Australian Government

Department of Health and Ageing

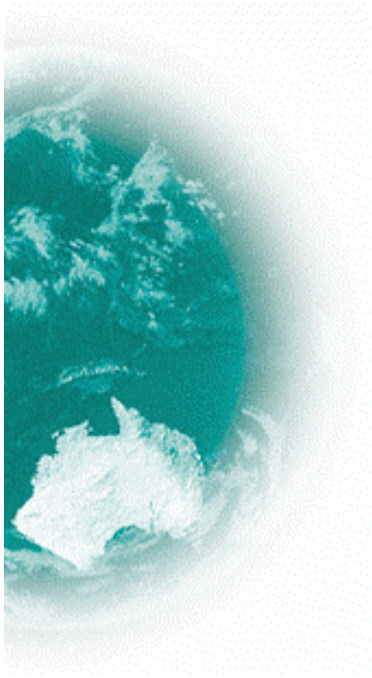
Therapeutic Goods Administration

Australian Public Assessment Report for Pandemrix

Proprietary Product Name: Pandemic H1N1 influenza vaccine

Submission No: PM-2009-03526-3-2

Sponsor: GlaxoSmithKline Australia Pty Ltd



October 2010

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation
Decision:	Approved
Date of Decision:	9 August 2010
Active ingredient(s):	Influenza Virus Haemagglutinin [H1N1]
Product Name(s):	Pandemrix H1N1 pandemic influenza vaccine
Sponsor's Name and Address:	GlaxoSmithKline Australia, 436 Johnston Street, Abbotsford, Victoria, 3067
Dose form(s):	Solution
Strength(s):	3.75 µg HA/dose
Container(s):	Two containers: 1 multidose vial contains antigen suspension 1multidose vial contains adjuvant emulsion The two components must be mixed prior to administration
Pack size(s):	50 doses per carton
Approved Therapeutic use:	Prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official recommendations.
Route(s) of administration:	Intramuscular injection
Dosage:	Adults [18-60 yr] to receive one or two doses, at least three weeks apart.
ARTG number(s):	174554

Product Background

In this application, GlaxoSmithKline Australia Pty Ltd (GSK) seeks the registration approval of Pandemrix vaccine which is an influenza vaccine formulated against the H1N1 "swine flu" strain. It is analogous to the seasonal influenza vaccines.

This is a Category 1 application for major variation. The sponsor seeks the registration of Pandemrix H1N1 vaccine as a strain variation to Pandemrix, the H5N1 vaccine. In June 2008, Pandemrix, the H5N1 vaccine, was registered in Australia for the prophylaxis of influenza in an officially declared pandemic situation. Pandemrix H5N1 vaccine was developed as a 'mock-up' vaccine using a H5N1 strain derived from A/Vietnam/1194/2004. It is a split virion, inactivated, AS03 adjuvanted H5N1 vaccine containing 3.75µg HA derived from A/Vietnam/1194/2004 strain. The registration of a 'mock-up' pandemic vaccine as part of a strategy to allow rapid updating of strain information in the event of a pandemic[1].

[1] EMEA, Committee for Medicinal Products for Human Use (CHMP), 18 December 2008. Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (revision). (EMEA/CHMP/VEG/4717/2003-Rev.1).

Pandemrix H1N1 vaccine has the same adjuvant component and manufacture site as the Pandemrix H5N1vaccine. Following the start of the H1N1 pandemic, the company replaced the virus strain in Pandemrix H5N1 with the H1N1 strain causing the 2009 pandemic, the A/California/7/2009 (H1N1)v-like virus. A/California/7/2009(H1N1)v-like is recommended by the World Health Organization (WHO) and approved by the Australian Influenza Vaccine Committee as the viral strain used to manufacture vaccine for combating the current H1N1 pandemic.

Regulatory Status

Pandemrix H1N1 vaccine is currently registered in the WHO, the European Union (EU; approved on 29 September 2009), Singapore (approved on 15 October 2009) and Switzerland (approved on 23 October 2009). Pandemrix H1N1 vaccine has now been used widely in many countries including Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Israel, Malaysia, Netherlands, Norway, Singapore, Spain, Sweden, Switzerland, and the United Kingdom (UK).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Purified haemagglutinin [HA] fraction of A/California/7/2009 [H1N1]-like strain [v NYMC X-179A vaccine virus strain]. Similar to H1N1 HA fraction of interpandemic [seasonal] influenza vaccines.

Manufacture

HA fraction manufacture is analogous to the method used for seasonal influenza vaccines and that approved for Pandemrix H5N1.

Physical and Chemical Properties

Similar to those for Pandemrix H5N1 vaccine.

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 36 months.

The company is committed to the completion of the stability studies to 36 months and send the data when available.

Drug Product

Formulation(s)

The vaccine consists of two components, an antigen suspension and an adjuvant emulsion. These are mixed in a 10 dose presentation prior to administration.

Pandemrix H1N1 vaccine is manufactured in Dresden. Each vaccine dose (0.5mL) contains 3.75ug of antigen derived from A/California/7/2009 (H1N1)v-like strain, and is adjuvanted with AS03 adjuvant. AS03 is GSK's proprietary adjuvant system, and each adjuvant dose is composed of squalene, DL-α-tocopherol and polysorbate 80.

The vaccine consists of two containers: one multidose vial containing the antigen (2.5 ml suspension) and the second multidose vial containing the adjuvant (2.5 ml emulsion). The suspension and emulsion vials, once mixed, form a multidose vaccine in a 10 dose vial. Preservative

content is 5µg ThimersalPh Eur[2] per 0.5mL dose or 2.5 micrograms organic mercury (Hg) per 0.5mL dose.

Manufacture

The product is manufactured by propagating the H1N1 vaccine strain in eggs, harvesting the allantoic fluid, concentrating, splitting, inactivating and fractionating the HA fraction [method analogous to the manufacture of the seasonal influenza vaccines]. The adjuvant consists of ά-tocopherol and squalene. The mixed vaccine is an oil-in-water emulsion where the H1N1 HA is in the aqueous phase. The adjuvant emulsion is sterilised by membrane filtration. The antigen suspension is manufactured aseptically and both components are 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

Stability studies commenced under real time conditions to characterise the stability profile of the H1N1 component. Proposed shelf life of the H1N1 antigen is 36 months at 2-8°C based on the stability of Pandemrix H5N1. Post approval stability commitment is made to complete real time and accelerated stability studies. The shelf life of the adjuvant suspension in the multi dose vials is 36 month at 2-8 °C. In-use stability data for Pandemrix H5N1 demonstrating in-use shelf life of 24 hours has been provided..

Bioavailability

Not relevant for this product

Quality Summary and Conclusions

There were no quality issues raised. Please note that the formulation evaluated may not be the one used in a pandemic. Minor adjustments in the manufacturing process may be necessary to accommodate strain-specific differences.

III. Nonclinical Findings

No new nonclinical data were submitted with the current Australian submission. Nonclinical data were previously submitted for Prepandemrix H5N1, upon which the nonclinical statements in the Pandemrix H1N1 Product Information (PI) are based.

IV. Clinical Findings

Introduction

The clinical data submitted to support the current application include:

- D-Pan H1N1-007 (Study 007, adult study, 18-60 years)
- D-Pan H1N1 008 (Study 008, adult 18 years and above)
- D-Pan H1N1 018 (Study 018, elderly 61 years and above)

All three studies submitted in this application were performed in compliance with Good Clinical Practice including the archiving of essential documents.

Pharmacokinetics

As mentioned in the European Union (EU) guideline "Note for Guidance on Clinical Evaluation of New Vaccines (CPMP/EWP/463/97), which has been adopted in Australia, pharmacokinetic (PK)

[2] European Pharmacopeia.

studies are generally not required for injectable vaccines as the kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations. PK studies were therefore not conducted.

Drug Interactions

No drug interactions studies were submitted with this application.

Pharmacodynamics

Pharmacodynamic evaluations were not conducted. 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 will be reported on in the section on *Immunogenicity*.

Efficacy

Introduction

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.

Immunogenicity of Pandemrix H1N1 vaccine was assessed in healthy adults (> 18 years) in Study 007, 008, and 018. The submitted interim study reports of the three studies provided the post-Dosepost-Dose 1 (Day 21 after the first dose of the vaccine) immunogenicity results. Although the studies were planned to assess the immune responses by both Haemagglutination Inhibition (HI) antibody and neutralization antibody, only the HI antibody responses post-Dose 1 are available at the time of the current submission.

The following three immunogenicity endpoints were evaluated in these studies:

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

SCF (or GMFI): seroconversion factor or 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).

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

These endpoints are consistent with the European Medicines Agency (EMA) guideline (CPMP/BWP/214/96) relating to evaluation of seasonal influenza vaccines. In the absence of specific criteria for influenza vaccines derived from pandemic strains, it is anticipated that a candidate pandemic vaccine should at least be able to elicit sufficient immunological responses to meet all three of the current Committee for Human Medicinal Products (CHMP) acceptance criteria (CPMP/BWP/214/96) for seasonal influenza vaccines in adults or elderly subjects (see the below)

Table 1: CHMP acceptance criteria for the three immunogenicity endpoints (CPMP/BWP/214/96).

Based on HI assay	acceptance criteria	
	18 – 60 years	**> 60 Years**
1. SPR: Protective titres, that is ≥ 1:40	> 70%	> 60%
2. SCR: seroconversion* or Significant increase#	> 40%	> 30%
3. SCF: Fold increase in GMT	> 2.5	> 2.0

* Subjects with antibody titre increase from < 1:10 (lower limit of detection) pre-vaccination to ≥ 1:40 post-vaccination.

Subjects with antibody titre ≥ 1:10 pre-vaccination (that is, seropositive at baseline) and showed at least 4 fold increase post-vaccination.

This requirement is specified in the EU "Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application" (CPMP/VEG/4717/03) and in "Guideline on Influenza Vaccines Prepared from Viruses with the Potential to cause a Pandemic and Intended for Use Outside of the Core Dossier Context (EMEA/CHMP/VWP/263499/2006) which has been adopted in Australia.

Two immunogenicity endpoints, SPR and SCR, are defined in the FDA guideline[3], The Center for Biologics Evaluation and Research (CBER) criteria for the effective immune response are also based on HI assay (See Table 2 below). There is no corresponding criterion regarding the fold increase in GMT (SCF or GMFI).

Table 2: 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%

The post-Dosepost-Dose 1 vaccine homologous virus HI antibody responses in the three studies are discussed below.

Study D-Pan H1N1-007

Study design and objectives

Study 007 was a single centre, randomized, observer-blind study. The primary objective was to demonstrate that vaccination with two doses of the Pandemrix H1N1 vaccine results in an immune response to the vaccine homologous virus that meets or exceeds the CHMP acceptance criteria for SCR, SPR), and SCF (or GMFR) at 21 days after the second dose of the vaccine in adults 18 to 60 years of age.

Only the post-Dosepost-Dose I immunogenicity and safety results were available in the submitted abridged Clinical Study Report (CSR).

[3] *Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, and also the FDA guideline for seasonal influenza vaccine.*

Study vaccines

Two types of the H1N1 vaccines, one adjuvanted with AS03A (Pandemrix H1N1 vaccine) and the other not adjuvanted with AS03A, were assessed in this study. The study subjects were randomised to Group A and Group B:

- Group A (H1N1 + AS03A group) was to receive the adjuvanted vaccine consisting of 3.75 µg of H1N1 (A/California/7/2009(H1N1)v-like) antigen plus AS03A adjuvant in a 0.5 mL injection volume
- Group B (H1N1 group) was to receive the non-adjuvanted vaccine consisting 15 µg of the H1N1 (A/California/7/2009(H1N1)v-like) antigen only in a 0.5 mL injection volume

The non-adjuvanted H1N1 vaccine contained a 4-fold higher antigen dose (15 µg) compared to the adjuvanted H1N1 vaccine (3.75 µg). The vaccines were administered intramuscularly in the deltoid region of the non-dominant arm at Day 0 and in the dominant arm at Day 21.

Study subjects

Healthy male or female adults 18 to 60 years of age were eligible to enter the study. The study subjects were to be randomized (1:1) to one of the two vaccine groups (adjuvanted and non-adjuvanted vaccine group). The study subjects were also to be stratified by age: between 18 and 40 years inclusive, above 41 to 50 years inclusive and above 51 to 60 years inclusive (ratio 2:1:1). It was planned to enrol 128 subjects with 64 subjects in each group. The actual enrolled number of subjects was 130:

- H1N1 + AS03A group (Group A, n = 64): 32 in the 18-40 years stratum, 16 in the 41-50 years stratum and 16 in the 51-60 years stratum;

- H1N1 group (Group B, n = 66): 33 in the 18-40 years stratum, 16 in the 41-50 years stratum and 17 in the 51-60 years stratum.

The subjects received the first dose of the study vaccines (adjuvanted or non-adjuvanted), and the analyses of blood samples obtained up to Day 21 were described in the sponsor's abridged study report.

Immunogenicity endpoints

In order to evaluate immune response in terms of H1N1 HI antibodies, the following parameters (with 95% confidence intervals) were calculated per age strata and overall for both study groups:

- GMTs of the H1N1 HI antibody titers at Days 0 and 21.
- SCRs at Day 21
- SCF at Day 21
- SPR at Days 0 and 21

Demographic characteristics of the study subjects

The results presented in the sponsor's abridged clinical study report are based on raw data.

The demographic characteristics of the total enrolled cohort is summarised in the table below: the mean age was 38.6 years for total enrolled subjects. The overall male-female distribution was 38.5% versus 61.5%.

Table 3: Summary of demographic characteristics (Total Enrolled cohort) - Study 007

		H1N1+ AS03 N = 64		H1N1 N = 66		Total N = 130	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years)	Mean	39.1	-	38.2	-	38.6	-
	SD	13.53	-	14.10	-	13.78	-
	Median	40.5	-	40.5	-	40.5	-
	Minimum	19	-	18	-	18	-
	Maximum	60	-	60	-	60	-
Gender	Female	41	64.1	39	59.1	80	61.5
	Male	23	35.9	27	40.9	50	38.5
Geographic Ancestry	Asian - east asian heritage	0	0.0	1	1.5	1	0.8
	White - caucasian / european heritage	64	100	65	98.5	129	99.2

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant; H1N1 = H1N1 containing HA antigen without adjuvant; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation

Post dose 1 immunogenicity results

The primary immunogenicity analysis was conducted on the total enrolled cohort (n = 130). The analysis was conducted as a descriptive analysis for each vaccine group overall and for each age stratum (18-40 years and 41-60 years) in each vaccine group. The results are presented in the Table 4 below.

Table 4: H1N1 HI Antibodies against A/California/7/2009 (H1N1) - Study 007

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	**N**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**%**	**LL**	**UL**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Group H1N1 + AS03$_A$ Overall																
PRE	64	32.8	21.6	45.7	8.6	6.9	10.9	9.4	3.5	19.3	-	-	-	-	-	-
PI(D21)	61	100	94.1	100	384.0	285.1	517.1	100	94.1	100	96.7	88.7	99.6	43.3	31.8	59.0
18-40 years stratum																
PRE	32	21.9	9.3	40.0	7.1	5.5	9.4	6.3	0.8	20.8	-	-	-	-	-	-
PI(D21)	29	100	88.1	100	561.2	371.9	846.9	100	88.1	100	100	88.1	100	75.7	52.1	110.0
41-60 years stratum																
PRE	32	43.8	26.4	62.3	10.4	7.1	15.2	12.5	3.5	29.0						
PI(D21)	32	100	89.1	100	272.2	180.5	410.6	100	89.1	100	93.8	79.2	99.2	26.1	17.1	39.8
Group H1N1 Overall																
PRE	66	42.4	30.3	55.2	10.7	8.1	14.1	18.2	9.8	29.6	-	-	-	-	-	-
PI(D21)	66	98.5	91.8	100	331.9	232.4	474.2	93.9	85.2	98.3	84.8	73.9	92.5	31.0	21.5	44.7
18-40 years stratum																
PRE	33	45.5	28.1	63.6	13.0	8.1	20.9	24.2	11.1	42.3	-	-	-	-	-	-
PI(D21)	33	100	89.4	100	640.0	423.8	966.5	97.0	84.2	99.9	87.9	71.8	96.6	49.2	29.1	83.4
41-60 years stratum																
PRE	33	39.4	22.9	57.9	8.8	6.6	11.8	12.1	3.4	28.2	-	-	-	-	-	-
PI(D21)	33	97.0	84.2	99.9	172.2	103.8	285.5	90.9	75.7	98.1	81.8	64.5	93.0	19.5	12.1	31.6

Group H1N1+ AS03$_A$ = H1N1 containing antigen-sparing dose of HA+AS03$_A$ adjuvant; H1N1 = H1N1 containing HA antigen without adjuvant; N = number of subjects with available results; HI = hemagglutination inhibition; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at Day 0; PI(21) = Post-vaccination at Day 21; SCR = Seroconversion rate defined as: For initially seronegative subjects, antibody titer ≥ 40 after vaccination; For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer; N = Number of subjects with pre- and post-vaccination results available; SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]); SPR = percentage of vaccinees with serum H1N1 HI antibody titer ≥1:40

Day 0 (baseline)

Seropositivity rates ranged from 32.8% to 42.4% in all subjects. GMT values before vaccination were low and ranged between 8.6 and 10.7.

Day 21 (post-Dosepost-Dose 1):

Seropositivity rates increased to 100% in the adjuvanted vaccine group (H1N1 + AS03A) and to 98.5% in the non-adjuvanted vaccine group (H1N1). The amplitude of the HI response was similar in both groups (GMTs of 384.0 for the H1N1+AS03A group and 331.9 for the H1N1 group). The immune responses (SCR, SCF, SPR) in subjects from both groups exceeded the European Committee for Human Medicinal Products (CHMP) and the US FDA Center for Biologics Evaluation and Research (CBER) acceptance criteria for influenza vaccines for adults. Overall, the SCR, SCF, and SPR in the group H1N1+AS03A were 96.7%, 43.3, and 100.0%, respectively. In the H1N1 group, SCR value was 84.8%, SCF 31.0 and SPR 93.9%. Although the observed immune response was similar with no marked difference between the two vaccine groups (the Confidence Intervals (CI) were broadly overlapping), all tested parameters (GMT, SCR, SCF, SPR) showed a general trend towards lower point estimates in the unadjuvanted group compared to the adjuvanted vaccine group, especially in the older age strata.

Immune response by baseline serostatus and by previous vaccination history

Further analyses showed that regardless of baseline serostatus (seropositive or seronegative), the CHMP criteria were satisfied in both vaccine groups and in each age strata. In addition, the CHMP criteria were also satisfied in both vaccination groups regardless of whether the subjects had prior history of seasonal vaccination (See Table 4B and 5B in Part B).

Study D-Pan H1N1-008

Study 008 was designed to evaluate the safety and immunogenicity of a single dose or two-dose schedule of the Pandemrix H1N1 vaccine in adults aged 18 years and above.

Study objectives

Study 008 had many objectives, and the primary objective was to demonstrate that one dose of the Pandemrix H1N1 vaccine can induce an HI immune response to the vaccine-homologous virus that meets or exceeds the EMA (CHMP) guidance targets in terms of SCR, SPR, and SCF at 21 days after the vaccination in adults within the 18 to 60 years and above 60 years age strata.

The study was also to assess, as secondary objectives, the immune response after two doses of the vaccine, the persistence of the immune response, the immune response measured by neutralizing antibodies, and immune response stratified by pre-vaccination serostatus and each age stratum. In the submitted abridged Clinical Study Report (CSR), only the post-Dose I immunogenicity and safety / reactogenicity results are described.

Study design

Study 008 is a Phase III, open-label, randomized and parallel groups study. A total of 240 subjects were to be randomized (1:1) to one of the two study groups and stratified by age: between 18 and 60 years inclusive and above 60 years old. Subjects received one or two doses of the study vaccine adjuvanted with AS03A.

The original design was that all enrolled 240 subjects were to receive two doses of the vaccine. The design was modified, so that only half (n = 120) of the enrolled subjects were to receive the two doses as planned, and the other half (n = 120) were to receive only the first dose, and were not to receive the second dose of the vaccine scheduled at Day 21. This modified design allows the evaluation of the persistence of the immune response after a single dose vaccination.

Study subjects

Healthy male or female adults 18 to 60 years of age and above were eligible to enter the study. It was planned to enrol 120 subjects aged 18-60 years and 120 subjects aged > 60 years.

A total of 240 subjects were actually enrolled into the study, including:

120 subjects in 18-60 years:

59 in the 18-40 years stratum,

61 in the 41-60 years stratum;

120 subjects > 60 years

75 in the 61-70 years stratum;

45 in above 70 years stratum

Treatment allocation

All 240 subjects were to receive the first dose of the Pandemrix H1N1 vaccine at Day 0. At Day 21, the subjects were to be randomised (1:1) to Group A and Group B

• Group A: 120 subjects were not to receive the second dose of the vaccine.

• Group B: 120 subjects were to receive the second dose of the vaccine at Day 21.

Study vaccine

The study vaccine, Pandemrix H1N1 vaccine, is a two-component vaccine consisting of 3.75 µg of HI antigen (A/California/7/2009(H1N1)v-like) and AS03 adjuvant presented separately (the antigen in a multidose vial and the adjuvant in a multidose vial, mixed before use).

Primary endpoints

Humoral immune response in terms of HI antibodies (SCR, SPR and SCF) in subjects vaccinated with Pandemrix H1N1 vaccine at Day 21.

Secondary endpoints

Humoral immune response in terms of HI antibodies (Seropositivity rate, GMT and SPR at Days 0 and 21, SCR and SCF at Day 21) in subjects vaccinated with Pandemrix H1N1 vaccine. The endpoints listed above are the ones that were analysed at the time of the report.

Demographic characteristics of the study subjects

All subjects (n = 240) received the first dose of the vaccine at Day 0. For the total vaccinated cohort (TVC, n = 240), the mean age was 39.7 years for subjects 18-60 years of age and 69.1 years for subjects > 60 years of age. The overall male-female distribution was 45.8% versus 54.2% for subjects 18-60 years of age; and was 56.7% versus 43.3% for subjects > 60 years of age. The demographic data are summarised in Table 5.

Table 5: Summary of demographic characteristics for the 18-40/41- 60/61-70/>70 stratification (Total vaccinated cohort) Study 008

		Gr 1							
		18-40 N = 59		41-60 N = 61		61-70 N = 75		>70 N = 45	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	26.9	-	52.0	-	65.0	-	76.0	-
	SD	6.59	-	5.13	-	2.57	-	3.71	-
	Median	24.0	-	52.0	-	65.0	-	76.0	-
	Minimum	19	-	42	-	61	-	71	-
	Maximum	40	-	60	-	70	-	85	-
Gender	Female	33	55.9	32	52.5	37	49.3	15	33.3
	Male	26	44.1	29	47.5	38	50.7	30	66.7
Geographic Ancestry	White - caucasian / european heritage	59	100	61	100	75	100	45	100

Gr 1=Subjects receiving D-PAN H1N1 vaccine (A/California/7/2009 (H1N1) v-like 3.75g + AS03A); 18-40 Subjects aged between and including 18 years to 40 years; 41-60=Subjects aged between and including 41 years to 60 years; 61-70=Subjects aged between and including 61 years to 70 years; >70=Subjects aged more than 70 years; N = total number of subjects; n/% = number / percentage of subjects in a given category; Value = value of the considered parameter; SD = standard deviation.

Immunogenicity results post-Dose 1

The results presented in the sponsor's abridged clinical study report are based on raw data. As all subjects received only one dose of study vaccine at Day 0, no distinction was done in terms of study groups in the sponsor's abridged report.

The post-Dose 1 immunogenicity analysis by age stratum (18-60 years and > 60 years) is presented in Table 6 below. The analysis was based on the total vaccinated cohort (TVC). The HI response to the vaccine-homologous virus was described on Days 0 and 21, by estimating the following parameters (with 95% CIs): GMT, SPR, SCR (except on Day 0) and SCF (except on Day 0) in both age strata:

Table 6: H1N1 HI Antibodies against A/California/7/2009 (H1N1)-Study 008

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
All subjects (Dose 1) 18-60 years stratum																
PRE	120	36.7	28.1	45.9	8.52	7.32	9.92	8.3	4.1	14.8	-	-	-	-	-	-
PI(D21)	120	100	97.0	100	359.25	287.18	449.40	97.5	92.9	99.5	95.0	89.4	98.1	42.15	33.43	53.16
All subjects (Dose 1) > 60 years stratum																
PRE	120	42.5	33.5	51.9	9.99	8.21	12.15	9.2	4.7	15.8	-	-	-	-	-	-
PI(D21)	120	98.3	94.1	99.8	136.44	110.52	168.43	87.5	80.2	92.8	79.2	70.8	86.0	13.66	10.88	17.14

N = number of subjects with available results; HI = hemagglutination inhibition; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit; PRE = Pre-vaccination at Day 0; PI(21) = Post-vaccination at Day 21; SCR = Seroconversion rate defined as: For initially seronegative subjects, antibody titer ≥ 40 after vaccination; For initially seropositive subjects, antibody titer after vaccination ≥ 4 fold the pre-vaccination antibody titer; N = Number of subjects with pre- and post-vaccination results available; SCF = Seroconversion Factor or geometric mean ratio (mean[log10(POST/PRE)]); SPR = percentage of vaccinees with serum H1N1 HI antibody titer ≥1:40. Note that in this abridged report Day 21 no distinction is done between group A and B of the protocol because till this Day 21 all subjects received only one dose of vaccine.

Day 0 (baseline)

In subjects 18-60 years of age, 36.7% were seropositive for H1N1 HI antibodies and in subjects > 60 years of age, 42.5% were seropositive for H1N1 HI antibodies. Low GMT values were observed before vaccination (8.52 in subjects 18 - 60 years of age and 9.99 in subjects > 60 years).

Day 21 (post-Dose 1)

Seropositivity rates increased to 100% and 98.3% in subjects of 18-60 and of >60 years of age, respectively. The magnitude of the observed HI response was more pronounced for subjects 18-60 years of age (GMT at Day 21: 359.25) in comparison to subjects > 60 years of age (GMT at Day 21: 136.44). In both age strata, the estimated immune response exceeded the respective for CHMP and CBER acceptance criteria for influenza vaccines. In subjects 18-60 years of age, the observed SCR, SCF and SPR were 95%; 42.15 and 97.5%, respectively. In subjects > 60 years of age, the observed SCR, SCF and SPR were 79.2%; 13.66 and 87.5%, respectively. All tested parameters (GMT, SCR, SCF, SPR) showed a general trend towards lower point estimates in the older age strata.

Immune responses by baseline serostatus

The analysis of the immune responses by baseline serostatus is presented in Table below 7. The results show that in subjects who were seronegative at baseline, the three CHMP criteria were met for both the younger (18-60 years) and older age group (> 60 years).

Table 7: Post-dose 1 HI responses by baseline serostatus in subject 18-60 and > 60 years of age

Vaccine strain	Age group	Baseline status	Day	Sero Positivity %	GMT	SCR %	SCF	SPR %
	18-60	S-	Day 0	0	5.00			0.0
			Day 21	100	253.67	96.1	50.73	96.1
		S+	Day 0	100	21.41			22.7
			Day 21	100	655.27	93.2	30.61	100
	> 60	S-	Day 0	0.0	5.00			0.0
			Day 21	97.1	100.71	81.2	20.14	81.2
		S+	Day 0	100	25.47			21.6
			Day 21	100	205.73	76.5	8.08	96.1

A post-hoc analysis was performed on additional age substrata, and the immune responses in older adults (> 60 years) by further classification of age, for example, 61-70, 71-80, and > 80 years, and by baseline serostatus is presented in Table 8 below:

Table 8: Post-dose 1 HI responses by baseline serostatus in subjects 61-70, 71-80, and >80 years of age

Age category	61-70 years		71-80 years		> 80 years	
HI responses	Total enrolled subjects N = 75	Seronegative At baseline N = 43	Total enrolled subjects N = 40	Seronegative At baseline N = 23	Total enrolled subjects N = 5	Seronegative At baseline N = 3
SPR	88.0%	81.4%	87.5%	82.6%	80.0%	66.7%
SCR	80.0%	81.4%	77.5%	82.6%	80.0%	66.7%
SCF	13.5%	20.3	13.5	20.67	18.4	17.95

Table 8 shows that:

- In the groups aged 61-70 and 71-80 years, all three CHMP criteria are met regardless of their baseline serostatus.
- In the group aged > 80 years, only five subjects were enrolled, of which three were seronegative at baseline. Overall, four out of five subjects were sero-converted and sero-protected 21 days after the first dose of vaccine (SPR = 80%, SCR = 80%), and the SCF was 18.4. For the subjects who were seronegative at baseline (n = 3), two out of three were sero-converted and sero-protected after the first dose of vaccine (SCR = 66.7%, SPR = 66.7%); and the SCF was 17.95. The CHMP acceptance criteria for SCR, SCF, and SPR are met regardless of their baseline serostatus in this age group.

Immune responses by history of prior seasonal vaccination

The post-Dose 1 HI responses (GMT and SPR) by baseline serostatus and history of prior seasonal vaccination is presented in Table 9 below. It is noted that in both age groups, the subjects who were seronegative at baseline and had received seasonal vaccination had the lowest GMT and SPR at Day 21; however, the SPR was 93% for 18-60 years and 79% for the > 60 years in this subgroup, meeting the CHMP acceptance criteria. Overall, the data do not show an important effect of prior seasonal vaccination on HI responses at Day 21 after a single dose.

Table 9: Post dose 1 HI responses by baseline serostatus and history of prior seasonal vaccination

Vaccine strain	Age group	Prior seasonal vaccination	Baseline status	Day	GMT	SPR
	18-60 years	yes	S-	Day 0	5.00	0.0
				Day 21	160.8	**93.3**
			S+	Day 0	17.55	10.5
				Day 21	533.29	100
			total	Day 0	7.26	3.1
				Day 21	228.82	95.3
		No	S-	Day 0	5.00	0.00
				Day 21	97.1	100
			S+	Day 0	24.89	32.0
				Day 21	766.32	100
			total	Day 0	10.24	14.3
				Day 21	601.56	100
	> 60 years	yes	S-	Day 0	5.00	0
				Day 21	95.64	**79.3**
			S+	Day 0	22.11	17.08
				Day 21	196.70	95.7
			total	Day 0	9.73	7.6
				Day 21	132.07	86.7
		No	S-	Day 0	5.00	0
				Day 21	132.28	90.9
			S+	Day 0	134.46	75.0
				Day 21	348.74	100
			total	Day 0	12.03	20.0
				Day 21	171.30	93.3

Study D-Pan H1N1-018

Study 018 is a Phase II, observer-blind, randomized study. The study aimed to assess the immunogenicity, safety and reactogenicity of a two-dose schedule with GSK Biologicals' Pandemrix H1N1 vaccine when co-administered with GSK Biologicals' seasonal 2009-2010 influenza vaccine Fluarix either at the time of first or second dose of Pandemrix H1N1 vaccination in elderly subjects aged 61 years and older. Only the post-Dose 1 result (immunogenicity and safety/reactogenicity) are described in the sponsor's abridged CSR.

Study objectives

The primary objectives of the study were:

• To assess whether vaccination with two doses of the Pandemrix H1N1 vaccine results in an HI immune response to the vaccine-homologous virus that meets or exceeds the EMA (CHMP) guidance targets for pandemic influenza vaccines (SCR, SPR, and SCF) at 21 days after the second dose of H1N1 vaccine when co-administered with Fluarix either at the time of first or second vaccination with the H1N1 vaccine in elderly subjects aged 61 years and older.

• To assess whether vaccination with one dose of Fluarix results in an HI immune response that meets or exceeds for each vaccine strain of the seasonal vaccine at least one of the EMA (CHMP) guidance targets for seasonal influenza vaccines (SCR, and/or SPR and/or SCF) at 21 days after vaccination when co-administered with either the first or second dose of the H1N1 vaccine in elderly subjects aged 61 years and older.

Study design

Study 018 is a randomized, observer-blind study with two parallel groups (n = 168 subjects in total). Subjects were randomized (1:1) to one of the following vaccine regimens stratified by age (61-70 years and >70 years in the ratio 2:1).

F-PAN Group

Day 0: first dose of the Pandemrix H1N1 vaccine and one dose of Fluarix.

Day 21: second dose of the Pandemrix H1N1 vaccine and one dose of placebo vaccine.

PAN-F Group

Day 0: first dose of the Pandemrix H1N1 vaccine and one dose of placebo vaccine.

Day 21: second dose of the Pandemrix H1N1 vaccine and one dose of Fluarix.

Analyses of blood samples obtained up to Day 21 after the first dose of the Pandemrix H1N1 vaccine are described in the sponsor's abridged study report.

Study subjects

Healthy male or female adults 61 years old and older at the time of first vaccination were eligible to enter the study. The study planned to enrol 168 subjects with 84 subjects in F-PAN group and 84 subjects in the PAN-F group. A total of 168 subjects (84 in each group) were actually enrolled into the study, and the subjects were stratified by age:

- 112 in the 61-70 years stratum
- 56 in the >70 years stratum.

All 168 subjects completed the vaccination on Day 0 and the Day 21 visit.

Study vaccines

The study vaccine, Pandemrix H1N1 vaccine, is a two-component vaccine consisting of 3.75 µg of HI antigen (H1N1) and AS03 adjuvant presented separately (the antigen in a multi-dose vial and the adjuvant in a multidose vial).

There were two other vaccines used in this study: one is Fluarix which is a seasonal influenza vaccine consisting of 3x15 µg of HI antigen (H1N1, H3N2 and B), the other is a placebo vaccine which is a saline solution.

Immunogenicity endpoints

The complete list of endpoints (immune responses in terms of HI antibodies) is listed as follows:

Primary endpoints:

• SCR at 21 days after the second dose of Pandemrix H1N1vaccine (Day 42)

• SPR at 21 days after the second dose of Pandemrix H1N1vaccine (Day 42)

• SCF at 21 days after the second dose of Pandemrix H1N1vaccine (Day 42)

• SCR at 21 days after vaccination with Fluarix

• SPR at 21 days after vaccination with Fluarix

• SCF at 21 days after vaccination with Fluarix

Secondary endpoints:

• GMTs and seropositivity rates at Day 0, Day 21, Day 42, Day 182 and Day 364

• SCR at Days 21; 182 and 364

• SPR at Days 0, 21, 182 and 364

• SCF at Day 21, 182 and 364.

Criteria for evaluation were the same for the primary and secondary endpoints. It should be noted that only the post-Dose 1 (21 days after the first dose of the vaccine) immunogenicity and safety results are described in the sponsor's abridged CSR.

Analysis of immunogenicity post-Dose 1

The primary immunogenicity analysis was based on the total vaccinated cohort (TVC = 168). For each treatment group, the following parameters (with 95% CIs) were calculated.

• GMTs of HI antibodies against H1N1 strain and each strain of Fluarix at Day 0 and 21.

• SCR for HI antibodies against H1N1 strain and each strain of Fluarix at Day 21.

• SCF for HI antibodies against H1N1 strain and each strain of Fluarix at Day 21.

• SPR for HI antibodies against H1N1 strain and each strain of Fluarix at Day 0 and 21.

The results presented in the sponsor's abridged clinical study report are based on raw data.

Demographic characteristics of the study subjects

For the total vaccinated cohort (n = 168), the mean age was 69.0 years. The overall male-female distribution was 47.0% versus 53.0%. The demographic data are summarised in Table 10 below.

Table 10: Summary of demographic characteristics (Total vaccinated cohort Study 018)

		F-PAN N = 84		PAN-F N = 84		Total N = 168	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%
Age (years)	Mean	68.9	-	69.1	-	69.0	-
	SD	4.63	-	4.70	-	4.65	-
	Median	68.0	-	68.0	-	68.0	-
	Minimum	61	-	61	-	61	-
	Maximum	85	-	81	-	85	-
Gender	Female	42	50.0	47	56.0	89	53.0
	Male	42	50.0	37	44.0	79	47.0
Geographic Ancestry	White - Caucasian / European heritage	84	100	84	100	168	100

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Post-Dose 1 immune response against A/California/7/2009 (H1N1)v-like

The immunogenicity analysis was performed on the total vaccinated cohort. The analysis was conducted as a descriptive analysis for each treatment arm in adults 61-70 years and >70 years of age. The post-Dose 1 immune responses against A/California/7/2009 (H1N1)v is presented in Table 11 below:

Table 11: Post dose 1 immune responses against A/California/7/2009 (H1N1)v-like (Study 018)

		≥10 1/DIL			GMT			SPR			SCR			SCF		
			95% CI			95% CI			95% CI			95% CI			95% CI	
Timing	N	%	LL	UL	value	LL	UL	%	LL	UL	%	LL	UL	value	LL	UL
Group F-PAN Overall																
PRE	84	23.8	15.2	34.3	7.4	6.1	9.0	7.1	2.7	14.9	-	-	-	-	-	-
PI(D21)	84	98.8	93.5	100	139.1	108.2	178.6	89.3	80.6	95.0	88.1	79.2	94.1	18.8	14.8	23.9
61-70 years stratum																
PRE	56	21.4	11.6	34.4	6.9	5.7	8.4	5.4	1.1	14.9	-	-	-	-	-	-
PI(D21)	56	100	93.6	100	155.0	112.9	213.0	87.5	75.9	94.8	87.5	75.9	94.8	22.4	16.5	30.2
> 70 years stratum																
PRE	28	28.6	13.2	48.7	8.4	5.4	13.0	10.7	2.3	28.2	-	-	-	-	-	-
PI(D21)	28	96.4	81.7	99.9	111.8	73.7	169.8	92.9	76.5	99.1	89.3	71.8	97.7	13.3	9.0	19.7
Group PAN-F Overall																
PRE	84	38.1	27.7	49.3	8.5	7.1	10.2	8.3	3.4	16.4	-	-	-	-	-	-
PI (D21	84	100	95.7	100	168.2	137.5	205.7	96.4	89.9	99.3	92.9	85.1	97.3	19.8	15.7	25.0
61-70 years stratum																
PRE	56	37.5	24.9	51.5	8.2	6.6	10.2	5.4	1.1	14.9	-	-	-			
PI (D21	56	100	93.6	100	180.0	139.7	231.9	94.6	85.1	98.9	92.9	82.7	98.0	22.0	16.7	29.0
> 70 years stratum																
PRE	28	39.3	21.5	59.4	9.2	6.3	13.3	14.3	4.0	32.7	-	-	-	-	-	-
PI (D21	28	100	87.7	100	146.8	103.8	207.5	100	87.7	100	92.9	76.5	99.1	16.0	10.3	24.9

PAN-F group (subjects received the H1N1 vaccine + placebo at Day 0)

At Day 0, 38.1% were seropositive for H1N1 HI antibodies. Baseline GMT was low at 8.5.

At Day 21, seropositive rate increased to 100% and GMT increased to 168.2.

The observed SCR, SCF, and SPR were 92.9%, 19.8 and 96.4%, respectively.

F-PAN group (subjects received the H1N1 vaccine + Fluarix at Day 0)

At Day 0, 23.8% were seropositive for H1N1 HI antibodies. Baseline GMT was low at 7.4.

At Day 21, seropositive rate increased to 98.8% and GMT increased to 139.1.

The observed SCR, SCF, and SPR were 88.1%, 18.8 and 89.3%, respectively.

Similar ranges of response were seen in adults aged 61-70 years and in those > 70 years (Table 8).

Further analyses showed that CHMP criteria against the H1N1 strain [A/California/7/2009 (H1N1)v] were met regardless of the baseline serostatus and regardless of whether Fluarix was co-administered with the first dose of Pandemrix H1N1 vaccine (Table 22B-25B in Part B).

Post_Dose 1 immune response against each viral strain of Fluarix

For the F-PAN group, at 21 days after the vaccination with Fluarix plus Pandemrix H1N1, the results of immune responses against each strain of Fluarix showed that:

• At Day 0, seropositivity rates ranged from 71.4% to 81% for A/Brisbane (H1N1) and from 67.9% to 70.2% for A/Uruguay (H3N2). Almost all subjects were seropositive for the B/Brisbane strain (91.7% in F-PAN and 100% in PAN-F groups).

• At Day 21, immune responses exceeded CHMP regulatory acceptance criteria for influenza vaccines for adults older than 60 years for all three seasonal strains. The observed SCR ranged between 36.9% and 48.8%, the SCF from 3.5 to 4.7. The SPR were 69.0%, 78.6% and 100% for the A/Brisbane (H1N1), A/Uruguay (H3N2) and B/Brisbane strains respectively.

Evaluator's overall conclusions on immunogenicity / efficacy

In this application, the sponsor applies to replace the H5N1 strain in Pandemrix (H5N1) with the pandemic H1N1 strain and to change the vaccine administration schedule from a two dose regimen (for Pandemrix H5N1) to the option of one dose or two dose regimen (for Pandemrix H1N1). Pandemrix H5N1 is registered as a 'mock-up' pandemic vaccine. The registration of a 'mock-up' pandemic vaccine allows rapid updating of the viral strain in the event of a pandemic.

The EU guideline (CPMP/VEG/4717/03) states that if the mock-up vaccine and the final pandemic vaccine are similar other than in strain content and the dose schedule is unchanged, the final pandemic vaccine may be approved for use by means of a variation that addresses only the quality issues and without the provision of clinical data. TGA considers that with the change of influenza subtype from H5N1 to H1N1, the clinical studies are relevant to assessment of the dose regimen. This application seeks not only the strain variation, but also the variation to the vaccine administration schedule. Three clinical studies are provided to support the requested changes. In all the three studies, SPR, SCR, and SCF were assessed as immunogenicity endpoints.
Study 007 was conducted in a total of 130 healthy adults aged 18-60 years. The Pandemrix H1N1 vaccine (AS03 adjuvanted) containing 3.75 µg of HA antigen was administered to 64 subjects and the non-adjuvanted H1N1 vaccine containing 15 µg of HA antigen was administered to 66 subjects. At 21 days after the first dose of the Pandemrix H1N1 vaccine, the SPR, SCR, and SCF in all age groups fulfilled the CHMP and CBER acceptance criteria for vaccine homologous virus HI antibody response. Administration of one dose (15 µg) of the non-adjuvanted H1N1 vaccine also induced the immune response meeting the regulatory criteria although a general trend was observed towards lower immune response parameters (GMT, SCR, SCF, SPR) compared to the adjuvanted vaccine, especially in the older age strata. The observed difference in point estimate of SCR of almost 12% (96.7% versus 84.8%) is considered clinically meaningful. AS03 adjuvanted H1N1 vaccine, the Pandemrix H1N1 vaccine, is considered the better vaccine formulation, as it elicits better immune responses especially in the older age strata.

Study 008 was conducted in a total of 240 healthy adults > 18 years of age (18-60 years and > 60 years). Half of these subjects (n = 120) received only the first dose of the Pandemrix H1N1 vaccine, and the other half received both the first and the second dose of the Pandemrix H1N1 vaccine. At 21 days after the first dose of the Pandemrix H1N1 vaccine, the HI immune responses to homologous virus fulfilled all the CHMP and CBER regulatory acceptance criteria in both age strata. The regulatory acceptance criteria were fulfilled regardless of age, baseline serostatus and prior history of seasonal vaccination. In the group aged > 80 years (n = 5), the CHMP acceptance criteria for SCR, SCF, and SPR were all met regardless of their baseline serostatus. Due to the limited number of subjects (n = 5) evaluated in this age group (>80 years), caution is required in the interpretation of the results for this subgroup.

Study 018 was conducted in elderly adults > 60 years of age. It was designed to evaluate the immunogenicity and reactogenicity of a two-dose schedule of the Pandemrix H1N1 vaccine when it is co-administered with Fluarix either at the time of first (F-PAN group) or second vaccination (PAN-F group). At 21 days after a first dose of the Pandemrix H1N1 vaccine, all CHMP and CBER acceptance criteria for HI antibody response were met in both study groups (that is, co-administered with Fluarix or not). Furthermore, at 21 days after co-administration of Fluarix and the Pandemrix H1N1 vaccine, all CHMP acceptance criteria were exceeded for HI antibody responses against all three seasonal viral strains. In conclusion, the Pandemrix H1N1 vaccine elicited a strong immune response against the vaccine strain (A/California/7/2009) in elderly subjects aged > 60 years. There was no interference due to co-administration with the seasonal influenza vaccine.

Based on the post-Dose 1 result from these three studies, it is considered acceptable to recommend a single dose regimen for Pandemrix H1N1 vaccine in adults > 18 years of age, as the single dose of the vaccine has been shown to elicit adequate immune responses that fulfil all the CHMP and CBER acceptance criteria. Caution is required for adults > 80 years of age as only limited number of subjects of this age group had been evaluated. It remains to be determined whether the two dose regimen would provide advantages with regard to immune persistency and cross reactivity to drift viral strains. It is therefore important that the further study results are provided as they become available; so the information with regard to immune persistency and cross reactivity to drift viral strains can be evaluated.

Safety

Introduction

For all three submitted studies, the safety analyses of Pandemrix H1N1 vaccine were assessed on the Total Enrolled Cohort. In the current submission, the safety analyses are only available up to 21 days after the first dose of vaccination.

For the solicited local and general adverse event (AEs), the incidence occurring during 7 days after the first vaccination was described. The same calculations were performed for symptoms of any intensity, those with intensity of Grade 3, as well as for solicited general events with a relationship to vaccination. All solicited local AEs were considered to be causally related.

The percentage of subjects with at least one report of an unsolicited AE classified by Medical Dictionary for Regulatory Activities (MedDRA; System Organ Class and Preferred Term) up to 21 days after the first vaccination was described. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs that are considered by the investigator to be possibly related to vaccination.

The proportion of subjects who started to receive at least one concomitant medication during the 21-day follow-up period after the first vaccination was calculated.

For serious adverse events (SAEs) and adverse event of specific interest (AESIs), the data up to 21 days after the first vaccination were collected and summarized. In addition, SAEs and withdrawals due to AEs were described.

Study D-Pan H1N1-007

The tables (12-14) below summarise the reporting rates for solicited local and general AEs during the 7 days after the first vaccination.

Table 12: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day post-vaccination period (Total Enrolled cohort).

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
H1N1+ AS03	64	59	92.2	82.7	97.4	64	37	57.8	44.8	70.1	64	56	87.5	76.8	94.4
H1N1	66	39	59.1	46.3	71.0	66	29	43.9	31.7	56.7	66	23	34.8	23.5	47.6

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant; H1N1 = H1N1 containing HA antigen without adjuvant; N= number of subjects with the administered dose; n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 13: Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 7-day post-vaccination period (Total Enrolled cohort).

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
H1N1+ AS03	64	4	6.3	1.7	15.2	64	4	6.3	1.7	15.2	64	1	1.6	0.0	8.4
H1N1	66	2	3.0	0.4	10.5	66	2	3.0	0.4	10.5	66	0	0.0	0.0	5.4

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant; H1N1 = H1N1 containing HA antigen without adjuvant; N= number of subjects with the administered dose; n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 14: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day post-vaccination period (Total Enrolled cohort).

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
H1N1+ AS03	64	58	90.6	80.7	96.5	64	33	51.6	38.7	64.2	64	56	87.5	76.8	94.4
H1N1	66	34	51.5	38.9	64.0	66	24	36.4	24.9	49.1	66	23	34.8	23.5	47.6

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant; H1N1 = H1N1 containing HA antigen without adjuvant; N= number of subjects with the administered dose; n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Solicited local symptoms

Solicited local symptoms were reported more frequently in the H1N1 + AS03A group compared to the H1N1 group. Pain at the injection site was the most frequently reported solicited AE (90.3% of the subjects in the adjuvanted vaccine group and 37.1% in the non-adjuvanted vaccine group). Grade 3 pain was infrequent (1.6% in the H1N1 + AS03A group and absent from the H1N1 group). Swelling and redness were observed at low frequencies in the H1N1 + AS03 A group (6.5% and 1.6%, respectively) and were absent from the H1N1 group.

Solicited general symptoms

Solicited general symptoms were reported in this descending order of frequency in H1N1 + AS03 A and H1N1 groups, respectively: fatigue (33.9% and 29.0%), muscle aches (33.9% and 11.3%), headache (27.4% and 17.7%), joint pain at other location (11.3% and 6.5%), sweating (9.7% in both groups) and shivering (8.1% and 6.5%). The frequency of Grade 3 solicited local or general symptoms was low and did not exceed 1.6%.

Unsolicited AEs

The most frequently reported unsolicited AEs in the AS03 adjuvanted group and non-adjuvanted group were upper respiratory tract infection, headache, rhinitis, oropharyngeal pain and diarrhoea. Two cases of lymphadenopathy were reported in the AS03 adjuvanted H1N1 vaccine group versus none in the non-adjuvanted group. The incidence of unsolicited AEs assessed as related to the vaccination by the investigator was relatively low and comparable in the two study groups (8%). Reports of Grade 3 unsolicited AEs and unsolicited AEs considered as related to vaccination were infrequent and reported in a similar number in both groups. No Grade 3 unsolicited AEs considered as related to vaccination were reported. No specific clinical pattern of unsolicited AEs could be identified in either group.

Deaths and Serious Adverse Events

No deaths were reported up to Day 21. One subject, a 41 year old male, experienced migraine fourteen days after the vaccination. On September 23, the subject experienced sudden onset of visual disorder and right hand paresthesias, then a few hours later had severe headache and nausea. He was referred to the emergency room by his general practitioner. Although all symptoms completely resolved by the evening of 23 September 2009, the subject was hospitalized until September 24 for observation. Neurological exam revealed mild photophobia, laboratory tests were normal and CT scan and MRI of the brain were normal. The differential diagnosis included migraine or transient ischemic attack. Although the most probable diagnosis was migraine, treatment with acetylsalicylic acid was initiated. The subject could leave the hospital in good condition. This SAE was considered as not related to vaccination.

Withdrawals

There were no withdrawals due to adverse events /serious adverse events.

AESIs

No AESIs were reported up to Day 21.

Incidence of concomitant medication

The incidence of taking any concomitant medication during the 21-day post-vaccination period was comparable in the adjuvanted and non-adjuvanted vaccine group (Table 15).

Table 15: Incidence of concomitant medication during the 21-day post-vaccination period. (Total Enrolled cohort)-Study 007

	H1N1+ AS03					H1N1				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	64	23	35.9	24.3	48.9	66	20	30.3	19.6	42.9
Any antipyretic	64	18	28.1	17.6	40.8	66	14	21.2	12.1	33.0
Prophylactic antipyretic	64	4	6.3	1.7	15.2	66	1	1.5	0.0	8.2

Study D-Pan H1N1-008

The safety analysis was performed on the total vaccinated cohort (TVC) of 240 subjects.

The following three tables (16-18 below) summarise the reporting rates for local and general solicited symptoms during the 7-day post-Dose 1 vaccination period for the 18-60 and > 60 years age group. It can be seen that the incidence of AEs was lower in the older age group (> 60) in comparison to the younger age group (18-60).

Table 16: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day post-Dose1 vaccination period for the 18-60 / > 60 stratification (TVC) Study 008.

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Gr 1	18-60	120	111	92.5	86.2	96.5	120	77	64.2	54.9	72.7	120	105	87.5	80.2	92.8
		>60	120	92	76.7	68.1	83.9	120	53	44.2	35.1	53.5	120	82	68.3	59.2	76.5

Gr 1=Subjects receiving D-PAN H1N1 vaccine (A/California/7/2009 (H1N1) v-like 3.75g + AS03A); 18-60=Subjects aged between and including 18 years to 60 years; >60=Subjects aged more than 60years; N= number of subjects with at least one administered dose; n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered; 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit.

Table 17: Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 7-day post-Dose 1 vaccination period for the 18-60 / > 60 stratification (TVC) Study 008.

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Gr 1	18-60	120	9	7.5	3.5	13.8	120	9	7.5	3.5	13.8	120	0	0.0	0.0	3.0
		>60	120	2	1.7	0.2	5.9	120	2	1.7	0.2	5.9	120	0	0.0	0.0	3.0

Table 18: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day post-Dose 1 for the 18-60 / > 60 stratification (TVC).

			Any symptom					General symptoms					Local symptoms				
						95% CI					95% CI					95% CI	
	Group	Sub-group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
Dose 1	Gr 1	18-60	120	109	90.8	84.2	95.3	120	67	55.8	46.5	64.9	120	105	87.5	80.2	92.8
		>60	120	86	71.7	62.7	79.5	120	42	35.0	26.5	44.2	120	82	68.3	59.2	76.5

Solicited local symptoms

Solicited symptoms were reported more frequently in subjects 18-60 years of age (87.5%) in comparison to subjects > 60 years of age (68.3%). Pain at the injection site was the most frequently reported one (87.5% in subjects 18-60 years of age and 65.0% in subjects > 60 years of age, see that table below). No Grade 3 pain was reported. Swelling and redness were observed at low frequencies in the two age strata (in subjects 18-60 years of age: 9.2 % and 0.8%, respectively and in >60 years of age: 10.0 % and 7.5%, respectively). Results are summarised in Table 19 below.

Table 19: Incidence of solicited local symptoms reported during the 7- day post-Dose 1 vaccination period for the 18-60 / >60 stratification (Total vaccinated cohort).

		Gr 1									
		18-60					>60				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	All	120	105	87.5	80.2	92.8	120	78	65.0	55.8	73.5
	Grade 1	120	64	53.3	44.0	62.5	120	65	54.2	44.8	63.3
	Grade 2	120	41	34.2	25.8	43.4	120	13	10.8	5.9	17.8
	Grade 3	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
Redness (mm)	All	120	1	0.8	0.0	4.6	120	9	7.5	3.5	13.8
	[20.1 - 50.1[	120	1	0.8	0.0	4.6	120	7	5.8	2.4	11.6
	[50.1 - 100.1[	120	0	0.0	0.0	3.0	120	2	1.7	0.2	5.9
	[100.1 - ...	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0
Swelling (mm)	All	120	11	9.2	4.7	15.8	120	12	10.0	5.3	16.8
	[20.1 - 50.1[	120	5	4.2	1.4	9.5	120	8	6.7	2.9	12.7
	[50.1 - 100.1[	120	6	5.0	1.9	10.6	120	4	3.3	0.9	8.3
	[100.1 - ...	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0

Solicited general symptoms

In the two age groups, solicited general symptoms were reported in this order of frequency:

- In subjects 18-60 years: headache (36.7%), fatigue (35.8 %), muscle aches (24.2%), shivering (19.2%), joint pain at other location (15.8%) and sweating (15.8%).
- In subjects > 60 years of age: fatigue (21.7 %), muscle aches (20.8%), headache (18.3%), joint pain at other location (14.2%), shivering (5.8%) and sweating (5.0%).

The frequency of Grade 3 solicited local or general symptoms, in subjects 18-60 years of age, was 7.5% (with 5.0% considered as related to vaccination) whereas in subjects > 60 years of age, it was lower and did not exceed 1.7% (all considered as related to vaccination). No Grade 3 local AE was reported.

Unsolicited AEs

Unsolicited AEs were reported in 44.2% (with 20.0% related to vaccination) in subjects 18-60 years of age and 25.8% (with 11.7% related to vaccination) in subjects > 60 years of age. The most frequently reported event was nasopharyngitis. There was no clinical pattern of the reported events. Reports of Grade 3 unsolicited AEs in subjects 18-60 years of age was 8.3% with 2.5% related to vaccination. Reports of Grade 3 unsolicited AEs in subjects > 60 years were infrequent (0.8%) with none consider as related to vaccination (see the Table 20 below).

Table 20: Percentage of subjects reporting Grade 3 unsolicited AEs with causal relationship to vaccination, within the 21-day post-Dose 1 for the 18-60 /> 60 stratification (Total vaccinated cohort).

		Gr 1							
		18-60 N = 120				>60 N = 120			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	2.5	0.5	7.1	0	0.0	0.0	3.0
General disorders and administration site conditions (10018065)	Influenza like illness (10022004)	2	1.7	0.2	5.9	0	0.0	0.0	3.0
Infections and infestations (10021881)	Gastroenteritis (10017888)	1	0.8	0.0	4.6	0	0.0	0.0	3.0

Withdrawal, SAE and AESIs

There were no withdrawals due to adverse events /serious adverse events. No SAEs and AESI were reported up to Day 21.

Incidence of concomitant medication

The incidence of taking concomitant medicines and of taking any antipyretic medicine was lower in the older age group: 35.8% in 18-60 age group and 17.5% in the > 60 age group (see Table 21).

Table 21: Incidence of concomitant medication during the 21-day (Days 0-20) post-Dose 1 vaccination period for the 18-60 / >60 stratification (Total vaccinated cohort).

	Gr 1									
	18-60					>60				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	120	43	35.8	27.3	45.1	120	21	17.5	11.2	25.5
Any antipyretic	120	31	25.8	18.3	34.6	120	11	9.2	4.7	15.8
Prophylactic antipyretic	120	0	0.0	0.0	3.0	120	0	0.0	0.0	3.0

Study D-Pan H1N1-018

The safety analysis was performed on the Total Vaccinated Cohort (primary analysis). The following five tables (Tables 22-26 below) summarise the reporting rates for local and general solicited symptoms during the 7-day post-Dose 1 vaccination period.

Table 22: Incidence and nature of symptoms (solicited and unsolicited) reported during the 7-day post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	84	61	72.6	61.8	81.8	84	36	42.9	32.1	54.1	84	59	70.2	59.3	79.7
PAN-F	84	71	84.5	75.0	91.5	84	32	38.1	27.7	49.3	84	67	79.8	69.6	87.7

F-PAN = Subjects receiving two doses of the H1N1 co-administered first with Fluarix then with placebo
PAN-F = Subjects receiving two doses of the H1N1 co-administered first with placebo then with Fluarix
N= number of subjects with the administered dose
n/%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine administered
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

Table 23: Incidence and nature of local symptoms (solicited and unsolicited) reported for each vaccine during the 7-day post-vaccination period (Total vaccinated cohort)

	Fluarix					H1N1+ASO3					PLACEBO				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	84	20	23.8	15.2	34.3	84	59	70.2	59.3	79.7	0	0	0.0	0.0	0.0
PAN-F	0	0	0.0	0.0	0.0	84	66	78.6	68.3	86.8	84	11	13.1	6.7	22.2

Table 24: Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the 7-day post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	84	1	1.2	0.0	6.5	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3
PAN-F	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3	84	1	1.2	0.0	6.5

Table 25: Incidence and nature of local Grade 3 symptoms (solicited and unsolicited) reported for each vaccine during the 7-day post-vaccination period (Total vaccinated cohort)

	Fluarix					H1N1+ASO3					PLACEBO				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	84	0	0.0	0.0	4.3	84	0	0.0	0.0	4.3	0	0	0.0	0.0	0.0
PAN-F	0	0	0.0	0.0	0.0	84	1	1.2	0.0	6.5	84	0	0.0	0.0	4.3

Table 26: Incidence and nature of symptoms (solicited and unsolicited) with causal relationship to vaccination, reported during the 7-day post-vaccination period (Total vaccinated cohort)

	Any symptom					General symptoms					Local symptoms				
				95% CI					95% CI					95% CI	
Group	N	n	%	LL	UL	N	n	%	LL	UL	N	n	%	LL	UL
F-PAN	84	61	72.6	61.8	81.8	84	29	34.5	24.5	45.7	84	59	70.2	59.3	79.7
PAN-F	84	71	84.5	75.0	91.5	84	25	29.8	20.3	40.7	84	67	79.8	69.6	87.7

Solicited local symptoms

Pain at the injection site was the most frequently reported solicited AE (69.0% of the subjects in the F-PAN group and 78.6% in the PAN-F group. There was no Grade 3 pain reported. Swelling and redness were observed at a frequency in the F-PAN group of 17.9% and 7.1%, respectively and were observed in a frequency of respectively 23.8% and 13.1% in the PAN-F group. Grade 3 solicited local symptoms were reported infrequently (1 subject in the PAN-F group reported Grade 3 swelling).

Solicited general symptoms

Solicited general symptoms (Table 34B, Part B) were reported in this order of frequency in F-PAN and PAN-F groups, respectively: fatigue (16.7% and 22.6%), headache (14.3% and 17.9%), joint pain at other location (8.3% and 10.7%), muscle aches (15.5% and 19.0%), shivering (8.3% and 11.9%) and sweating (1.2% and 4.8%). No Grade 3 general symptoms were reported.

Unsolicited symptoms

A total of 27 subjects reported at least one unsolicited symptom during the 21-day post-vaccination period: 13 in the F-PAN group and 14 in the PAN-F group. No clinical pattern of events could be distinguished. Reports of Grade 3 unsolicited AEs and unsolicited AEs considered as related to vaccination were infrequent and reported in a similar number in both groups. No Grade 3 unsolicited AEs considered as related to vaccination were reported. Results are summarised in Tables 27-28 below.

Table 27: Summary of unsolicited AEs within the 21-day post-vaccination period (Total vaccinated cohort).

	Group		
	F-PAN	PAN-F	Total
Number of subjects with at least one unsolicited symptom reported	13	14	27
Number of doses followed by at least one unsolicited symptom	13	14	27
Number of unsolicited symptoms classified by MedDRA Preferred Term*	18	24	42
Number of unsolicited symptoms reported	19	24	43

Table 28: Percentage of subjects reporting Grade 3 unsolicited AEs classified within the 21-day post-vaccination period (Total vaccinated cohort).

		F-PAN N = 84				PAN-F N = 84			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		1	1.2	0.0	6.5	1	1.2	0.0	6.5
Respiratory, thoracic and mediastinal disorders (10038738)	Epistaxis (10015090)	0	0.0	0.0	4.3	1	1.2	0.0	6.5
Vascular disorders (10047065)	Hypertension (10020772)	1	1.2	0.0	6.5	0	0.0	0.0	4.3

Serious adverse events

One SAE was reported. This was a 69 year old male who was hospitalized for worsening of hypertension 4 days after the vaccination. The condition lasted for 2 days and was subsequently resolved. The subject recovered and this SAE was not considered to be related to vaccination.

AESIs

No AESIs were reported up to Day 21.

Withdrawals

No withdrawals due to adverse events /serious adverse events occurred up to Day 21.

Post-marketing experience

The first simplified Periodic Safety Update Reports (12 October 2009 to 08 November 2009)

The first doses of Pandemrix H1N1 were shipped on 7 October 2009. Per the CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) included provisions for the submission of monthly simplified Periodic Safety Update Reports (PSURs) accompanied by a summary of vaccine distribution. The clock start date for submission of simplified PSURs was 12 October 2009, as this was the first Monday after shipping commenced. This is the first simplified PSUR for Pandemrix H1N1. The reporting period for this report is 12 October 2009 to 08 November 2009. The cumulative reporting period is also 12 October 2009 to 08 November 2009. It is important to note that no post-marketing AE reports for Pandemrix H1N1 were received by GSK prior to 12 October 2009. During the reporting period, a total of 472 AE reports were received by GSK Biologicals. No change to the benefit-risk profile of Pandemrix H1N1 has been identified from this PSUR. Specific analyses were conducted on reports with fatal outcome and reports of anaphylaxis, angioedema, and urticaria. Signals were validated for anaphylaxis, angioedema, and urticaria. These events were added to the Reference Safety Information and a variation to update the EU Summary of Product Characteristics (SPC) has been submitted. In addition to the signals, an analysis was performed for reports with fatal outcome.

The second simplified PSUR (09 November 2009 to 06 December 2009

During the reporting period, a total of 5,278 AE reports were received by GSK Biologicals, bringing the cumulative number of reports to 5,785. Specific analyses were conducted on reports with fatal outcome and reports of anaphylaxis (updated analysis), convulsions, dysgeusia, facial palsy, fever and febrile convulsions, pregnancy outcomes, transplant rejection, and worsening of asthma. No changes to the Reference Safety Information for Pandemrix H1N1 were made as a result of these analyses. No change to the benefit-risk profile of Pandemrix H1N1 has been identified. During or immediately after the current reporting period, specific analyses were conducted on reports with fatal outcomes and reports of anaphylaxis (updated analysis), convulsions, dysgeusia, facial palsy, fever and febrile convulsions, pregnancy outcomes, transplant rejection, and worsening of asthma. None of these signals were validated and no changes were made to the Reference Safety Information for Pandemrix H1N1. At the request of EMA, the term 'febrile convulsions' was added to the EU SPC.

Evaluator's overall conclusions on clinical safety

The safety data is only available up to 21 days after the first dose of vaccination in all three studies.

In Study 007, a higher reactogenicity was observed in the adjuvanted H1N1 vaccine group (Pandemrix H1N1) compared to non-adjuvanted vaccine group. Grade 3 solicited local or general symptoms were infrequently reported. One subject reported an SAE which was considered as not related to vaccination.

The safety profile post-Dose 1 in Study 008 was comparable to that seen in Study 007. No deaths or other SAEs were reported, and there were no AEs leading to withdrawal up to Day 21 post-Dose 1. The incidence of AEs appears to be lower in the older age group (> 60) in comparison to the younger age group (18-60).

The reactogenicity profile of Pandemrix H1N1 observed in Study 018 was comparable to that seen in Study 007 and 008 conducted in adults. The most common solicited local and general AEs were pain in both age strata and fatigue. No deaths were reported. One unrelated SAE was reported and there were no AEs leading to withdrawal up to Day 21 postDose 1. Co-administration with a licensed seasonal vaccine, Fluarix, did not impact the overall reactogenicity profile.

Overall, the limited post-Dose 1 safety data from the three submitted studies indicates that the Pandemrix H1N1 vaccine has a similar safety profile to that of the seasonal influenza vaccines, and no specific safety concerns were raised from these results.

With regard to the post-marketing experience, the first and second simplified PSURs covering period from 12 October 2009 to 06 December 2009 are submitted. Based on the information from the PSURs, anaphylaxis, angioedema, urticaria, and convulsion are added to the EU SPC, and these events are also included in the Australian PI under the subheading of "Post-marketing data".

Clinical Summary and Conclusions

Clinical benefits

Based on the results from the three submitted studies, the immune responses (SCR, SCF, and SPR) following the first dose of the Pandemrix H1N1 vaccine have fulfilled all the CHMP and CBER acceptance criteria regardless of the age range, baseline serostatus, and prior history of seasonal vaccination.

The three studies covered the adult population of different age cohorts: 18-60 years (Study 007), 18-60 and > 60 years (Study 008), and > 60 years (Study 018). There was reasonable number of subjects over 60 years old (120 in Study 008 and 168 in Study 018) and of subjects over 70 years old (45 in Study 008 and 56 in Study 018). Although there was a trend towards lower immune responses with increased age, the post-Dose 1 immune response (SPR, SCR, and SCF) in older

subjects have met all the CHMP and CBER acceptance criteria. Based on these results, it is considered acceptable to propose a single dose regimen for adults >18 years of age.

It is noted that only limited number of the very elderly (> 80 years old) were assessed in these studies. This information has been reflected in the Product Information. Despite this limitation, it is considered that the option of the single dose regimen should be offered to adults over 80 years of age. The benefits of the two dose regimen remain to be seen. The two dose regimen may offer longer duration of immune responses and better cross protection for drift viral strains. It is important that the sponsor will submit further study results as they become available.

It is notable that in Study 007, the immunogenicity elicited after the first dose of the Pandemrix H1N1 vaccine (3.75 µg) was comparable to that induced by 15 µg unadjuvanted H1N1 vaccine, but the adverse events were reported more frequently with the adjuvanted Pandemrix H1N1 vaccine.

Risk assessment

The safety profile of the Pandemrix H1N1 vaccine appears to be generally comparable with that reported with seasonal influenza vaccines and Pandemrix H5N1 vaccine in adults aged 18-60 years and in older subjects. The reporting rates in older adults were generally lower than in the younger cohort. There were no new safety issues raised from the post-Dose 1 safety results of the submitted studies.

Conclusion

The clinical evaluator concluded that there is a favourable benefit / risk balance with the administration of Pandemrix H1N1 vaccine in adults over 18 years old, and recommended registration approval of Pandemrix H1N1 vaccine for the following indication:

"Prophylaxis of influenza in an officially declared pandemic situation. PANDEMRIX H1N1 vaccine should be used in accordance with official recommendations."

The recommended dose regimen for adults greater than 18 years of age is one or two doses of Pandemrix H1N1 vaccine.

Recommended condition for registration

Pandemrix H1N1 vaccine should be granted registration approval providing that the sponsor is committed to the following conditions:

- To submit the results from all the ongoing studies
- To conduct Pharmacovigilance activities as agreed with the Office of Medicine Safety Monitoring (OMSM).
- To amend the Product Information to the satisfaction of the TGA.

V. Pharmacovigilance Findings

Most of the following Pharmacovigilance activities will occur for anaphylaxis, autoimmune hepatitis (AIH), Bell's palsy, convulsion, demyelinating disorders, encephalitis, Guillain-Barré syndrome (GBS), increased concentrations of hepatic enzymes, neuritis, vasculitis and vaccination failure

- Weekly signal detection
- Use of targeted follow-up questionnaires
- Individual reports expedited to regulators
- Included in Table 3 of simplified PSURs
- Cumulative analysis included in full PSUR following end of pandemic period
- Incidence will be estimated in participants in the post-authorisation safety study

The European Risk Minimisation Plan was also submitted in Australia. It comprises routine activities for the potential safety risks with additional activities for potential medication errors due to confusion with vaccine and adjuvant vials, and contamination of multiple-dose vials. The activities for the potential safety risks are tabulated below.

Potential risk	**Proposed risk minimisation activities (routine and additional)**
Anaphylaxis	Contraindication in the proposed labelling; Precaution in the proposed labelling regarding use in persons with known hypersensitivity, other than anaphylaxis, to vaccine components
Autoimmune hepatitis	NA
Bell's palsy	NA
Convulsion	NA
Demyelinating disorders	NA
Encephalitis	NA
Guillain-Barré syndrome	NA
Increased concentrations of hepatic enzymes	NA
Neuritis	NA
Vasculitis	NA
Vaccination failure	NA
Missing data in pregnant women	NA
Missing data in children	No inclusion of children in the indication section of the proposed labelling; Statement in proposed labelling that there is no experience in children.
Limited data in subjects with compensated underlying disease. No data in subjects with severe underlying medical conditions/immunocompromise	NA

NA=not applicable.

The Risk Minimisation Activities for potential medication errors proposed for Europe and submitted in Australia are tabulated below.

Potential safety concern	Medical errors/misidentification of vaccine
Routine risk minimisation activities	The package leaflet and the **Use and Handling** section of the SPC provides detailed instructions for mixing the vaccine; the labelling of the vials has been designed in order to enable easy distinction between the antigen vial (Vial A) and the adjuvant vial (Vial B).
Additional risk minimisation activity 1	*Objective and rationale:* Demonstrate the proper mixing of the antigen and adjuvant independent of vaccine packaging because the packaging may not be retained.
	Proposed action: Provide stand-alone instructional materials (pictograms and a video) that demonstrate proper mixing to governments who purchase the vaccine.
	Criteria to be used to verify the success of proposed risk minimisation activities: Review of spontaneous reports of medical errors; feedback from national agencies.
	Proposed review period: Duration of H1N1 influenza pandemic.
Additional risk minimisation activity 2	*Objective and rationale:* Facilitate identification of administered vaccine to prevent using different brands to complete the immunisation series; and to facilitate inclusion of batch numbers in adverse event reports, which will assist in signal detection.
	Proposed action: Provide stickers in each package of vaccine that include the vaccine brand name and batch number; the stickers can be affixed to the healthcare records of the vaccine recipients or other document that governments will foresee to record the identity of vaccine recipients.
	Criteria to be used to verify the success of proposed risk minimisation activities: Review percentage of spontaneous adverse event reports that contain the vaccine brand name and batch number.
	Proposed review period: Duration of H1N1 influenza pandemic.
Potential safety concern	Contamination of multiple-dose vials
Routine risk minimisation activities	The package leaflet and the **Use and Handling** section of the SPC provides detailed instructions for mixing and administration of the vaccine with instructions to discard the vaccine for any variation in appearance and to replace the needle used for withdrawal of vaccine with a needle suitable for intramuscular injection. **Shelf-Life** section of the SPC states, "After mixing, the vaccine should be used within one working day." Vaccine contains thimerosal as a preservative.
Additional risk minimisation activity 1	*Objective and rationale:* Demonstrate proper mixing and administration of vaccine independent of vaccine packaging because the packaging may not be maintained
	Proposed action: Provide stand-alone instructional materials (pictograms and a video) that demonstrate proper mixing and administration of vaccine to governments who purchase the vaccine
	Criteria to be used to verify the success of proposed risk minimisation activities: Review of spontaneous reports of injection site infection, injection site abscess, injection site cellulitis.
	Proposed review period: Duration of H1N1 influenza pandemic.

OMSM Comment: The Risk Management Plan (RMP) for Pandemrix H1N1 Vaccine- Pandemic influenza vaccine was prepared in September 2009. Since this time, the Pandemrix H1N1 vaccine has been used widely in countries including Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Israel, Malaysia, Netherlands, Norway, Singapore, Spain, Sweden, Switzerland, and the UK. In the most recent EMA pandemic pharmacovigilance update (17 February 2010), it is indicated that, as at 5 February 2010, at least 84.7 million doses of Pandemrix have been distributed with at least 27.6 million patients vaccinated.

As the H1N1 vaccine had not been assessed in trials prior to the RMP, the plan is based on information from studies conducted on the H5N1 formulation of Pandemrix. It is considered that experience with seasonal trivalent influenza vaccines (TIV) suggests that there is no reason to suspect differences between the demonstrated safety profile of the H5N1 formulation and an H1N1 formulation. This is because:

- The strains will be derived and processed in the same way.
- There will be no differences in the antigen manufacturing process.
- The formulation will not change except for the strain.
- The controls and specifications will not change.
- The dose will not change (3.8 mcg HA).
- The AS03 will remain the same and the same quantity will be administered.

Comprehensive information is provided on the safety profile of H5N1 vaccines obtained from eight clinical trials. In presentation of these data, there is particular reference to adverse events of special interest (AESI) specified in the CHMP recommendations (EMEA/359381/2009) for pharmacovigilance planning for pandemic influenza vaccine. Also, there is consideration of thiomersal (a preservative), the adjuvant squalene (derived from shark liver oil), and egg (a residue) due to concerns with allergic reactions.

It is concluded that extensive experience with seasonal TIV suggests that there is no reason to suspect differences between the demonstrated safety profile of the H5N1 formulation of Pandemic influenza vaccine and an H1N1 formulation. Of note, the recent EMA update states: "The vast majority of the adverse reactions that had been reported as of 31 January 2010 are considered to be non-serious. The benefit-risk balance of the pandemic vaccines being used for the current H1N1 influenza pandemic continues to be positive."

The following risks are addressed:

- Important identified risks: None.
- Important potential risks: AESI for close monitoring following the administration of H1N1 pandemic vaccines events specified in the CHMP recommendations, anaphylaxis, Bell's palsy, convulsion, demyelinating disorders, encephalitis, GBS, neuritis, vasculitis, and vaccination failure; AIH and increased concentrations of hepatic enzymes.
- Important missing information: Safety data in pregnant women, individuals with clinically severe underlying medical conditions, and immunocompromised individuals; limited safety data in children.

Consideration of AIH and increased concentrations of hepatic enzymes is due to a request by the EMA subsequent to several reports of these AE with H5N1.

Detailed information on routine Pharamcovigilance (PhV) activities is presented and also on enhanced PhV done by GSK for vaccines. This entails close monitoring of GBS, thrombocytopaenia and sudden unexplained infant death. Modified PhV activities based on the CHMP recommendations are also described.

An overview of proposed post marketing studies was presented. These include a cohort study and pregnancy register as per the CHMP recommendations. No study protocols were provided.

Subsequent to assessment of the requirement for risk minimisation activities, the sponsor considered that routine activities are adequate for the potential safety concerns. Routine and additional risk minimisation activities are proposed to mitigate the potential for medication errors due to confusion between the vaccine vials and adjuvant vials and contamination of the multiple dose vials.

The proposed PI, based on information available at the time of the application, was reviewed. The most recent European Union (EU) Summary of Product Characteristics (SmPC) was also reviewed.

This contained additional information to reflect the current status of knowledge gained from post marketing surveillance and studies.

It is considered that these activities are acceptable. However, it is noted that the proposed labelling does not include (or exclude) children in the Indication section and that it states there is no experience in children. When there has been information in the age group gained from clinical trials and post marketing experience, these will need to be updated in the Australian PI to reflect current knowledge.

As there has been extensive post marketing use of H1N1 Pandemrix and data from post marketing studies and surveillance, if this product is registered, the following should occur prior to its launch in Australia:

- An updated RMP including current data from post marketing studies and surveillance should be provided to the TGA.
- The PI for health professionals and consumers should be updated to correspond with information known at the time of the proposed launch.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Application.

This application is for a major variation to pandemic influenza vaccine (H5N1) split virion, inactivated, AS03 adjuvanted (Pandemrix) to amend the HA strain to A/California/7/2009 like strain and to amend the dosage regimen. Pandemrix (H5N1) was registered in 2008 as a 'mock up' pandemic influenza vaccine.

Pandemrix H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official recommendations. The recommended dose in adults aged 18 years and older is one or two doses of 0.5 mL. Immunogenicity data obtained at 3 weeks after administration of Pandemrix H1N1 in clinical studies suggest a single dose may be sufficient. If a second dose is administered there should be an interval of at least 3 weeks between the first and second dose. Limited data have been generated below 18 years and above 60 years of age. The immunogenicity and reactogenicity profile of Pandemrix in this population is therefore unknown.

Note: Pandemrix is also referred to as D-Pan.

Quality

The HA fraction manufacture methods are analogous to those used for seasonal influenza vaccines and approved for Pandemrix. The H1N1 vaccine strain is propagated in eggs, harvested, concentrated, split, inactivated and fractionated. The adjuvant consists of α-tocopherol and squalene. The mixed vaccine is an oil-in-water emulsion where the H1N1 HA is in aqueous phase. The quality aspects of the current submission were approved in two category 3 applications in December 2009.

There are no outstanding quality issues for this application.

Nonclinical

No new nonclinical data were submitted for this application.

Clinical

Clinical data were provided in interim (post-Dose 1) abridged reports of three clinical immunogenicity and safety studies all conducted in adults ≥ 18 years. These are studies D-Pan H1N1-007, D-Pan H1N1-008 and D-Pan H1N1-018.

D-Pan H1N1-007 is a single centre, randomised, observer blind study to assess immune response with two doses of Pandemrix H1N1 vaccine in adults 18-60 years. Treatments studied were 3.75 µg of HA (A/California/7/2009 (H1N1) like) + AS03 adjuvant or 15 µg of HA (A/California/7/2009 (H1N1) like) unadjuvanted. Immunogenicity endpoints were consistent with "Guideline on dossier content and structure for pandemic influenza vaccine (CPMP/VEG/4717/03)". HI assays were conducted by GSK.

A total of 130 subjects were enrolled, stratified in 18-40 years, 41-50 years and 51-60 years strata. Mean age was 38.6 years, 61.5% were female and 99% were Caucasian.

Antibody results were reported for 127 subjects. At baseline antibody seropositivity was present in 32.8% to 42.4% of subjects. At Day 21 seroprotective titres were reported in 100% in the AS03 treatment group and 93.9% of the unadujvanted group overall. Seroconversion rates were 96.7% in AS03 group and 84.8% in adjuvanted group overall. The observed immune response comfortably met all 3 CHMP (and also FDA) criteria after a single dose in both treatment groups although there was some trend to lower rates in the unadjuvanted group especially in the over 40 age stratum. CHMP criteria were also met regardless of baseline serostatus.

Neutralising antibodies were measured but results are not available in the interim analysis.

D-Pan H1N1-008 is a Phase III, randomised, open label study which assessed Pandemrix H1N1 vaccine given in 1 or 2 doses to health adults > 18 years of age. Immune response was measured by HI antibodies with endpoints consistent with CPMP/VEG/4717/03.

A total of 240 subjects were enrolled, 120 to a stratum 18-60 years and 120 to a >60 year stratum. A total of 55.9% were female and 100% were Caucasian.

Day 21 results were reported for all enrolled subjects. At baseline antibody seropositivity was present in 36.8% to 42.5% of subjects. At day 21 seroprotective titres were reported in 97.5% in the younger age stratum and in 87.5% in the >60 year stratum. Seroconversion rates were 95% in the younger stratum and 79.2% in the >60 year stratum. In both age stratum CHMP and FDA immunogenicity criteria were comfortable met. All tested parameters showed a trend to lower point estimates in the older age stratum. HI response according to baseline serostatus is shown in Table 7. CHMP criteria were also met regardless of baseline serostatus in both age stratum, and were also met in analysis of age categories 61-70 years, 71-80 years and >80 years. Immune response was also assessed based on history of seasonal vaccination. Subjects who were seronegative at baseline and who had history of prior seasonal vaccination had lowest GMT and SPR rates at day 21, however this subgroup still met the three CHMP criteria.

D-Pan H1N1-018 is a Phase II randomised, observer blind study to assess a two dose schedule of Pandemrix H1N1 vaccine when co-administered with 2009-2010 seasonal influenza vaccine (Fluarix) in elderly subjects aged 61 years or older.

Two groups were randomised to receive either Day 0 Pandemrix H1N1+ Fluarix and Day 21 Pandemrix H1N1 + placebo or Day 0 Pandemrix H1N1 + placebo and Day 21 Pandemrix H1N1 +Fluarix.

A total of 168 subjects were enrolled and completed vaccination on Day 0 and the Day 21 visit. Demographics are summarised in Table 10. Mean age was 69 years and male distribution was 47%.

HI antibody results against H1N1 (2009) at 21 days post-Dose 1 are shown in Table 11. In the group who received Pandemrix H1N1+placebo 38.1% showed seropositivity at baseline. At 21 days seroprotection rate was 96.4%, seroconversion rate was 92.9% and fold increase was 19.8. In the group who received Pandemrix H1N1+ Fluarix 23.8% showed seropositivity at baseline. At 21 days seroprotection rate was 89.3%, seroconversion rate was 88.1% and fold increase was 18.8. Responses were similar for the strata 61-70 years and >70 years. CHMP criteria against H1N1

were met regardless of baseline serostatus and whether Fluarix was co-administered. Day 21 responses exceeded CHMP criteria for adults >60 years for all 3 strains.

Safety

Safety was assessed in the total enrolled cohort in clinical studies. In the current submission safety AE analyses are available up to 21 days post-vaccination. SAEs and withdrawals were also described.

In Study D-Pan H1N1-007 rates of solicited local and general symptoms are shown in Table 12. In the AS03 group 92.2% reported symptoms compared to 59.1% in the unadjuvanted group. The rate of both general symptoms (57.8%) and local symptoms (87.5%) was higher in the AS03 group. The rate of any Grade 3 symptoms was 6.3% in the AS03 group and 3% in unadjuvanted group. The rate of both Grade 3 general symptoms (6.3%) and local symptoms (1.6%) was higher in the AS03 group.

No deaths were reported in 007. One SAE was reported in a 41 year old who experienced migraine and transient neurological deficit with hospitalisation after 14 days post-vaccination. Use of concomitant medication was more frequent in the AS03 group.

In Study D-Pan H1N1-008 rates of solicited local and general symptoms are shown in Table 16. The majority of subjects in both age strata reported symptoms with the rate in the 18-60 year group (92.5%) similar to the previous study. The predominant local symptom was pain. Grade 3 symptoms were reported by 7.5% in the 18-60 year group and 1.7% in the >60 group. There were no SAEs or withdrawals to day 21.

The rates of solicited local and systemic symptoms were not higher for Pandemrix H1N1 co-administered with Fluarix compared to co-administered with placebo in Study D-Pan H1N1-018. The incidence of Grade 3 symptoms was 1.2% when co-administered with both Fluarix and placebo, due to epistaxis or hypertension. One SAE was hypertension 4 days after vaccination which resolved after 2 days and was not considered related to vaccination.

Simplified PSURs covering the period 12 Oct 09 to 6 Dec 09 were submitted. No change to the benefit/risk profile of Pandemrix H1N1 was concluded.

Clinical evaluator recommendation

The HI antibody response following 1st dose of Pandemrix H1N1 satisfied all CHMP and FDA criteria for pandemic influenza vaccines in studies in subjects 18 years and older. It remains to be determined if the two dose regimen may provide advantage with regard to immune persistence or cross-reactivity. In Study 007, the unadjuvanted 15 µg vaccine also satisfied all CHMP and FDA criteria. Higher rates of lower and general symptoms were reported with Pandemrix H1N1 compared to unadjuvanted vaccine in Study 007, and with a modest but higher rate of Grade 3 symptoms. No SAEs related to vaccine were reported in clinical studies. Post-marketing experience reported in first and second simplified PSURs has let to inclusion of anaphylaxis, angioedema, urticaria and convulsion to EU SPC. The safety profile of Pandemrix H1N1 appears to be generally comparable to seasonal influenza vaccine and Pandemrix H5N1 vaccine. The clinical evaluator considered that there is a favourable benefit/risk balance and registration is supported for adults aged 18 years or older.

Risk Management Plan.

A European Risk Management Plan (RMP) for Pandemrix H1N1 Vaccine was prepared in September 2009 which has been reviewed by OMSM.

In the most recent European Medicines Agency (EMA) pandemic pharmacovigilance update (17 February 2010), it is indicated that, as at 5 February 2010, at least 84.7 million doses of Pandemrix H1N1 have been distributed with at least 27.6 million patients vaccinated.

Risk-Benefit Analysis

Pandemrix (H5N1) was registered by TGA in 2008 based on the EMA Guidance for a core pandemic dossier and mock-up vaccine. Adequate quality data have been submitted to amend the HA strain variation to A/California/7/2009 like strain.

This application has also provided interim clinical study reports that demonstrate a single 3.75 µg H1N1 (2009) dose of ASO3 adjuvanted vaccine in adult subjects is adequate to elicit HI antibody responses that satisfy EMA and FDA requirements for pandemic influenza vaccine. There were significant baseline seropositivity rates (21% to 45% across study subgroups) to H1N1 2009 in the clinical study populations. The interim clinical study reports provide no information on possible infection with H1N1 2009 virus during the course of studies which might have contributed the high antibody responses observed.

The adverse event profile of Pandemrix H1N1 in clinical studies is considered acceptable and in line with the profile demonstrated for Pandemrix H5N1. There is now relatively extensive post-marketing experience which reports (to 31 January 2010) that the vast majority of the adverse reactions that had been reported are considered to be non-serious and the benefit-risk balance of the pandemic vaccines being used for the current H1N1 influenza pandemic continues to be positive.

This product is a 10 dose multidose presentation which is considered acceptable in the context of the indications for use in accordance with official recommendations in an officially declared pandemic.

The Delegate supported the clinical evaluator's conclusion that there is a favourable benefit/risk balance and that Pandemrix H1N1 vaccine could be registered.

Conditions of registration recommended in the CER include submission of results of ongoing clinical studies with Pandemrix H1N1 vaccine, conduct of Pharmacovigilance activities as agreed with OMSM and amendment of product information.

Proposed Action

The Delegate proposed to register pandemic influenza vaccine (H1N1) split virion, inactivated, AS03 adjuvanted (Pandemrix H1N10 which contains 3.75 µg haemagglutinin of A/California/7/2009 like strain per 0.5 mL dose.

Pandemrix H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official recommendations. The recommended dose in adults aged 18 years and older is one or two doses of 0.5 mL. Immunogenicity data obtained at 3 weeks after administration of Pandemrix H1N1 in clinical studies suggest a single dose may be sufficient. If a second dose is administered there should be an interval of at least 3 weeks between the first and second dose.

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.

ACPM recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register a new fomulation and change to dosage regimen for pandemic influenza vaccine (H1N1) for the indication:

> *"Pandemrix H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. Pandemrix should be used in accordance with official recommendations."*

In making this recommendation the ACPM advised that safety and efficacy of the formulation and the dosage regimen for the proposed indication has been sufficiently demonstrated and acknowledged that the post marketing surveillance will mitigate the lack of safety evidence

associated with the studies being limited to 21 days. The ACPM noted the data provided evidence for one dose of vaccine only.

The ACPM expressed strong interest in the sponsor presenting data that reflects the recent pandemic experience and expressed their continued concern about multi-dose dosage formulations.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pandemrix H1N1 pandemic influenza vaccine split virion, inactivated, AS03 adjuvanted 0.5 mL vaccine dose containing 3.75 µg of haemagglutinin of A/California/7/2009(H1N1)v-like strain indicated for:

> Prophylaxis of influenza in an officially declared pandemic situation. Pandemrix H1N1 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.

PANDEMRIX™ H1N1 PRODUCT INFORMATION
Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted)

NAME OF THE MEDICINE

PANDEMRIX H1N1, emulsion and suspension for emulsion for injection.
Pandemic influenza vaccine (split virion, inactivated, AS03 adjuvanted).

DESCRIPTION

Each 0.5mL vaccine dose contains 3.75 micrograms[1] of antigen[2] of A/California/7/2009 (H1N1)v-like strain and is adjuvanted with AS03[3].
[1]haemagglutinin
[2]propagated in eggs
[3]The GlaxoSmithKline proprietary AS03 adjuvant system is composed of squalene (10.68 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.85 milligrams)

This vaccine complies with the World Health Organisation (WHO) recommendation for the pandemic.

Each 0.5mL vaccine dose also contains the excipients Polysorbate 80, Octoxinol 10, Thiomersal, Sodium Chloride, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, Potassium Chloride and Magnesium chloride. The vaccine may also contain the following residues: egg residues including ovalbumin, gentamicin sulfate, formaldehyde, sucrose and sodium deoxycholate.

CLINICAL TRIALS

This section describes the clinical experience with *PANDEMRIX* (H1N1) after a single dose in healthy adults aged 18 years and older and the mock-up vaccines (Pandemrix H5N1) following a two-dose administration .

Mock-up vaccines contain influenza antigens that are different from those in the currently circulating influenza viruses. These antigens can be considered as “novel” antigens and simulate a situation where the target population for vaccination is immunologically naïve. Data obtained with the mock-up vaccine will support a vaccination strategy that is likely to be used for the pandemic vaccine: clinical efficacy and safety data obtained with mock-up vaccines are relevant for the pandemic vaccines.

Immune response to *PANDEMRIX H1N1*

Adults aged 18-60 years

Two clinical studies (D-Pan H1N1-007 and D-Pan H1N1-008) evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like strain in healthy adults aged 18-60 years. In D-Pan H1N1-007 pre-vaccination antibody reciprocal

titres ≥1:10 were present in 32.8% of adults and in D-Pan H1N1-008 pre-vaccination antibody reciprocal titres ≥1:10 were present in 36.7% of adults aged 18 to 60 years. The anti-HA antibody responses 21 days after a first dose were as follows:

anti-HA antibody	**Immune response to A/California/7/2009 (H1N1)v-like strain**			
	D-Pan H1N1-007		**D-Pan H1N1-008**	
	Total enrolled subjects N = 61 [95% CI]	**Seronegative subjects prior to vaccination N = 40 [95% CI]**	**Total enrolled subjects N = 120 [95% CI]**	**Seronegative subjects prior to vaccination N = 76 [95% CI]**
Seroprotection rate[1]	100% [94.1;100]	100% [91.2;100]	97.5% [92.9;99.5]	96.1% [88.9;99.2]
Seroconversion rate[2]	96.7% [88.7;99.6]	100% [91.2;100]	95.0% [89.4;98.1]	96.1% [88.9;99.2]
Seroconversion factor[3]	43.3 [31.8;59.0]	56.7 [39.9;80.5]	42.15 [33.43;53.16]	50.73 [37.84;68.02]

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

Elderly (>60 years)

Study D-Pan H1N1-008 also evaluated the immunogenicity of AS03-adjuvanted vaccine containing 3.75 µg HA derived from A/California/7/2009 (H1N1)v-like in healthy subjects aged above 60 years. The mean age was 69.1 years. Pre-vaccination antibody reciprocal titres ≥1:10 were present in 42.5% of adults > 60 years The anti-HA antibody responses 21 days after a first dose were as follows:

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

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

Immune response to Pandemrix H5N1

Two clinical studies have evaluated the immunogenicity of the monovalent pandemic influenza A vaccine (H5N1).

A dose finding study tested different haemagglutinin dosages of the vaccine in a vaccine volume of 1 ml, which is twice the vaccine volume of the final formulation. In this study, approximately 200 unprimed subjects aged 18-60 years received the adjuvanted vaccine following a 0, 21 days schedule. Fifty out of these 200 subjects received 3.75 µg HA/AS03, which is the haemagglutinin dosage of the final formulation.

In a consistency study, more than 900 unprimed subjects aged 18-60 years received 3.75 µg HA/AS03 per 0.5 ml, which is the final formulation of the vaccine following a 0, 21 days schedule.

Immune response against vaccine strain:

Twenty-one days after the first and second dose of the vaccine, the seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody in the subjects who had received the final formulation of the vaccine were as follows:

anti-HA antibody	21 days after 1st dose	21 days after 2nd dose
Seroprotection rate*†	44.5%	94.3%
Seroconversion rate†	42.5%	93.7%
Seroconversion factor†	4.1	39.8

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty-one days after administration of the second dose, 96.0% of subjects had a 4-fold increase in serum neutralising antibody titres.

Information from non clinical studies

The ability to induce protection against homologous and heterologous vaccine strains was assessed non-clinically using ferret challenge models. In each experiment, four groups of six ferrets were immunised intramuscularly with an AS03 adjuvanted vaccine containing HA derived from H5N1/A/Vietnam/1194/04 (NIBRG-14). Doses of 15, 5, 1.7 or 0.6 µg HA were tested in the homologous challenge experiment, and doses of 15, 7.5, 3.8 or 1.75 µg HA were tested in the heterologous challenge experiment. Control groups included ferrets immunised with adjuvant alone, non-adjuvanted vaccine (15 µg HA) or phosphate buffered saline solution. Ferrets were vaccinated on days 0 and 21 and challenged intratracheally on day 49 with a lethal dose of either H5N1/A/Vietnam/1194/04 or heterologous H5N1/A/Indonesia/5/05. Of the animals receiving

adjuvanted vaccine, 87 % and 96% were protected against the lethal homologus or heterlogous challenge, respectively. Viral shedding into the upper respiratory tract was also reduced in vaccinated animals relative to controls, suggesting a reduced risk of viral transmission. In the unadjuvanted control group, as well as in the adjuvant control group, all animals died or had to be euthanized as they were moribund, three to four days after the start of challenge.

Persistence of immunogenicity:

In the dose finding study, persistence of immunogenicity up to 6 months after the second dose was evaluated in the 50 subjects who have received the 3.75 µg HA/AS03 formulation. The seroprotection rate, the seroconversion rate and seroconversion factor for anti-haemagglutinin (anti-HA) antibody at day 180 were respectively 54.0%, 52.0% and 4.4. A 4-fold increase in serum neutralising antibody titers at this time point was observed in 72% of subjects.

Cross-reactivity:

In both studies, the candidate vaccine showed the ability to induce a cross-reactive immune response against variants of the vaccine strain.

In the dose finding study, the seroprotection rate, seroconversion rate and seroconversion factor against H5N1 drift variants 21 days after the second dose in a subset of subjects were as follows:

anti-HA antibody	A/Indonesia/5/2005 N = 50	A/Anhui/01/2005 N = 20	A/Turkey/Turkey/1/2005 N = 20
Seroprotection rate*†	20.0%	35.0%	60.0%
Seroconversion rate†	20.0%	35.0%	60.0%
Seroconversion factor†	2.0	3.4	4.7

* anti-HA ≥1:40

† seroprotection rate (i.e. proportion of subjects with HI titre ≥ 1:40); seroconversion rate (i.e. proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); seroconversion factor (i.e; ratio of the post-vaccination GMT and the pre-vaccination GMT)

Twenty one days after the second dose, a 4-fold increase in serum neutralising antibody titers was obtained in 77.1% of subjects against the A/Indonesia/5/2005 strain, in 75.0% of subjects against A/Anhui/01/2005 and in 85.0% of subjects against A/Turkey/Turkey/1/2005.

The consistency study confirmed that the candidate vaccine induces a cross-reactive immune response against A/Indonesia/5/2005. Twenty-one days after the second dose, seroconversion and seroprotection rates against this strain variant were both 50.2% with a seroconversion factor of 4.9. A 4-fold increase in serum neutralising antibody titers was obtained in 91.4% of subjects.

INDICATIONS

PANDEMRIX H1N1 is indicated for prophylaxis of influenza in an officially declared pandemic situation. *PANDEMRIX* 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.

PANDEMRIX should under no circumstances be administered intravascularly or intradermally. There are no data with *PANDEMRIX* using the subcutaneous route. Therefore healthcare providers need to assess the benefits and potential risks of administering the vaccine in individuals with thrombocytopenia or any bleeding disorder that would contraindicate intramuscular injection unless the potential benefit outweighs the risk of bleeding.

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

A protective immune response may not be elicited in all vaccinees.
There are limited data are available from *PANDEMRIX H1N1* in adults aged over 60 years and very limited data with *PANDEMRIX H1N1* or with a version of the vaccine containing H1N1 antigen in adults aged over 80 years.

There are no safety, immunogenicity or efficacy data to support interchangeability of *PANDEMRIX* with other H1N1 pandemic vaccines.

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 Pandemrix H5N1 30 days prior to mating and on gestation days 6, 8, 11 and 15 (see also Use in Pregnancy*).*

Carcinogenicity:
No carcinogenicity studies have been conducted with *PANDEMRIX* or AS03 adjuvant.

Genotoxicity:
In standard genotoxicity tests, AS03 adjuvant was not mutagenic in *Salmonella typhimurium, E. coli* WP2*uvr*A 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 *PANDEMRIX* and with the AS03 adjuvant contained in the vaccine. Data from vaccinations with intrapandemic 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 female rats intramuscularly injected with Pandemrix H5N1 (6µg H5 antigen and 0.1mL AS03 adjuvant), 30 days prior to mating and on gestation days 6, 8, 11 and 15, 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 Pandemrix H5N1 in female rats, maternal treatment prior to mating and during gestation had no effect on pup bevelopment, assessed to lactation day 25. There was evidence of maternal antibodies to pup (see also Use in Pregnancy).

Interactions
No data are available on the concomitant administration of *PANDEMRIX* with other vaccines.

Therefore, *PANDEMRIX* 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

The solicited local and general adverse events reported within 7 days of vaccination with Pandemrix H1N1, in the studies, D-Pan H1N1-007 and D-Pan H1N1-008 are provided below.

D-Pan-H1N1-007

This clinical study evaluated the reactogenicity of the first dose of Pandemrix (H1N1) in healthy subjects aged 18-60 years. A concurrent group of subjects received the vaccine without AS03 adjuvant.

D-Pan-H1N1-007 (Day 0 to Day 6 solicited adverse events following 1 dose of 3.75 µg HA+ AS03 vaccine versus 1 dose of 15 µg HA unadjuvanted H1N1 vaccine) - Adverse Events with a causal relationship

Symptom	H1N1+AS03 N=63	H1N1 N=65
Pain at the injection site	90.5%	35.4%
Redness at the injection site	1.6%	0.0%
Swelling at the injection site	7.9%	0.0%
Fatigue	33.3%	24.6%
Headache	23.8%	12.3%
Arthralgia	11.1%	4.6%
Myalgia	31.7%	6.2%
Shivering	9.5%	3.1%
Sweating	9.5%	7.7%
Fever ≥38°C	0.0%	0.0%
Fever ≥39°C	0.0%	0.0%

H1N1+ AS03 = H1N1 containing antigen-sparing dose of HA+AS03 adjuvant
H1N1 = H1N1 containing HA antigen without adjuvant

D-Pan-H1N1-008 – post dose 1

This clinical study evaluated the reactogenicity of the first dose Pandemrix (H1N1) in healthy adults aged 18-60 and above 60 years.

D-Pan H1N1-008 (Day 0 to Day 6 solicited adverse events following a single dose of 3.75 µg HA + AS03 vaccine) - Adverse Events with a causal relationship

Symptom		
	18-60 years N=120	>60 years N=120
Pain at the injection site	87.5%	65.0%
Redness at the injection site	0.8%	7.5%
Swelling at the injection site	9.2%	10.0%
Fatigue	33.3%	20.0%
Headache	35.8%	17.5%
Arthralgia	14.2%	11.7%
Myalgia	20.8%	19.2%
Shivering	18.3%	5.8%
Sweating	14.2%	5.0%
Fever ≥38°C	0.8%	0.0%
Fever ≥39°C	0.0%	0.0%

The following adverse events have also been reported during post-marketing experience with *PANDEMRIX* H1N1v:

Immune system disorders: Anaphylaxis.

Nervous system disorders: Febrile convulsions.

Skin and subcutaneous tissue disorders: Angioedema, urticaria.

From Post-marketing surveillance with interpandemic trivalent vaccines, the following adverse events have been reported:

Blood and lymphatic system disorders: Transient thrombocytopenia.

Immune system disorders: Allergic reactions, in rare cases leading to shock.

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

Vascular disorders: Vasculitis with transient renal involvement.

Skin and subcutaneous tissue disorders: Generalised skin reactions including urticaria

DOSAGE AND ADMINISTRATION

Dosage

Adults aged 18 years and older:

One or two doses of 0.5 ml.

Immunogenicity data obtained at three weeks after administration of *PANDEMRIX H1N1* in clinical studies suggest a single dose may be sufficient.

If a second dose is administered there should be an interval of at least three weeks between the first and the second dose.

Vaccination should be carried out by intramuscular injection.

Method of Administration

PANDEMRIX 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 *PANDEMRIX* (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.

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

PANDEMRIX H1N1 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 *PANDEMRIX H1N1* is 3 years 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:

GlaxoSmithKline Biologicals SA
Rue de l'Institut 89
1330 Rixensart, Belgium.

DISTRIBUTED IN AUSTRALIA BY:

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

Date of TGA approval: 9 August 2010

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

Version 1.0