
<b>Q-Pan-002 (2 dose schedule at 0, 21 days) in 18 to 64 years old</b>											
H5N1 Quebec (HA 3.8µg) + AS03	4453	Total	80.5	79.3	81.6	4.9	4.3	5.6	7.1	6.3	7.8
	4453	Grade 3	3.6	3.1	4.2	0.1	0.0	0.2	0.1	0.0	0.2
Placebo	1482	Total	14.0	12.3	15.9	0.5	0.2	1.0	0.5	0.2	1.0
	1482	Grade 3	0.4	0.1	0.9	0.0	0.0	0.2	0.0	0.0	0.2

N = number of doses followed by at least one solicited symptom sheet completed;

% = percentage of doses followed by a report of the specified symptom;

95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Grade 3 pain = severe pain that prevents normal activity; Grade 3 redness, swelling = largest surface diameter >100mm

**Table 37:** The percentage of doses followed by solicited local symptoms including those of Grade 3 intensity in subjects aged older than 64 years in study Q-Pan-H5N1-002 (TVC)

Study (schedule)	N	Intensity	Pain			Redness			Swelling		
			%	95%CI		%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL	LL	UL	
<b>Q-Pan-002 (2 dose schedule at 0, 21 days) in &gt;64 years old</b>											
H5N1 Quebec (HA 3.8µg) + AS03	2194	Total	58.0	55.9	60.1	5.7	4.8	6.8	6.1	5.1	7.2
	2194	Grade 3	0.8	0.5	1.2	0.0	0.0	0.2	0.0	0.0	0.3
Placebo	727	Total	8.0	6.1	10.2	0.1	0.0	0.8	0.1	0.0	0.8
	727	Grade 3	0.3	0.0	1.0	0.0	0.0	0.5	0.0	0.0	0.5

N = number of doses followed by at least one solicited symptom sheet completed;

% = percentage of doses followed by a report of the specified symptom;

95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Grade 3 pain = severe pain that prevents normal activity; Grade 3 redness, swelling = largest surface diameter >100mm

**Table 38:** The percentage of doses followed by solicited general symptoms including those of Grade 3 and those considered to be related to vaccination in subjects aged 18-64 years old in Study Q-Pan-H5N1 -002 (TVC)

Study (schedule)	N	Relationship to Vaccination/ Intensity	Fatigue			Fever			Headache			Muscle aches			Shivering		
			%	95%CI		%	95%CI		%	95%CI		%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	
<b>Q-Pan-002 (2 dose schedule at 0, 21 days) in 18-64 years old</b>																	
H5N1 Quebec (HA 3.8µg) + AS03	4449	Total	27.2	25.9	28.6	2.8	2.3	3.3	27.8	26.5	29.2	39.3	37.8	40.7	12.0	11.0	13.0
	4449	Grade 3	2.1	1.7	2.6	0.6	0.4	0.9	2.1	1.7	2.6	2.3	1.9	2.8	1.3	1.0	1.7
	4449	Related	25.2	24.0	26.5	2.3	1.9	2.8	25.1	23.9	26.4	37.2	35.8	38.6	11.1	10.2	12.1
Placebo	1483	Total	15.8	14.0	17.8	2.4	1.6	3.3	21.3	19.2	23.5	13.3	11.6	15.1	7.1	5.8	8.5
	1483	Grade 3	1.4	0.9	2.2	0.7	0.3	1.2	1.8	1.1	2.6	1.1	0.7	1.8	0.6	0.3	1.1
	1483	Related	13.6	11.9	15.4	1.3	0.8	2.0	17.1	15.2	19.1	11.5	9.9	13.3	5.7	4.6	7.0

Study (schedule)	N	Relationship to vaccination/ Intensity	Sweating			Joint pain at other location		
			%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL
<b>Q-Pan-002 (2 dose schedule at 0, 21 days) in 18-64 years old</b>								
H5N1 Quebec (HA 3.8µg) + AS03	4449	Total	8.2	7.4	9.1	18.8	17.6	19.9
	4449	Grade 3	0.6	0.4	0.9	1.3	1.0	1.7
	4449	Related	7.5	6.7	8.3	17.7	16.6	18.8
Placebo	1483	Total	5.4	4.3	6.7	7.9	6.6	9.4
	1483	Grade 3	0.7	0.4	1.3	0.5	0.2	1.1
	1483	Related	4.2	3.2	5.3	6.7	5.5	8.1

N = number of doses followed by at least one solicited symptom sheet completed; % = percentage of doses followed by a report of the specified symptom;

95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit

Grade 3 = severe (symptom that prevents normal activity); Grade 3 fever = >39°C

**Table 39:** The percentage of doses followed by solicited general symptoms including those of Grade 3 and those considered to be related to vaccination in subjects aged older than 64 years in study Q-Pan-H5N1-002 (TVC)

Study (schedule)	N	Relationship to Vaccination/ intensity	Fatigue			Fever			Headache			Muscle aches			Shivering		
			%	95%CI		%	95%CI		%	95%CI		%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	LL	UL	
Q-Pan-002 (2 dose schedule at 0, 21 days) in >64 years old																	
H5N1 Quebec (HA 3.8µg) + AS03	2190	Total	15.2	13.7	16.8	1.6	1.1	2.2	14.4	12.9	15.9	21.1	19.4	22.8	5.5	4.6	6.5
	2190	Grade 3	0.8	0.5	1.3	0.1	0.0	0.4	0.4	0.2	0.8	0.7	0.4	1.1	0.4	0.2	0.7
	2190	Related	13.5	12.1	15.0	1.1	0.7	1.7	12.4	11.1	13.9	19.7	18.1	21.5	4.8	3.9	5.8
Placebo	727	Total	10.6	8.4	13.1	0.8	0.3	1.8	10.2	8.1	12.6	8.7	6.7	11.0	3.7	2.5	5.4
	727	Grade 3	0.7	0.2	1.6	0.0	0.0	0.5	0.4	0.1	1.2	0.6	0.2	1.4	0.4	0.1	1.2
	727	Related	9.2	7.2	11.6	0.6	0.2	1.4	8.1	6.2	10.3	7.4	5.6	9.6	2.2	1.3	3.5

Study (schedule)	N	Relationship to vaccination/ intensity	Sweating			Joint pain at other location		
			%	95%CI		%	95%CI	
Group			LL	UL	LL	UL	LL	UL
Q-Pan-002 (2 dose schedule at 0, 21 days) in >64 years old								
H5N1 Quebec (HA 3.8µg) + AS03	2190	Total	2.3	1.7	3.1	11.5	10.2	12.9
	2190	Grade 3	0.1	0.0	0.3	0.4	0.2	0.7
	2190	Related	2.1	1.6	2.8	10.3	9.0	11.6
Placebo	727	Total	2.3	1.4	3.7	6.3	4.7	8.3
	727	Grade 3	0.3	0.0	1.0	0.3	0.0	1.0
	727	Related	1.7	0.9	2.9	4.4	3.0	6.2

N = number of doses followed by at least one solicited symptom sheet completed; % = percentage of doses followed by a report of the specified symptom; 95% CI = exact 95% confidence interval; L.L. = lower limit, U.L. = upper limit  
Grade 3 = severe (symptom that prevents normal activity); Grade 3 fever = >39°C

## Unsolicited AEs

The most commonly reported unsolicited AEs are summarized in the table below.

**Table 40:** Most frequent unsolicited AEs (> 2%, in any treatment group, or age stratum), by MedDRA preferred term for Days 0-84 (Total vaccinated cohort)

Preferred Term, n (%)	Q-Pan Overall N = 3422	Placebo Overall N = 1139	Q-Pan 18-64 yrs N = 2304	Placebo 18-64 yrs N = 768	Q-Pan > 64 yrs N = 1118	Placebo > 64 yrs N = 371
At least 1 unsolicited event	1484 (43.4)	451 (39.6)	1017 (44.1)	321 (41.8)	467 (41.8)	130 (35.0)
Nasopharyngitis	156 (4.6)	40 (3.5)	116 (5.0)	29 (3.8)	40 (3.6)	11 (3.0)
Oropharyngeal pain	125 (3.7)	51 (4.5)	91 (3.9)	39 (5.1)	34 (3.0)	12 (3.2)
Headache	101 (3.0)	39 (3.4)	73 (3.2)	31 (4.0)	28 (2.5)	8 (2.2)
Upper respiratory tract infection	100 (2.9)	38 (3.3)	73 (3.2)	25 (3.3)	27 (2.4)	13 (3.5)
Cough	95 (2.8)	34 (3.0)	66 (2.9)	28 (3.6)	29 (2.6)	6 (1.6)
Nausea	98 (2.9)	24 (2.1)	78 (3.4)	20 (2.6)	20 (1.8)	4 (1.1)
Diarrhoea	91 (2.7)	25 (2.2)	57 (2.5)	14 (1.8)	34 (3.0)	11 (3.0)
Sinusitis	73 (2.1)	18 (1.6)	56 (2.4)	13 (1.7)	17 (1.5)	5 (1.3)
Nasal congestion	70 (2.0)	22 (1.9)	59 (2.6)	20 (2.6)	11 (1.0)	2 (0.5)
Back pain	64 (1.9)	22 (1.9)	43 (1.9)	19 (2.5)	21 (1.9)	3 (0.8)
Injection site pruritus	62 (1.8)	4 (0.4)	39 (1.7)	3 (0.4)	23 (2.1)	1 (0.3)
Influenza like illness	46 (1.3)	20 (1.8)	38 (1.6)	12 (1.6)	8 (0.7)	8 (2.2)

The vaccine had a relatively low incidence of unsolicited AEs in all groups. No unsolicited event was reported by more than 4.6% of subjects in a treatment group and the types of events reported most frequently were the same in the Q-Pan and placebo groups. The incidence of unsolicited AEs was slightly lower in the > 64 years age group compared with the 18 to 64 years age group, both in the Q-Pan and placebo groups.

Only ten subjects (six subjects [0.2%] in the Q-Pan group, four subjects [0.3%] in the placebo group) reported unsolicited symptoms that were Grade 3, vaccine-related, and resulted in a medically attended visit (through Day 84), including sinusitis, dizziness, headache, migraine, paraesthesia, throat irritation and erythema in the Q-Pan group (one subject each) and abdominal pain upper, influenza, urinary tract infection and oropharyngeal pain in the placebo group (one subject each). Unsolicited symptoms requiring a medically attended visit

were reported by 22.7% of subjects in the Q-Pan group and 21.6% of subjects in the placebo group, with no obvious difference between treatment groups or age stratum through Day 182. The incidence of unsolicited AE reports of lymph node pain and lymphadenopathy was low overall and not notably different between treatment groups. These events were typically mild and transient.

### **Adverse Events of Special Interest (AESI)**

Overall, eight subjects reported adverse events of special interest (AESI) / potentially immune-mediated disorders (IMDs), including seven subjects (0.2%) in the Q-Pan group and one subject (0.08%) in the placebo group. One subject each in the Q-Pan group reported facial palsy, fourth cranial nerve palsy and erythema nodosum and two subjects each reported psoriasis and polymyalgia rheumatica. One subject in the placebo group reported ocular myasthenia. None of these events was considered serious or vaccine-related by the investigators.

### **Serious Adverse Events:**

There were 119 SAEs reported in 88 subjects (67 of 3422 in the Q Pan group [1.9%], 21 of 1139 [1.8%] in the placebo group) through Day 182; none were considered by the investigator to be related to study vaccine. Four deaths occurred in Q-Pan subjects due to the SAEs of myocardial infarction, metastases to the liver and metastatic ovarian cancer, malignant neoplasm, aggravated diabetes mellitus and exacerbation of liver disease. Two deaths occurred in placebo subjects due to SAEs of malignant brain neoplasm and cardiomegaly.

### **Withdrawals due to AEs/SAEs:**

Nine subjects (four Q-Pan subjects [0.1%] and five placebo subjects [0.4%]) experienced an SAE that led to premature discontinuation from the study. Only five subjects (three Q-Pan subjects [0.1%] and two placebo subjects [0.2%]) experienced a non-serious AE that led to premature discontinuation from the study. There was no imbalance in the frequencies of withdrawals due to AE between the treatment groups.

### **Pregnancies:**

Three subjects became pregnant during the initial period of the study (through Day 42). Two underwent elective abortions for reasons unrelated to the study; one subject in the placebo group delivered a healthy term infant who developed complications in the perinatal period which were all considered to be resolved, except for an atrial septal defect, at the cut-off date for this report. Nine additional subjects became pregnant between Days 43 and 182. First notification for all of these pregnancies occurred after the interval covered by this report (28 January 2008 - 15 October 2008). Two subjects delivered healthy infants at term and another subject underwent elective abortion for socioeconomic reasons. Follow-up of the remaining six subjects continues.

### **Safety data in supportive studies**

Given the close similarity between the Q-Pan and D-Pan vaccines (both were formulated with the same content of H5N1 split virus antigens and containing the same dosage of AS03 adjuvant), Studies D-Pan-H5N1-002, -007, -008 are included in the dossier as supportive data to the safety of the Q-Pan candidate vaccine.

The safety profile of the D-Pan vaccine in Study D-Pan-H5N1-002, -007, and -008 had been evaluated in the previous submissions to the TGA. Overall, the safety profile of the D-Pan vaccine was found to be comparable across the groups and studies. Although a higher

reactogenicity was observed with the adjuvanted vaccine as compared to the non-adjuvanted formulation across the three studies, incidences of solicited local and general symptoms of Grade 3 intensity were low. No marked differences were observed between groups receiving different antigen doses (Study D-Pan-H5N1-007), suggesting that the observed increased reactogenicity of the vaccine is essentially attributable to the presence of the adjuvant. Although unsolicited symptoms considered to be related to vaccination tended to be more frequently reported in the adjuvanted groups as compared to the non-adjuvanted groups, incidences reported remained low.

Of note, the safety data for follow-up to Day 180 in Study H5N1-008 indicated a higher incidence of NOCD in the elderly vaccinated group (1.8%) compared to the elderly control group (0%). Although the numbers were small, it is noteworthy that all cases (7/390) occurred in the vaccinated group compared with none (0/129) in the control group. The imbalance (all cases occurred in the vaccine group) in NOCD in elderly subjects, despite small numbers, was considered as a potential safety signal.

### Integrated Summary of Safety (ISS)

An Integrated Summary of Safety (ISS) was developed based on the first 9,873 adults across eight completed clinical trials in adults performed with the AS03 adjuvanted H5N1 Q-Pan or D-Pan vaccine. These include the five studies already mentioned (Q-Pan-H5N1-001, Q-Pan-H5N1-002, D-Pan H5N1-002, -007, -008). The remaining three additional studies (D-Pan-H5N1-010, H5N1-012 and H5N1-015) were conducted with D-Pan vaccine. Taken altogether, the safety database obtained with AS03 H5N1 vaccine (Q-Pan and D-Pan) is based on a total of 9873 vaccinated subjects, allowing to identify with 99.3% confidence any AEs occurring at a frequency of at least 0.05%.

**Table 41:** Overview of three additional studies with D-Pan AS03-adjuvanted H5N1 vaccine, included in the Q-Pan and D-Pan integrated summary of safety

Study number(s) (Country)	Study period (FSFV-LSLV)	Age range	Majority race	Blinding	H5N1 strain	Control Agent(s)	N per formulation	Number of doses (interval)
H5N1-010/-021 (Belgium, Italy)	02MAR2007-06MAR2008	61-89 years	White/Caucasian	open	A/Vietnam/1194/2004	H5N1 antigen	7.5+diluent = 52 3.8+diluent = 61 7.5+2/1 AS03 = 159 3.8+1/1 AS03 = 165	2 (21 days)
H5N1-012 (Germany)	05FEB2007-08NOV2007	18-60 years	White/Caucasian	open	A/Vietnam/1194/2004 or A/Indonesia/5/2005	Non-controlled	3.8+1/1AS03 = 512 (2 doses/21 day interval = 255)	2 (6 months)† 2 (12 months)† 3 (21 days/6 months)† 3 (21 days/12 months)†
H5N1-015 (Belgium)	02AUG2007-29NOV2007	19-61 years	White/Caucasian	open	A/Indonesia/5/2005	Non-controlled	3.8+1/1 AS03 = 350 (300 primed subjects + 50 unprimed subjects††)	1 or 2 (21 days)

FSFV = first subject, first visit; LSLV = last subject, last visit; N= number of subjects enrolled and vaccinated

Formulations: vaccine formulations are indicated in quantity of HA (µg) administered; 2/1 indicates double dose AS03 adjuvant, 1/1 indicates full dose AS03 adjuvant, 1/2 indicates half dose AS03 adjuvant; diluent = saline solution

† Third dose data and second dose data (when this dose is administered at an interval of 6 months), were not included in the integrated analysis, which considers only primary dosing series.

†† Only unprimed subjects will be included in the integrated analysis

For the integrated summary of safety, two different analyses were performed:

- Analysis 1 was performed on data obtained in the two studies that incorporated concurrent non-H5N1 controls, either a licensed trivalent influenza vaccine (*Fluarix*) or placebo, in blinded designs: respectively D-Pan-H5N1-008/011 and Q-Pan-H5N1-002.
- Analysis 2 was performed on data across the eight completed study database, that is, Q-Pan-H5N1-001, Q-Pan-H5N1-002, D-Pan-H5N1-002, D-Pan-H5N1-007, D-Pan-H5N1-008/011, D-Pan-H5N1-010/021, D-Pan-H5N1-012 and D-Pan-H5N1-015.



Analysis 2 included a total of 12,281 subjects; with 9873 subjects administered H5N1/AS03 vaccine.

### **Local and systemic solicited AEs**

Analysis 1 data were used to analyse all solicited AEs and the results of the analysis showed that both local and systemic solicited AEs are clearly increased relative to control preparations following H5N1/AS03 doses. However, they do not appear to worsen with consecutive doses, are predominantly mild or moderate in severity and are apparently tolerable to subjects.

### **Unsolicited adverse events**

All unsolicited AEs were evaluated in Analysis 1 and Analysis 2 for the period including Days 0 to 50 after Dose 1 and Days 0 to 29 after Dose 2, a time period for which a uniform dataset containing all AEs was available in all studies.

Among unsolicited AEs, eight MedDRA Preferred Terms (PTs) were associated with an increased relative Risk (RR: lower limit of 95% CI for  $RR \geq 1.0$ ) among H5N1/AS03 recipients in contrast to controls. Injection site reaction, injection site warmth, injection site pruritus, malaise, nausea and insomnia demonstrate increased RR in both Analyses 1 and 2. All have a close temporal association with injections, are transient and differ little in duration when H5N1/AS03 and control group cases are compared. The sponsor considers these as elements of short-term reactivity.

### **Medically-attended adverse events (MAEs) and SAEs**

MAEs and SAEs were evaluated in Analysis 1. As a class, MAEs do not occur with disproportionate frequency among H5N1/AS03 recipients relative to controls, nor do subsets such as Grade 3 MAEs, vaccine-related MAEs, or Grade 3 and vaccine-related MAEs. Every Preferred Term (PT) for which MAEs occurred in  $> 0.1\%$  of the H5N1/AS03 population occurred at a generally similar (or greater) rate among control recipients, with substantial overlap in 95% CIs.

Similar considerations apply to the SAE dataset. The two most common SAE PTs, appear to be over-represented in the H5N1/AS03 group: myocardial infarction in five H5N1/AS03 subjects and no control subjects, and pneumonia in six H5N1/AS03 subjects and one control subject. However, consideration of all SAE PTs indicative of coronary artery disease leads to a more balanced distribution: seven of 7224 subjects in the H5N1/AS03 group (0.1%) versus four of 2,408 subjects in the control group (0.2%). Similarly, the inclusion of the PTs of "pneumonia bacterial" and "pneumonia pneumococcal" with the term "pneumonia" yields a contrast of six of 7224 subjects in the H5N1/AS03 group (0.1%) versus three of 2408 subjects in the control group (0.1%).

Overall, there is no apparent increased incidence of either MAEs or SAEs among H5N1/AS03 recipients, nor is there an obvious clustering of MAEs or SAEs in a particular Primary System Organ Class among H5N1/AS03 recipients.

### **Adverse Events of Special Interest (AESI):**

AESI or pIMDs (potential Immune-Mediated Disease) were evaluated in Analysis 1 and Analysis 2. Fourteen AESI/pIMDs occurred in the H5N1/AS03 group in Analysis 1 and 16 in Analysis 2. This is in contrast with one such event among control subjects.

Of the 17 cases reported in total, there is no obvious concentration for any of the antigens, with nine cases in subjects that received vaccine derived from Dresden antigen and 7 cases in subjects that received vaccine derived from Quebec antigen. The antigen dose that the subjects received was 15 µg (7 subjects), 7.5 µg (1 subject) or 3.75 µg (8 subjects), and no unusual concentration appeared in any of those dose groups (relative to the proportion of subjects contributing to the database). All subjects in the H5N1/AS03 group received a full dose of AS03, with the exception of the subject in Study H5N1-010, who received both a double dose of AS03 adjuvant and antigen.

A limitation of the ISS analysis is the 3:1 treatment allocation. In order to provide a more meaningful comparison to the H5N1/AS03 group, the sponsor also evaluated the AESI/pIMDs in a pool of clinical trial data from five trials where 11,721 subjects had received either saline placebo or licensed seasonal trivalent inactivated influenza vaccine. The trials selected included all clinical trials since 2004 that used the Company's licensed seasonal trivalent inactivated influenza vaccines and/or placebo controls in observer-blind controlled designs and included approximately 6 months of safety follow-up for at least medically-attended AEs. The dataset mimicked the control and H5N1/AS03 groups in the ISS closely in terms of demographics, in terms of test article exposure and in duration of safety follow-up. The subject incidence rate of the aggregate AESI/pIMDs in this historical control dataset was 18 of 11,721 subjects, which is similar to that seen for the H5N1/AS03 recipients in the Analysis 1 or Analysis 2 datasets. When the proportions of H5N1/AS03 recipients with AESI/pIMDs from Analysis 1 or Analysis 2 were compared to the proportions of subjects with AESI/pIMDs in the control groups, no significant differences were observed, as shown in the table below.

**Table 42:** Proportions of H5N1/AS03 recipients with AESI/pIMDs contrasted to various control datasets

	H5N1/AS03 Group	Control Group	p value*
<b>Analysis 1 Data Only</b>	<b>N = 7224</b>	<b>N = 2408</b>	
Subjects with Any AESI/pIMD	14	1	0.137
<b>Analysis 2 Data Only</b>	<b>N = 9873</b>	<b>N = 2408</b>	
Subjects with Any AESI/pIMD	16	1	0.223
<b>Analysis 1 H5N1/AS03 vs. Recent Trials Dataset</b>	<b>N = 7224</b>	<b>N = 11721</b>	
Subjects with Any AESI/pIMD	14	18	0.585
<b>Analysis 2 H5N1/AS03 vs. Recent Trials Dataset</b>	<b>N = 9873</b>	<b>N = 11721</b>	
Subjects with Any AESI/pIMD	16	18	1.00
<b>Analysis 1 H5N1/AS03 vs. All Control Data</b>	<b>N = 7224</b>	<b>N = 14129</b>	
Subjects with Any AESI/pIMD	14	19	0.357
<b>Analysis 2 H5N1/AS03 vs. All Control Data</b>	<b>N = 9873</b>	<b>N = 14129</b>	
Subjects with Any AESI/pIMD	16	19	0.609

\* Fisher's exact test

Overall, no unexpected findings were revealed in the ISS analysis; in particular, the analysis of AESI/pIMDs and a comparison with historical clinical trials databases did not provide any strong evidence to support a causal relationship between the incidence of AESI/pIMD and the use of AS03 adjuvanted H5N1 vaccine. However, the limited number of events in each study precludes an assessment of consistency, and the available data are considered insufficient to either confirm or refute the causal relationship. The association between the occurrence of these rare AESI/pIMD events and the use of the vaccine can neither be established nor ruled out.

## Post-marketing experience

Not applicable.

## Evaluator's overall conclusions on clinical safety

The safety profile of the Q-Pan H5N1 vaccine has been assessed in the two pivotal studies. The results showed that there was an increased local and general reactogenicity with the adjuvanted Q-Pan or D-Pan vaccine when compared to the non-adjuvanted formulations or placebo. However, the incidences of Grade 3 symptoms were low and no qualitatively unexpected AEs were reported. Symptoms reported after vaccination with Q-Pan vaccine were mostly mild to moderate, and resolved within a few days. No reported SAE was considered as vaccine-related. It is noted that there was an apparent disparity in the incidence of AESI/pIMDs in Study Q-PAN-002, with seven events in the Q-Pan group (0.2%) and one in the placebo group (0.08%).

Safety data from studies conducted with D-Pan vaccine (H5N1-007, H5N1-008 and H5N1-002) are considered supportive for the safety profile of the candidate Q-Pan vaccine. In these three studies, a total of 4963 subjects were administered 9772 doses of adjuvanted D-Pan vaccine, among which 405 subjects aged > 60 years old (Study H5N1-008). The previous evaluation of Study H5N1-008 indicated a higher incidence of NOCD in the elderly vaccinated group (1.8%) compared to the elderly control group (0%). The imbalance (all cases occurred in the vaccine group) was considered as a potential safety signal.

An integrated safety analysis performed across eight completed adult trials evaluating either Q-Pan or D-Pan adjuvanted vaccines is also provided to further confirm the safety profile of the candidate Q-Pan vaccine. The ISS analysis did not reveal any unexpected safety findings, and the analysis of AESI/pIMDs indicate that there was no strong evidence to support a causal relationship between the use of AS03 adjuvanted H5N1 vaccine (Q-Pan or D-Pan) and the incidence of AESI /pIMDs.

## List of Questions

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

A number of questions were raised by the TGA during the evaluation phase and satisfactory answers were provided by the sponsor.

## Clinical Summary and Conclusions

The two pivotal studies (Q-Pan-H5N1-001 and 002) demonstrated that the selected dose and formulation of the Q-Pan candidate vaccine (3.75 µg antigen with full strength of AS03 adjuvant) is able to elicit a strong immune responses against the vaccine strain and the Day 42 HI responses (SPR, SCR, and SCF) exceeded all three CHMP criteria. The two studies involved adults greater than 18 years old and Q-Pan-H5N1002 also have data in more than 500 subjects aged > 60 years old.

The capacity of the candidate Q-Pan vaccine to induce cross-reactive immune response against a heterologous strain of A/Vietnam /1194/2004 was assessed in terms of HI antibodies and neutralising antibodies in Q-Pan-H5N1-001. The HI and MN results (at Day 42) showed that comparing to the immune response against the homologous vaccine strain, the immune response against the heterologous strain (A/Vietnam /1194/2004) was lower in magnitude, but was still indicative of induction of the cross-reactive immunity. Study Q-Pan-H5N1-001 also showed that Q-Pan H5N1 vaccine could induce neutralising antibodies against another two draft strains (A / Anhui and A / turkey/Turkey) in a reasonable

percentage of the vaccinated subjects. Similar responses against A/Vietnam/1194/2004 strain measured by neutralizing antibodies were also observed in Q-Pan-H5N1- 002.

The persistence of the immune response up to 6 months after vaccination with Q-Pan vaccine have been generated in younger adults up to 64 years and in a cohort of approximately 100 elderly aged > 60 years. The results showed that the immune response at Day 182 was lower than that on Day 42, and the SPR values no longer fulfilled the CHMP criteria, although more than 50% of the vaccine recipients retained reciprocal HI titers  $\geq 40$  (SPR) against the vaccine strain at Day 182. The HI responses against the drift variant (A/Vietnam) were much lower at Day 182 and remain only marginally higher among recipients of adjuvanted vaccine than un-adjuvanted vaccine antigen.

It is acknowledged that the criteria currently set for immunological assessment of inter-pandemic influenza vaccines may not necessarily be valid for pandemic influenza vaccines, however, given that there are no other criteria available for assessing pandemic influenza vaccines, assessment by the same endpoints as for seasonal influenza vaccines was the approach recommended by the EMEA (see CPMP/VEG/4717/03).

With regards to safety, the incidence of the solicited local and general AEs appeared to be similar with the Q-Pan and D-Pan H5N1 vaccines (Study Q-Pan-001). Of note, there was an apparent disparity in the incidence of AESI/pIMDs in Study Q-PAN-002, with seven events in the Q-Pan group (0.2%) and one in the placebo group (0.08%). There were a number of rare reported cases of AESI / pIMD in subjects vaccinated with Q-Pan or D-Pan vaccine in the ISS analysis, however, the casual relationship with the vaccination has not been established. The sponsor added the comment that the incidence of reports of AESIs/pIMDs was low and there was no statistically significant difference in the incidence or types of AESIs/pIMDs reported between subjects who received AS03-adjuvanted vaccine and control groups.

No paediatric data are submitted with the current submission.

## **Risks and benefits assessment**

### **Benefits**

Vaccination against potentially pandemic viruses is one of the ways in which such a pandemic may be mitigated; it is also one of the key options by which the severity of symptoms caused by the pandemic influenza infection may be reduced. In a pandemic situation, vaccination, among other possible containment strategies, is considered as instrumental to protect population against avian influenza infection.

The Q-Pan candidate vaccine has been shown to be highly immunogenic, inducing a strong immune response against homologous as well as heterologous H5N1 virus strains. By the use of the AS03 adjuvant, the required antigen dose is 3.75  $\mu\text{g}$  which is less than 10% of the total antigen content of a single seasonal vaccine dose; this would allow production of a large number of vaccine doses in a limited time frame. The registration of the Q-Pan H5N1 vaccine would make it possible for the GSK to extend its manufacturing capacities, the huge demand for pandemic vaccines can therefore be met in an officially declared pandemic situation.

### **Risks**

The data from the pivotal Q-Pan studies, supportive D-Pan studies, and the ISS analysis showed that the Q-Pan H5N1 candidate vaccine has an acceptable safety profile in adults aged 18 and older. There were a number of rarely reported cases of AESI/pIMD in subjects vaccinated with Q-Pan or D-Pan vaccine, however, the casual relationship has not been

established. The sponsor commented that cases of AESIs/pIMDs were also reported in subjects who received unadjuvanted vaccine or placebo.

### **Conclusion regarding risks / benefits balance**

Based on the above evaluation, the benefit and risk profile of the Q-Pan candidate vaccine is considered acceptable, especially when it is only to be used in an official declared pandemic situation.

### **RECOMMENDATION**

The clinical evaluator recommended the approval for the registration of Arepanrix H5N1 vaccine for the following indication:

“Prophylaxis of influenza in an official declared pandemic situation.

Arepanrix H5N1 vaccine should be used in accordance with official recommendations.”

The registration approval should be subject to:

Revision of the proposed Product Information document to the satisfaction of the TGA

- The results of all the ongoing clinical trials should be submitted to the TGA as they become available
- Compliance with the pharmacovigilance plan as agreed with the Office of Medicines Safety Monitoring

## **V. Pharmacovigilance Findings**

### **Risk Management Plan**

#### **Summary of ongoing safety concerns**

#### **Important identified risks**

No important risks were identified in the adult clinical studies included in the integrated safety analysis. At the request of European Medicines Agency (EMA), fever in children is included in the Risk Management Plan (RMP) as an identified risk, although only limited data are available.

#### **Important potential risks**

It is indicated that the AESIs specified in the CHMP guideline are considered as potential theoretical risks. Also, at the request of EMA, autoimmune hepatitis (AIH) and increased concentrations of hepatic enzymes are included as potential theoretical risks.

#### **Important missing information**

It is stated that missing or incomplete information comprises the following:

- Safety data in children, pregnant women, individuals with clinically severe underlying medical conditions, and immunocompromised individuals; and
- Efficacy or effectiveness of the pandemic vaccine, which is not possible to evaluate prior to the circulation of an H5N1 influenza strain.

**OPR Comment:** As aforementioned, reference to children is queried given that the vaccine is not indicated in this age group. Also, the relevance of the Pandemrix H1N1 vaccine narcolepsy reports for the QPAN H5N1 vaccine is queried, and hence whether there is a consequent potential safety concern.

#### **Proposed pharmacovigilance actions and plan**

The CHMP recommendations for Pharmacovigilance (PhV) plans for pandemic influenza vaccines (PIVs) specify activities to be carried out once a pandemic has been declared. This includes modified activities based on spontaneous reporting and additional activities based on post-marketing studies.

### Summary of the risk management plan

The summary of the RMP provided by the sponsor is presented in the table below.

**Table 43:** Risk Management Plan

Potential theoretical safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anaphylaxis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs†</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 1/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindication in the proposed labelling</li> <li>• Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components</li> </ul>
Autoimmune hepatitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 20/100,000 doses distributed</li> </ul> </li> </ul>	NA*
Bell's palsy	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 24/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Convulsion	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 3,000/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Demyelinating disorders	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds published incidence rate</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Encephalitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance               <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 7/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA

Table continued on the next page.

Guillain-Barré syndrome	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed</li> <li>○ Active monitoring in collaboration with national groups/agencies</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Increased concentrations of hepatic enzymes	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if signal detected</li> </ul> </li> </ul>	NA
Neuritis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds published incidence rate</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vasculitis	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> <li>○ Ad hoc analyses if reporting rate exceeds 2/100,000 doses distributed</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vaccination failure	<ul style="list-style-type: none"> <li>• Enhanced pharmacovigilance <ul style="list-style-type: none"> <li>○ Weekly signal detection</li> <li>○ Use of targeted follow-up questionnaires</li> <li>○ Individual reports expedited to regulators</li> <li>○ Included in Table 3 of simplified PSURs</li> <li>○ Cumulative analysis included in full PSUR following end of pandemic period</li> </ul> </li> <li>• Incidence will be estimated in participants of the post-authorisation safety study</li> </ul>	NA
Vaccine effectiveness	GSK Biologicals will obtain data from ECDC vaccine effectiveness studies	NA
Fever in children	<ul style="list-style-type: none"> <li>• Additional clinical trial (Q-Pan-021)</li> <li>• Routine pharmacovigilance</li> <li>• Cumulative analysis in full PSUR prepared after the pandemic period</li> </ul>	Safety data indicating higher incidence of fever in the undesirable effects section of the proposed labelling
Missing data in pregnant women	Routine pharmacovigilance, including follow-up of cases of pregnancy: <ul style="list-style-type: none"> <li>• spontaneously reported by patients and HCPs</li> <li>• enrolled/observed during post-authorisation safety study</li> <li>• observed during clinical trials</li> <li>• reported via Pregnancy Registry</li> </ul>	NA
Missing data in children	<ul style="list-style-type: none"> <li>• Clinical trial Q-Pan-021</li> <li>• Post-authorisation safety study (depending on vaccination policy)</li> </ul>	Statement in proposed labelling that there is limited experience in children
Limited data in subjects with compensated underlying conditions; No data in subjects with severe underlying medical conditions and immunocompromise	<ul style="list-style-type: none"> <li>• Routine pharmacovigilance</li> <li>• Post-authorisation cohort study: individuals will be included based on national recommendations, underlying medical conditions will be documented for <i>post hoc</i> analyses</li> </ul>	NA

Routine pharmacovigilance practices involve the following activities:

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

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

**OPR Comment:** It is recommended to the Delegate that the sponsor should update the RMP summary to include reference to safety concerns regarding medication errors, contamination of multi dose vials and coring of the rubber stopper in the antigen vial.

## CONCLUSION AND RECOMMENDATIONS TO THE DELEGATE

This is a clearly presented RMP. However, there is lack of clarity about use of the vaccine in children, additional information that should be included and issues to consider. The key concerns are that:

- Fever in children is presented as an identified risk even though the vaccine is not indicated for use in this age group;
- It is not indicated how additional PhV activities would be undertaken if first use of the vaccine occurred in the Southern Hemisphere including Australia; and
- The proposed PI is non-specific and no Consumer Medicines Information (CMI) was provided.

It is recommended to the Delegate that the sponsor should:

### 1. Indicate whether the Pandemic Influenza Vaccine will be available as single dose syringe and/or multi-dose vials

*Sponsor response:* Arepanrix H5N1 will not be supplied as single dose syringe. With pandemic influenza vaccines, multi-dose vials will be used, as was made available with Pandemrix H1N1 and Arepanrix H1N1 vaccines.

### 2. Clearly state whether the vaccine is indicated for use in children and, if not, how the EMA recommendation to specify fever in children as an identified safety concern will be considered.

*Sponsor response:* Use in children is not being proposed with this current application for Arepanrix H5N1. Therefore the EMA recommendation to specify fever in children as an identified safety concern is not applicable to the Arepanrix H5N1 registration in Australia.

### 3. Consider the relevance of the Pandemrix H1N1 vaccine narcolepsy reports for the QPan H5N1 vaccine

*Sponsor response:* As of 28 Oct 2010, four reports of narcolepsy after Arepanrix H1N1 have been received. All of the reports were from a single reporter in Canada, and were received as a letter to the editor of *Sleep*. The number of reports of narcolepsy received after Arepanrix is less than the number of reports expected, given the historical incidence rate in Canada and the number of individual vaccinated. With regards to the narcolepsy reports received in Europe following Pandemrix H1N1 administration, GSK and the EMA have each concluded that the information available is insufficient to assess the likelihood of a causal relationship between Pandemrix H1N1 and narcolepsy. Efforts, including observational studies, to further investigate this matter are ongoing.

### 4. Indicate which reports will be expedited taking into account TGA policy

*Sponsor response:* GlaxoSmithKline Australia complies with the reporting requirements of adverse events of the “Australian Guideline for Pharmacovigilance Responsibilities of sponsors of registered medicines regulated by TGA”. For Arepanrix H5N1 too, this guideline will be complied with.

### 5. Provide the case definitions and questionnaires that will be used for AESIs

*Sponsor response:* The case definitions, or references to the published Brighton Collaboration case definitions, are already included in the RMP under the discussions of each of the events.



**6. Specify how the vaccine effectiveness, post-authorisation studies, paediatric investigation plan and pregnancy register will be undertaken if the vaccine is first used in Australia**

*Sponsor response:* All of these are parts of the H1N1 requirements for Europe. It is not clear how any of them would be implemented in Europe for H5N1, as this will be considered (by EMA) after the results from H1N1 are available and evaluated.

**7. Provide the protocols, including statistical analysis plans for vaccine effectiveness and post-authorisation cohort studies and studies in the paediatric investigation plan**

*Sponsor response:* The Company will provide the requested information when an application to register use of Arepanrix H5N1 in children is submitted in Australia.

**8. Provide the pregnancy register data elements and proposed approach to analysis of these data**

*Sponsor response:* For H1N1, this is an EU requirement for a registry in the EU. As discussed above, we speculate that this may be clarified for H5N1 after the H1N1 registry and data from the study are available and analysed and would not be before third quarter of 2011.

**9. Indicate whether the type of activity recommended by the CHMP for rare events is being considered; if it is under consideration details of the proposed activity should be provided; if it is not being considered, reasons for this should be presented.**

*Sponsor response:* We have not been able to engage the EMA in discussions about future, potential H5N1 activities.

**10. Provide information on the outcome of the effectiveness review regarding the additional activities undertaken with the H1N1 vaccine, indicate whether these will occur with the H5N1 vaccine, and if they are not planned specify the reasons for this.**

*Sponsor response:* We do not know if we will be able to have the same risk minimization activities for future pandemic vaccines. The European Union (EU) review of these activities is ongoing for Pandemrix

**13. Prepare H5N1 specific PI and CMI that:**

- Clearly indicate the situation around the use in children taking into account the EMA requirement to include fever in children as an identified risk;
- Specify populations where there is missing information and implications of this for vaccine use; and
- Includes post marketing experience with the Arepanrix H1N1 Vaccine

*Sponsor response:* The Arepanrix H5N1 PI and CMI have been amended to clearly state that:

- it is for use in adults greater than 18 years only
- there is limited experience for use with children
- post marketing experience with H1N1 pandemic vaccines is included

**VI. Overall Conclusion and Risk/Benefit Assessment**

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

## Quality

Arepanrix H5N1 is based on A/Indonesia/5/2005 strain of H5N1 produced using reverse genetics wherein the HA & NA<sup>7</sup> genes are contributed by H5N1 and the backbone is from A/PR/8/34 which is also used in seasonal reassortants. The drug substance is prepared from virus grown in chicken eggs. Clinical lots have been tested.

The proposed shelf life is the antigen and adjuvant vial is 18 months and 36 months respectively stored at 2-8°C. The product was presented to the 132<sup>nd</sup> meeting of Pharmaceutical Subcommittee (PSC) held on 24 May 2010. The Committee was unable to recommend approval at that stage and has agreed to consider it further. The committee was concerned about the bioburden and the use of multi-dose vials and recommended that the sponsor also be asked to provide the following, in addition to other matters raised by the TGA evaluators:

- **Provide validation data on the most recent three consecutive batches for both the drug substance and the drug product.**
- **Carry out post-filling dye tests also on the antigen vials and to repeat the tests on both the antigen and adjuvant vials at the end of their shelf life.**

The TGA's quality evaluators have since reviewed response from the sponsor and report that the bioburden levels of the intermediates are higher than TGA would prefer. The application went back to the November 2010 meeting of PSC for another review:

In this meeting, the PSC agreed that the main issues of concern raised at its 132<sup>nd</sup> meeting held May 2010 were still unresolved. In particular, the PSC considers that the absence of data on pre- and post filter integrity testing; the high bioburden action limit proposed for the antigen and even higher bioburden limit for the adjuvant emulsion and the sponsor's continued reliance on precedence as a justification for not improving and/or updating its processes with regards to sterility aspects do not instil confidence in this product.

The PSC reiterated its objection to the multi-dose vial presentation of this product.

The PSC agreed that the attention of the Advisory Committee on Prescription Medicines (ACPM) should be drawn to the issues in relation to squalene and the high incidence of narcolepsy.

The PSC therefore concluded that the approval of this application should be based on clinical data.

## Nonclinical

The nonclinical dossier was appropriately based on H5N1 data. However, the initial intention of the sponsor was to register Arepanrix H1N1 vaccine. The nonclinical evaluation report thus refers to Arepanrix H1N1. This should be disregarded as it is now intended that Arepanrix H5N1 mock-up vaccine will be registered.

The nonclinical dossier relies on previously submitted data for Pandemrix H5N1 based on Vietnam strain as well as data based Indonesia strain and new data generated with Q-Pan.

The nonclinical evaluators conclude that immunogenicity and protective efficacy have been demonstrated in animals as was the ability of the adjuvant to increase the immune response. The report also noted the inflammatory response due to adjuvant. The data were consistent with the applicable European guidelines and considered sufficient to support the registration.

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<sup>7</sup> Neuraminidase

## Clinical

### Efficacy:

The outcomes in a previous dose ranging study previously with Pandemrix H5N1 (StudyD-Pan-H5N1- 007) was used to carry forward the 3.75µg-adjuvanted dose for manufacture of the new vaccine. A new dose ranging study was not conducted with Arepanrix H5N1. This is considered acceptable.

The dossier was also cross-referenced to the previous clinical studies with Pandemrix H5N1 (Studies D-Pan-H5N1-002 and 008). These three studies have been previously evaluated by the TGA and have been considered by the (then) Australian Drug Evaluation Committee (ADEC) in connection with Pandemrix H5N1 vaccine.

Arepanrix H5N1 was studied in two new clinical trials: Q-Pan-H5N1- 001 and Q-Pan-H5N1-002.

For Study Q-Pan-H5N1- 001, the reported results included HI<sup>8</sup> and MN<sup>9</sup> outcomes against homologous (vaccine) and heterologous strains on Days 21 and 42.

For Study Q-Pan-H5N1- 002, the reported results included HI and MN responses against the homologous (vaccine) and heterologous strains on Day 42.

Persistence of immunity was also assessed (Day 182) in both studies.

In the absence of known correlates of protective efficacy against H5N1 infection/disease in humans, the serological correlates used for seasonal influenza vaccines are used for the assessment of H5N1 (mock-up) vaccines.

Based on European Guidelines which the TGA has adopted, these correlates are (1) SCR<sup>10</sup> (> 40% in adults, > 30% in elderly) (2) SCF<sup>11</sup> (> 2.5 in adults, > 2.0 in elderly), and (3) SPR<sup>12</sup> (> 70% in adults, > 60% in elderly) using HI assay. HI titre of 1:40 is considered protective in the case of seasonal influenza, where the population is expected to possess some degree of partial immunity.

Please note also that FDA criteria are more conservative by preferring to use lower limit of 95% confidence interval rather than point estimates. However, the European guidelines require that pandemic flu vaccines must pass all three criteria instead of any one as is the case with seasonal flu vaccines.

Please see the Clinical Evaluation Report (CER) for details of the results.

In Study Q-Pan-H5N1- 001, the candidate vaccine (3.75µg-adjuvanted formulation) fulfilled all three CHMP criteria on Day 42 that is, 21 days after completion of two doses of vaccination given 21 days apart (see Table 31).

The results for MN were as follows:

<sup>8</sup> Haemagglutination Inhibition (antibodies using)

<sup>9</sup> Microneutralisation (antibodies using)

<sup>10</sup> Seroconversion Rate

<sup>11</sup> Seroconversion Factor (fold increase)

<sup>12</sup> Seroprotection Rate

**Table 44:**

Days post vaccination	Viral strain against which MN response was measured	MN response (%)		
		≥ 1:28	≥ 1:40	≥ 1:80
Day 21	Vaccine strain (A/Indonesia)	100	93.6	80.9
	heterologous strain (A/Vietnam)	100	97.9	95.7
Day 42	Vaccine strain (A/Indonesia)	100	100	100
	heterologous strain (A/Vietnam)	100	100	95.7

The pre-vaccination titres indicate that the studied population was naive (Tables 8 & 12) with respect to HA antigen indicating its specificity compared to sizeable proportion of participants (1/3) having neutralising antibodies at baseline (Tables 10 & 11).

For MN response at Day 182, please see Tables 18 & 19, which indicates drop in titres to will below those after Dose 2 but above those after Dose 1.

For MN responses to other variants (Anhui & Turkey) please see Tables 15 & 16.

In Study Q-Pan-H5N1-002, the lot to lot consistency between Q-Pan and D-Pan vaccine was satisfactorily demonstrated in pairwise statistical comparison (Table 22).

The immunogenicity results in Study Q-Pan-H5N1- 002 are tabulated in Table 30 above.

The three CHMP criteria were fulfilled on Day 42 in both age strata (18-60 years old and > 60 years old) following completion of two doses of vaccine given 21 days apart. The values had dropped by day 182 in both groups but the three criteria were still nominally met except seroprotective rate in 18-60 years age group which was below 70%. This was similar to that seen previously in the study 001. The placebo control validates the HA naive population at the start and the subsequent immune response to the vaccine.

As in Study Q-Pan-H5N1-001, there was a significant level of pre-existing neutralising antibodies especially in the elderly group (> 60 years age). At Day 42, 96-100% participants had titres above 1/80 for the homologous vaccine strain (Indonesia):

**Table 45:**

Study (Age vaccination)	Age group	Time-point	Study group	N	≥ 1:28		≥ 1:40		≥ 1:80				
					%	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	178	100	18.1	91.1	18.5	13.9	24.0	11.8	8.0	18.5
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	179	100	97.9	100	100	98.3	100	100	98.3	100
	>60 years	Pre	Q-Pan H5N1 (3.8µg) Indonesia + AS03	58	100	63.7	84.2	62.5	50.7	73.3	44.8	33.3	56.5
		Post II (D42)	Q-Pan H5N1 (3.8µg) Indonesia + AS03	56	100	91.8	98.9	98.2	91.8	98.9	95.4	89.2	99.4

The pre-existing neutralising antibodies and heterologous (Vietnam strain) response to vaccination at Day 42 were as seen in Table 27 above.

**Safety:**

The combined safety experience with Arepanrix in the above two clinical studies consists of 7048 doses of the candidate vaccine in 2456 recipients. The safety follow-up included solicited adverse events (AE) within 7 days of a vaccine dose, unsolicited AEs within 21 days, and follow-up for SAEs (and other medically attended events, events of special interest such as potentially immune mediated disease or new onset of chronic disease) up to 182 and 364 days in Studies Q-Pan 001 and 002 respectively.

In Study Q-Pan-H5N1001, the reported AEs included:

**Table 46:**

(%)	Q-Pan zero adjuvant	Q-Pan ½ adjuvant	Q-Pan full adjuvant	D-Pan full adjuvant	D-Pan ½ adjuvant
Solicited AEs					
Pain	14.8	74.9	81.7	85.2	72.9
Redness	0.0	0.7	2.3	4.0	2.1
Swelling	0.0	3.7	6.0	9.1	3.4
Fatigue	12.9	21.7	29.2	30.2	32.3
Fever	0.0	1.7	1.7	4.0	3.8
Headache	20.6	26.4	31.2	30.2	28.9
Muscle ache	11.0	39.8	36.5	41.6	30.9
Shivering	3.2	7.7	8.3	10.4	6.2
At least one unsolicited AE	44.9	47.0	50.7	53.6	60.1
Lymphadenopathy	0	2.0	2.0	4.6	2.7

Overall, 21% participants required medically attended visit and < 3% were reported with potentially immune-mediated event through to the Day 182 with no differences between the groups. One instance of breast mass was reported. Fifteen SAEs included eight in a single individual. None were considered treatment related. No deaths were reported. There were three reports of pregnancies (D-Pan) with healthy baby delivered in one and information pending in others.

In Study Q-Pan-H5N1002, the reported AEs included:

**Table 47:**

(% )	Q-Pan		Placebo	
	18-64 years	> 64 years	> 64 years	18-64 years
Solicited AEs				
Pain	80.5	58.0	8.0	14
Redness	4.9	5.7	0.1	0.5
Swelling	7.1	6.1	0.1	0.5
Fatigue	27.2	15.2	10.6	15.8
Fever	2.8	1.6	0.8	2.4
Headache	27.8	14.4	10.2	21.3
Muscle aches	39.3	21.1	8.7	13.3
Shivering	12.0	5.5	3.7	7.1
Sweating	8.2	2.3	2.3	5.4
Joint pain at other location	18.8	11.5	6.3	7.9
At least one unsolicited AE	44.1	41.8	35.0	41.8
Influenza like illness	1.6	0.7	2.2	1.6

The percentage requiring medically attended visit was 22.7% in Q-Pan compared to 21.6% in placebo through to the Day 182. Eight participants reported AEs of special interest or potentially immune related of which seven were in Q-Pan group and included one participant each reporting facial palsy, 4<sup>th</sup> cranial nerve palsy and erythema nodosum, and two participants each reporting psoriasis and polymyalgia rheumatica. The one instance of report in placebo group was ocular myasthenia. A total of 119 SAEs were reported in 88 participants [67 (1.9%) in Q-Pan and 21 (1.8%) in placebo] through to the Day 182 and were not considered treatment-related by the sponsor. Four deaths occurred in Q-Pan and two deaths in placebo group during the study (CER Table 13B). Three pregnancies were reported during the study. Two underwent elective termination and the third delivered a baby with unresolved atrial septal defect at the time of reporting (placebo group). Nine more pregnancies were reporting between Days 43-182. Two healthy deliveries and one elective termination were reported with the outcome pending in the remaining six cases.

An integrated safety analysis of all eight Q/D-Pan studies is also included in the CER.

### Emerging safety issues: post market data

A number of cases of narcolepsy have been reported in Europe in association with the use of Pandemrix H1N1 vaccine. The EMA last posted information on its website on 23 September 2010 concluding<sup>13</sup> that the available evidence did not confirm a link and more information was being gathered. The analysis was based on 81 reports from health professionals through spontaneous reporting; 34 from Sweden, 30 from Finland, 10 from France, 6 from Norway, and one from Portugal. In addition, 13 consumer reports from Sweden and two from Norway were also received. The EMA communiqué suggested that Pandemrix H1N1 has been used in at least 30.8 million Europeans.

<sup>13</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Press\\_release/2010/09/WC500096998.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096998.pdf)

The sponsor has also been in communication with the TGA, most recently in October 2010 providing updated safety assessment current to 20 September 2010. The narcolepsy case reports tally now stands at 83.

This issue has likely implications for all Pandemrix and Arepanrix H5N1 products as well because this effect has not been reported with other H1N1 vaccines.

The issue is currently being assessed and may also require input from the Advisory Committee of Safety of Medicines (ACSOM).

However, pending finalisation of attribution of causality and quantification of risk, it seems advisable that this occurrence be acknowledged in the Arepanrix and Pandemrix PI documents.

### **Risk Management Plan**

The RMP has been evaluated by the Office of Product Review and the sponsor is requested to address the OPR comments in its Pre-ACPM response.

### **Risk-Benefit Analysis**

This is an application for a new manufacturing site. In the context of a biological product a full developmental dossier was required and the product is treated as a new entity (Arepanrix H5N1). The related registered product is Pandemrix H5N1 vaccine which has same specifications, indications and directions for use.

The data provided in the quality, toxicology and clinical dossiers were consistent with European requirements for pandemic influenza vaccines. The H5N1 vaccine is a mock-up vaccine implying that the actual product to be used in the event of a pandemic is expected to be based on a different strain but for which it will serve as a model.

The registration of mock-up vaccines is intended to expedite the process of updating vaccine strain and supply in an actual pandemic situation. In Australia, however, it is understood that new immunogenicity data and dosing information will be required for such updates.

The influenza virus A/H5N1, which causes highly lethal infection in humans and has been circulating in water birds for many years, has so far not domesticated to pigs or humans. In light of accumulating knowledge about the reassortment of H1N1, there is increased awareness among scientific community that heightened surveillance of pig herds is needed. The H1N1 2009 strain is now widely circulating in humans and in its current form no longer considered pandemic potential. It is also now part of trivalent seasonal influenza vaccines.

The immunogenicity data obtained in Studies Q-Pan 001 and 002 with Arepanrix were consistent with those previously seen with Pandemrix. All CHMP criteria were satisfactorily met after two doses of vaccine using HI assay, but not after Dose 1. The immunity drops to post-Dose 1 level at 6 months mark.

The use of functional antibody measurements such neutralising titre is generally preferred for establishing serological correlates of protection against clinical infection or disease. However, such correlate has never been established for influenza.

The serological correlates using HA antibodies (measured by HI or SRH<sup>14</sup>) continue to be used for seasonal flu vaccines.

As has been noted in the past in registering pandemic influenza vaccines, it is reasonable to extrapolate these criteria to avian strains such as H5N1. However, for a strain which is not

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<sup>14</sup> Single Radial Haemolysis

circulating in humans (naive population), the validity of such criteria remains unknown. The regulatory guidelines require concomitant measurement of neutralising antibodies. The functional neutralising antibodies response in Studies Q-Pan 001 and 002 was also similar to that known previously as well as between vaccines manufactured at Dresden or Quebec.

Similarly, the adverse effects profile in Studies Q-Pan 001 and 002 was unchanged relative to that seen previously as well as between Dresden and Quebec products. The solicited adverse events clearly point towards dose effect and adjuvant effect.

The long term consequences of ASO3 adjuvant system, if any, are unknown. Its use is associated with heightened immune response as reflected in the smaller amount of antigen (3.75µg per adult dose) required which is considered an advantage from supply point of view. Please note that an ASO3 based vaccine (Arepanrix H1N1) has only now been used extensively in Europe in unselected population. In this context any long-term effects as well as the significance of reports of narcolepsy remain of interest. To the extent of knowledge of prescription medicines area in TGA, there has not been any supply of Arepanrix H1N1 in Australia (such as through avenues for supply of unregistered medicines).

The Advisory Committee on Prescription Medicines (ACPM) is requested to comment and provide guidance to the following matters, in addition to any other issue which it may take up:

- Quality aspects.
- Multi-dose vials: it is not clear whether single dose vials are feasible and what kind of quality data may be needed for a product supplied as separate antigen & adjuvant multi-dose vials which are mixed at the time of administration. The sponsor may wish to address this in its pre-ACPM response. Please note that Pandemrix H5N1 and H1N1 have been approved as multi-dose vials.
- Advice and any input into the reports of narcolepsy associated with Arepanrix H1N1 vaccine in Europe.

## **PROPOSED ACTION**

Pending consideration by the ACPM and subject to satisfactory resolution of product quality aspects, the Delegate proposes to approve of the application PM-2009-03131-3-2 for registration of Arepanrix H5N1 pandemic influenza vaccine manufactured in Quebec. The vaccine is supplied in multi-dose vials (antigen and adjuvant separately) such that each 0.5mL of mixed vaccine contains 3.75µg HA antigen adjuvanted to ASO3 complex.

The vaccination schedule is two IM doses (0.5mL each) given at least 21 days apart in adults 18 years old and above.

The Committee's advice is requested.

## **Response from Sponsor (1-5)**

### **1. Manufacturing Issues raised by PSC**

PSC is requesting tighter limits for bioburden limits of antigen intermediates. It should be noted that the pre-filtration bioburden action limit for monovalent bulks of Arepanrix H5N1 are in line with that approved for the other pandemic influenza vaccines, Pandemrix H5N1 and Pandemrix H1N1.



In view of the characteristics of the filter units employed to sterile filter the H5N1 drug substance, the Company considers that the limit of  $\geq 10$ CFU/10mL (equivalent to 100CFU/100mL) prior to the pre-filtration through a bacteria-retaining filter provides an acceptable sterility assurance level for the product comparable to or exceeding the limit of 10 CFU/100mL commonly used in the pharmaceutical industry for aseptically manufactured products.

To further demonstrate the safety margin with respect to bioburden removal a risk assessment based on the ICH Guideline Q5A (appendix 5)<sup>15</sup> was made and submitted to the TGA.

## **2. Non Clinical Data**

Non clinical data has been presented on both Pandemrix H5N1 and Arepanrix H5N1 and considered sufficient to support registration of Arepanrix H5N1. The labelling recommendations in the TGA's non-clinical evaluation report have been reviewed and Arepanrix H5N1 PI amended accordingly.

## **3. Clinical Efficacy Data**

Two pivotal studies (Q-Pan-001 and Q-Pan-002) demonstrated that Arepanrix H5N1 is able to elicit a strong immune response against the vaccine strain and met the CHMP criteria for the immunological endpoints (seroprotective rate, seroconversion rate and seroconversion factor) of a pandemic influenza vaccine.

Persistence of the immune response up to 6 months after vaccination with Arepanrix H5N1 was also demonstrated.

The labelling recommendations in the TGA's clinical evaluation report have been reviewed and Arepanrix H5N1 PI amended accordingly.

## **4. Safety**

No unexpected safety findings were identified with the clinical trials submitted with Arepanrix H5N1 application.

Following the use of H1N1 pandemic vaccines in 2009/10, post-marketing experience with AS03-containing vaccines containing 3.75 µg HA derived from A/California/7/2009 H1N1, Pandemrix H1N1 and Arepanrix H1N1 are now available.

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<sup>15</sup> ICH Topic Q 5 A (R1) Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. CPMP/ICH/295/95.  
[www.ema.europa.eu/pdfs/human/ich/029595en.pdf](http://www.ema.europa.eu/pdfs/human/ich/029595en.pdf)

We would like to state that Arepanrix H1N1 was not marketed/supplied in Australia or in Europe, but only in Canada.

We confirm that all the recently EU reported narcolepsy reports were following administration of Pandemrix H1N1 only. Therefore the statements in the Delegate's Overview regarding narcolepsy reports with Arepanrix H1N1 are incorrect.

As of 28 Oct 2010, 4 reports of narcolepsy after Arepanrix H1N1 have been received. All of the reports were from a single reporter in Canada, and were received as a letter to the editor of *Sleep*. The number of reports of narcolepsy received after Arepanrix H1N1 is less than the number of reports expected, given the historical incidence rate in Canada and the number of individual vaccinated.

With regards to the narcolepsy reports received in Europe following Pandemrix H1N1 administration, GSK and the EMA have each concluded that the available information is insufficient to assess the likelihood of a causal relationship between Pandemrix H1N1 and narcolepsy. Efforts, including observational studies, to further investigate this matter are ongoing.

## **5. Risk Management Plan**

The questions raised in the RMP evaluation have been responded to as a separate response. The major concerns highlighted in the RMP evaluation were clarification of pharmacovigilance processes in a pandemic situation and use in paediatrics.

It should be noted that the EU H5N1 RMP that we provided was prepared without guidance from the EMA.

Following the recent experience with Pandemrix H1N1, the registry details and findings are still being analysed and reviewed by both the company and EMA. Once these evaluations have been completed, it is likely that due consideration to developing requirements for H5N1 will be developed in consultation with the EMA.

We anticipate that the Pandemrix H5N1 and Arepanrix H5N1 RMP will be revised when more specific guidance is available and we commit to providing the TGA with a copy of the updated Arepanrix H5N1 RMP when available.

As the current Arepanrix H5N1 application is only for use in adults, the requested information on paediatric trials is not being provided.

### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

1. ACPM recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register the new chemical entity pandemic influenza A H5N1 inactivated, split-virion,

ASO3 adjuvanted monovalent vaccine (AREPANRIX) suspension for injection 2.5 mL vial with adjuvant emulsion 2.5 mL vial for the indication:

*Prophylaxis of influenza in an officially declared pandemic situation.*

*Arepanrix should be used in accordance with official recommendations.*

In making this recommendation the ACPM considered that the risk benefit profile was appropriate to support the proposed indication. However, the ACPM advised that the incidence of narcolepsy reported with Pandemrix H1N1 vaccine in Europe was not a clear safety signal. The ACPM noted the concern raised by the sponsor in relation the feasibility of complying with strict bioburden limits for multi dose vials.

The ACPM expressed concern about the lack of paediatric data as this population group would be vulnerable in a declared epidemic and noted the sponsor's undertaking on this matter.

2. The specific conditions of registration should include:

Specific inclusion in the Risk Management Plan (RMP) of:

The continuation of the monitoring of the adverse event continuum of sleepiness to narcolepsy.

Use in paediatric population.

3. Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

- Amendments in the Dosage and Administration section to ensure the safe use of multi dose vials.
- Amendments in the Precautions and Side-Effects section on the possibility of sleepiness and narcolepsy as adverse events.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Arepanrix H5N1 pandemic influenza vaccine suspension for injection (2.5mL vial with adjuvant emulsion 2.5mL vial), indicated for:

*Prophylaxis of influenza in an officially declared pandemic situation.*

*Arepanrix H5N1 should be used in accordance with official recommendations.*

### **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## **PRODUCT INFORMATION**

### **Arepanrix™ H5N1 Pandemic Influenza Virus Vaccine (split virion, inactivated, AS03 adjuvanted)**

#### **NAME OF THE MEDICINE**

Arepanrix H5N1 Pandemic Influenza Virus Vaccine ( split virion, inactivated, AS03 adjuvanted).

#### **DESCRIPTION**

Suspension and emulsion for combination into an emulsion for injection.

The antigen composition will be determined depending on the strain for the pandemic influenza that will be recommended by the World Health Organisation (WHO).

Each 0.5mL vaccine dose contains 3.75 micrograms<sup>1</sup> of antigen<sup>2</sup> of the recommended strain and is adjuvanted with AS03<sup>3</sup>.

<sup>1</sup>haemagglutinin

<sup>2</sup>propagated in eggs

<sup>3</sup>The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL- $\alpha$ -tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

Each 0.5mL vaccine dose also contains the excipients thiomersal, sodium chloride, sodium phosphate dibasic, potassium phosphate monobasic, potassium chloride and water for injections. The vaccine may also contain the following residues: egg residues including ovalbumin, formaldehyde, sucrose and sodium deoxycholate.

#### **CLINICAL PHARMACOLOGY**

##### **Clinical Trials**

Clinical studies have been generated with H5N1 strain with pandemic potential.

##### **Immune response against A/Indonesia/5/2005 (H5N1) strain**

Two clinical studies have evaluated the immunogenicity of Arepanrix H5N1 containing the A/Indonesia/5/2005 (H5N1) strain in subjects from the age of 18 years onwards following a 0, 21 days schedule.

In study Q-Pan-001, the immunogenicity of Arepanrix H5N1 containing the A/Indonesia/5/2005 (H5N1) strain up to twenty-one days after the second dose was evaluated in more than 1,500 subjects 18-60 years and above 60 years of age.

The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) twenty-one days after the second dose were as follows:

Table 1: Anti-HA antibodies against vaccine strain at Day 21 after second dose (Study Q-Pan 001)

anti-HA antibody	Against A/Indonesia/5/2005	
	18-60 years	>60 years
Seroprotection rate* <sup>1</sup>	91%	76.8%
Seroconversion rate <sup>2</sup>	91%	76.4%
Seroconversion factor <sup>3</sup>	51.4	17.2

\*anti-HA  $\geq$ 1:40

<sup>1</sup>seroprotection rate (i.e. proportion of subjects with HI titre  $\geq$  1:40);

<sup>2</sup>seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq$  1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

<sup>3</sup>seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

Percentage of subjects with a 4-fold increase in serum neutralising antibody titre twenty-one days after the second dose was 94.4% for the subjects aged 18-60 years and 80.4% for the subjects over 60 years of age.

In another clinical study, (Q-Pan-002), where different formulations of Arepanrix H5N1 containing the A/Indonesia/5/2005 (H5N1) strain were compared, a group of subjects aged 18-64 years (N=145) received 3.75  $\mu$ g HA/AS03 per 0.5 ml. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) twenty-one days after the first and second dose were as follows:

Table 2: Anti-HA antibodies against vaccine strain at Day 21 after first and second doses (Study Q-Pan 002)

anti-HA antibody	Against A/Indonesia/5/2005	
	21 days after 1 <sup>st</sup> dose	21 days after 2 <sup>nd</sup> dose
Seroprotection rate* <sup>1</sup>	41.7%	97.2%
Seroconversion rate <sup>2</sup>	41.7%	97.2%
Seroconversion factor <sup>3</sup>	4.5	92.9

\*anti-HA  $\geq$ 1:40

<sup>1</sup>seroprotection rate (i.e. proportion of subjects with HI titre  $\geq$  1:40);

<sup>2</sup>seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq$  1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

<sup>3</sup>seroconversion factor (i.e. ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody titres was observed in 76.6% of subjects at day 21 and 97.9% at day 42.

#### Persistence of immunogenicity:

In the study Q-Pan-002, persistence of immunogenicity up to 6 months after the second dose was also evaluated. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.6%, 54.6% and 5.6. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 91.5% of subjects.

#### Cross-reactivity

The candidate vaccine showed the ability to induce a cross-reactive immune response against A/Vietnam/1194/2004.

In the study Q-Pan-001, percentage of subjects with a 4-fold increase in serum neutralising antibody titre twenty-one days after the second dose was 65.5% for the subjects aged 18-60 years and 24.1% for the subjects over 60 years of age.

In the study Q-Pan-002, the seroprotection rate, seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody were as follows:

Table 3: Anti-HA antibodies against vaccine strain A/Vietnam/1194/2004 at Day 21 after first and second doses (Study Q-Pan 002)

anti-HA antibody	Against A/Vietnam/1194/2004	
	21 days after 1 <sup>st</sup> dose	21 days after 2 <sup>nd</sup> dose
Seroprotection rate* <sup>1</sup>	15.3%	63.9%
Seroconversion rate <sup>2</sup>	13.2%	61.8%
Seroconversion factor <sup>3</sup>	1.9	7.6

\*anti-HA  $\geq$  1:40

<sup>1</sup>seroprotection rate (i.e. proportion of subjects with HI titre  $\geq$  1:40);

<sup>2</sup>seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of  $\geq$  1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre);

<sup>3</sup>seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

A 4-fold increase in serum neutralising antibody titres was obtained in 44.7% of subjects twenty-one days after the first dose, 53.2% twenty-one days after the second dose and 38.3% six months after the second dose.

#### Information from non-clinical studies

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically with A/Indonesia/05/05 (H5N1) using ferret challenge models.

#### Challenge with a homologous pandemic H5N1 strain (A/Indonesia/5/05)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing three different doses of H5N1 antigen (7.5, 3.8 and 1.9  $\mu$ g of HA antigen) adjuvanted with the standard dose or half dose of AS03. Control groups included ferrets immunized with adjuvant alone and non-adjuvanted vaccine (7.5 micrograms HA). Ferrets immunized with the non adjuvanted H5N1 influenza vaccine were not protected from death and showed similar lung viral loads and degree of viral shedding in the upper respiratory tract as those exhibited by ferrets immunized with the adjuvant alone. Conversely the combination of a range of doses of H5N1 antigen with AS03 adjuvant was able to protect against mortality and to reduce lung virus loads and viral shedding after intra-tracheal challenge with a homologous wild type H5N1 virus. Serological testing indicated a direct correlation between vaccines induced HI and neutralising antibody titres in protected animals compared to antigen and adjuvant controls.

### Challenge with a heterologous pandemic H5N1 strain (A/Hong Kong/156/97)

In this protection experiment, the ferrets (six ferrets/group) were immunized intramuscularly with vaccine candidate containing four different doses of H5N1 antigen (3.75, 1.5, 0.6 and 0.24 µg of HA antigen) adjuvanted with half dose of AS03. In addition, one group of six ferrets were immunized with vaccine candidate containing 3.75 µg H5N1 + full dose of AS03 and one control group included ferrets immunized with non-adjuvanted vaccine (3.75 micrograms HA). The results of this heterologous challenge study indicate 80.7%-100% protection in all adjuvanted candidate vaccines compared to 43% protection with the non adjuvanted vaccine, showing the benefit of AS03 adjuvantation.

### **INDICATIONS**

Prophylaxis of influenza in an officially declared pandemic situation.

Arepanrix H5N1 should be used in accordance with official recommendations.

### **CONTRAINDICATIONS**

History of an anaphylactic reaction (i.e. life-threatening) to any of the constituents or trace residues of this vaccine. (Also see Precautions section).

### **PRECAUTIONS**

Caution is needed when administering this vaccine to persons with a known hypersensitivity (other than anaphylactic reaction) to the active substance, to any of the excipients and to residues.

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

If the pandemic situation allows, immunisation should be postponed in patients with severe febrile illness or acute infection. However, healthcare providers need to assess the benefits and potential risks of administering the vaccine to those patients.

Arepanrix H5N1 should under no circumstances be administered intravascularly or intradermally.

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

A protective immune response may not be elicited in all vaccinees.

#### **Effects on Fertility:**

There were no effects on the mating performance or fertility of female rats in a reproductive and developmental toxicity study in which rats were intramuscularly injected with Arepanrix H5N1 (1.5 µg H5 antigen, 0.1mL AS03) 28 days prior to mating, and on gestation days 7, 9, 12 and 16, and postnatal day 7 (see also Use in Pregnancy).

**Carcinogenicity:**

No carcinogenicity studies have been conducted with Arepanrix H5N1 or AS03 adjuvant.

**Genotoxicity:**

In standard genotoxicity tests, AS03 adjuvant was not mutagenic in *Salmonella typhimurium*, *E. coli* WP2uvrA, or mouse lymphoma L5178Y cells *in vitro*, nor did it induce micronuclei in rat bone marrow erythrocytes *in vivo*.

**Use in Pregnancy (Category B2):**

No data have been generated in pregnant women with Arepanrix H5N1 and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with interpandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine.

In a reproductive and developmental toxicity study in which female rats were intramuscularly injected with Arepanrix H5N1 (1.5 µg H5 antigen, 0.1mL AS03) 28 days prior to mating, and on gestation days 7, 9, 12 and 16, and postnatal day 7, there were no significant toxicological effects on the dams, or their foetuses or pups. Anti-H5 antibodies were detected in all vaccine-treated females, and their foetuses and pups.

Healthcare providers need to assess the benefits and potential risks of administering the vaccine to pregnant women.

**Use in Lactation:**

No data have been generated in breast-feeding women.

In a reproductive and developmental toxicity study with Arepanrix H5N1 in female rats, maternal treatment prior to mating, during gestation and lactation had no effects on pup development, assessed to lactation day 25. There was evidence of transfer of maternal antibodies to pups (see also Use in Pregnancy).

**Interactions**

No data are available on the concomitant administration of Arepanrix H5N1 with other vaccines. Therefore, Arepanrix H5N1 is not intended to be given at the same time as other vaccines. However, if co-administration with another vaccine is indicated, immunisation should be carried out on separate limbs. It should be noted that the adverse reactions may be intensified.

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



False positive ELISA serologic tests for HIV-1, Hepatitis C, and especially HTLV-1 may occur following influenza vaccination. These transient false-positive results may be due to cross-reactive IgM elicited by the vaccine. For this reason, a definitive diagnosis of HIV-1, Hepatitis C, or HTLV-1 infection requires a positive result from a virus-specific confirmatory test (e.g, Western Blot or immunoblot).

## **ADVERSE REACTIONS**

### **Clinical Trial Experience**

Clinical studies have been generated with H5N1, strain with pandemic potential.

These studies have evaluated the incidence of adverse reactions in approximately 3,800 subjects from the age of 18 years onwards who received Arepanrix H5N1 containing A/Indonesia/5/2005 (H5N1) strain with at least 3.8 µg HA.

The reactogenicity of vaccination was solicited by collecting adverse events using standardised forms for 7 consecutive days following vaccination with Arepanrix H5N1 or placebo (Day 0 to Day 6). The average frequencies of solicited local and general adverse events reported within 7 days after vaccination dose are presented below:

Table 4: Percentage of doses followed by Solicited Local or General Adverse Events within 7 days of any vaccination with Arepanrix H5N1 (Total Vaccinated Cohort)

	<b>AREPANRIX H5N1</b>	<b>Placebo</b>
<b>Local</b>	<b>N = 6647 doses</b>	<b>N = 2209 doses</b>
Pain	73.1	12.0
Swelling	6.7	0.4
Redness	5.25	0.4
<b>General</b>	<b>N = 6639 doses</b>	<b>N = 2210 doses</b>
Muscle Aches	31.4	10.2
Headache	20.9	14.2
Fatigue	21.4	12.1
Joint Pain	15.2	6.0
Shivering	9.0	4.6
Sweating	5.7	3.3
Fever, ≥38°C	1.9	1.0

A clinical study evaluated also the reactogenicity in children 3 to 5 and 6 to 9 years of age who received either a full or a half dose of an AS03-adjuvanted vaccine manufactured using a different process and containing 3.75 µg HA derived from A/Vietnam/1194/2004 (H5N1). In addition to the solicited adverse reactions reported for adults (Table 4), solicited adverse reactions

reported very commonly in this age group were injection site induration, drowsiness, irritability and loss of appetite.

Undesirable effects reported are listed within body systems and categorised by frequency according to the following definitions:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data).

**Blood and lymphatic system disorders:** Uncommon: lymphadenopathy

**Psychiatric disorders:** *Uncommon:* insomnia

**Nervous system disorders:** *Uncommon:* dizziness, paraesthesia

**Ear and labyrinth disorders:** *Uncommon:* vertigo

**Respiratory, thoracic and mediastinal disorders:** *Uncommon:* dyspnoea

**Gastrointestinal disorders:** *Common:* nausea, diarrhoea; *Uncommon:* abdominal pain, vomiting, dyspepsia, stomach discomfort

**Skin and subcutaneous tissue disorders:** *Uncommon:* pruritus, rash

**Musculoskeletal and connective tissue disorders:**

*Uncommon:* back pain, musculoskeletal stiffness, neck pain, muscle spasms, pain in extremity

**General disorders and administration site conditions:** *Uncommon:* injection site reactions (such as bruising, induration, pruritus, warmth), asthenia, chest pain, malaise

### **Post Marketing Data**

No post-marketing surveillance data are available following Arepanrix H5N1. In addition to the adverse reactions reported in the clinical trials, the following have been reported during post-marketing experience with AS03-containing vaccines containing 3.75  $\mu\text{g}$  HA derived from A/California/7/2009 (H1N1):

**Immune system disorders:** Anaphylaxis, allergic reactions

**Nervous system disorders:** Febrile convulsions

**Skin and subcutaneous tissue disorders:** Angioedema, generalised skin reactions, urticaria

In addition, from Post-marketing surveillance with inter-pandemic trivalent vaccines, the following additional adverse events have been reported:

**Blood and lymphatic system disorders:** Transient thrombocytopenia.

**Nervous system disorders:** Neuralgia, convulsions, neurological disorders, such as encephalomyelitis, neuritis and Guillain Barré syndrome.

**Vascular disorders:** Vasculitis with transient renal involvement.

## **DOSAGE AND ADMINISTRATION**

### **Dosage**

Adults from the age of 18 years onwards should receive two doses of Arepanrix H5N1, the first administered at an elected date, the second at least three weeks after the first dose for maximum efficacy.

Vaccination should be carried out by intramuscular injection.

### **Populations**

#### ***Children***

The experience of Arepanrix H5N1 in children is limited.

### **Method of Administration**

Arepanrix H5N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The suspension is a colourless light opalescent liquid. The emulsion is a whitish homogeneous liquid.

Prior to administration, the two components should be mixed.

#### **Instructions for mixing and administration of the vaccine:**

1. Before mixing the two components, the emulsion and suspension should be shaken and inspected visually for any foreign particulate matter and/or abnormal physical appearance.
2. The vaccine is mixed by withdrawing the contents of the vial containing the emulsion by means of a syringe and by adding it to the vial containing the suspension.
3. After the addition of the emulsion to the suspension, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of Arepanrix H5N1 (5 ml) after mixing corresponds to 10 doses of vaccine.
5. The vial should be shaken prior to each administration.
6. Each vaccine dose of 0.5 ml is withdrawn into a syringe for injection. The vaccine should be allowed to reach room temperature before use.
7. The needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

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

### **OVERDOSAGE**

Insufficient data are available.

For advice on management of over dosage, please contact the Poisons Information Centre on 131126

### **STORAGE**

Arepanrix H5N1 must be stored in a refrigerator between +2°C and +8°C and be protected from light. DO NOT FREEZE.

The expiry date of the vaccine is indicated on the label and packaging. The shelf life of Arepanrix H5N1 is 18 months for antigen vial and 3 years for adjuvant vial from the date of manufacture if stored between temperatures of +2°C and +8°C.

After mixing, the vaccine should be used within one working day.

### **PRESENTATIONS**

2.5 ml suspension in a vial (type I glass) for 10 doses with a stopper. Pack size of 50.  
2.5 ml emulsion in a vial (type I glass) for 10 doses with a stopper. Pack size of 25 X 2.

### **MANUFACTURER:**

ID Biomedical Corporation of Quebec  
2323 Parc Technologique Blvd  
Sainte Foy QC G1P4R8  
Canada

### **DISTRIBUTED IN AUSTRALIA BY:**

GlaxoSmithKline Australia Pty Ltd,  
Level 4,  
436 Johnston Street,  
Abbotsford, Victoria, 3067.

Date of TGA approval: 10 February 2011

Arepanrix™ is a trademark of the GlaxoSmithKline group of companies.

Version 1.0

## **Therapeutic Goods Administration**

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