European Medicines Agency

London, 29 May 2009
EMEA/CHMP/352183/2009

ASSESSMENT REPORT
FOR

Pandemrix

Common Name:
pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) A/VietNam/1194/2004 NIBRG-14

Procedure No. EMEA/H/C/000832/II/0005

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

INTRODUCTION

Pandemrix was granted Marketing Authorisations in the EU in May 2008, with use being restricted to subjects aged 18-60 years in section 4.2 of the summary of product characteristics (SPC) due to lack of data outside of this age range.

The currently approved vaccine contains split influenza virus with a haemagglutinin content equivalent to 3.75 micrograms derived from the A/VietNam/1194/2004 (H5N1) like strain (NIBRG-14). This strain was produced by reverse genetics at NIBSC.

The vaccine also contains the marketing authorisation holder's (MAH) proprietary adjuvant AS03, which is composed of squalene, DL-α-tocopherol and polysorbate 80.

The virus is propagated in eggs and the approved vaccine is manufactured in Dresden.

The MAH applied to update sections 4.2, 4.8 and 5.1 of the SPC to extend the use of Pandemrix in adults above 60 years of age. The annex II and package leaflet (PL) were updated accordingly.
In support of this variation the MAH initially submitted new clinical data from Study 010 (for more details see below, under the "clinical aspects" section) which included safety and immunogenicity data to Day 51. The MAH further submitted immunogenicity and safety data up to Day 180 in answers to questions.

In submitting the above mentioned data from study 010 the MAH also fulfilled the commitments 21 (initial report of study 010), 25.1 (cell mediated immunity (CMI) data from study 010) and 21.1 (D180 data from study 010).

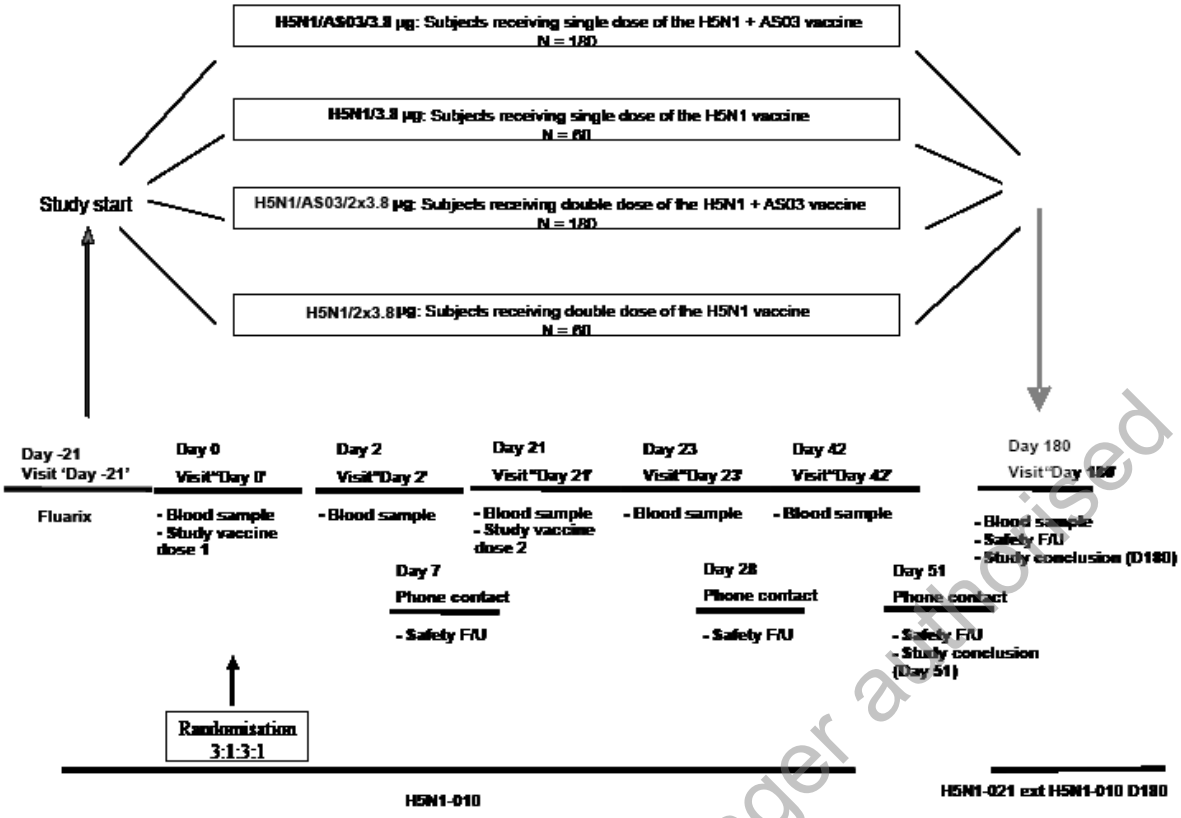
CLINICAL ASPECTS

CLINICAL IMMUNOGENICITY

Study 010

The study commenced 15 November 2006 and was conducted at 7 sites in Belgium and 5 sites in Italy.

This open label study compared administration of two single or two double doses on D0 and on D21. Double doses were given as two injections of the licensed vaccine *i.e.* one injection into each arm. The comparative groups received single or double doses of non-adjuvanted vaccine of the same HA content. Randomisation (by the MAH's automated system) was arranged such that the ratio of subjects receiving adjuvanted:non-adjuvanted vaccine was 3:1 regardless of the HA dose. After D180 there would be an extended follow-up for subjects enrolled in Belgium with visits at Month 12 and at Month 24.



The study planned to enrol 480 subjects aged 61 years and above (no upper age limit). At randomisation subjects in each group were stratified by age group: 61-65 years, 66-70 years and >70 years with the allocation ratio 1:1:1.

A breakdown of subjects by age subgroups (60-65, 66-70, 71-75, 76-80 and >80 year-old) was requested. The number of subjects was low in each of the age strata above 71 years of age (see below).

Number of subjects by age groups: 61-65, 66-70, 71 to 75, 76 to 80 and >80 years (ATP cohort for Immunogenicity)

	61 to 65 year-old	66 to 70 year-old	71 to 75 year-old	76 to 80 year-old	81 and above
7.5/NoAS	12	14	7	5	6
3.8/NoAS	15	19	9	6	5
7.5/AS	46	46	27	16	10
3.8/AS	45	46	30	18	13

1. 7.5/NoAS = H5N1 7.5µg HA, 3.8/NoAS = H5N1 3.8µg HA, 7.5/AS = H5N1 7.5µg HA + AS03, 3.8/AS = H5N1 3.8µg HA + AS03

Subjects were not eligible for the study if any of the following applied:

- Administration of licensed MF59-containing vaccines or virosome-based influenza vaccines during the 2006-2007 influenza season
- Administration of licensed vaccines within 2 weeks (for inactivated vaccines) or 4 weeks (for live vaccines) prior to enrolment or planned administration of another vaccine before D51
- Chronic administration of immune-modifying drugs within 6 months of D0 or any immunodeficiency
- Alcohol or drug abuse
- History of hypersensitivity to vaccines, allergic disease or reactions likely to be exacerbated by any component of the vaccine
- Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality
- Acute disease at the time of enrolment
- Serious chronic disease
- Administration of immunoglobulin and/or any blood products within 3 months of D0
- Use of any investigational or non-registered product (drug or vaccine) within 30 days of D0

Subjects were randomised to the groups shown in the diagram with a ratio 3:1:3:1.

All subjects not previously vaccinated with an influenza vaccine for the 2006-2007 season received Fluarix (a split virion, inactivated seasonal influenza vaccine) at least 3 weeks before D0 in order to help standardise any effect of prior seasonal influenza vaccination on responses to H5N1 vaccine.

Blood samples were to be collected at D0, 21, 42 and 180 for all subjects, and at visits Month 12 and Month 24 for subjects in Belgium. In addition, blood and urine was collected for safety assessments (biochemistry and haematology) at Day 0, 2, 21 and 23.

The primary objectives were:

- To evaluate immune responses to single or double doses at D21 and D42 for haemagglutination inhibition (HI) and at D42 for NA (neutralising antibodies).
- To assess antibody persistence at D180, Month 12 and Month 24

The secondary objectives were:

- To evaluate safety/reactogenicity of the dosing regimens studied
- To measure percentage, intensity and relationship to vaccination of solicited local and general signs and symptoms during a 7-Day follow-up period after each dose of vaccine and overall
- To measure percentage, intensity and relationship to vaccination of unsolicited local and general signs and symptoms during 21 days after the first and 30 days after the second dose
- To record SAEs (serious adverse events) during the entire study period
- To evaluate haematological and biochemical parameters
- To evaluate CMI at D0, 21, 42 and 180 for all subjects and at Month 12 and 24 for Belgian subjects

The target sample size of 480 (180 subjects in each adjuvanted group and 60 in each non-adjuvanted group) was expected to provide 456 evaluable subjects taking into account a 5% drop out rate. Based on HI GMTs (geometric mean titres) 170 evaluable subjects would provide 86% power to detect a 1.7-fold difference between the two adjuvanted vaccine groups assuming standard deviations of 0.738 and 0.656 (log10 unit) for the double and single adjuvanted vaccine dose groups (based on results from study 007 results) and using a t-test with a 0.05 two-sided significance level (PASS, 2005).

To address the FDA CBER criteria it was calculated that 85 evaluable subjects in the geriatric age range (> 65 years) in the 7.5/AS03 and 3.8/AS03 vaccine groups would provide the following estimates for probabilities of success:

- If the true seroconversion rate observed in the adjuvanted AS03 group was 82.0%, the probability of obtaining an observed lower limit ≥ 30% was larger than 99%.
- If the true seroprotection rate observed in the adjuvanted AS03 group was 84.0%, then the probability of obtaining an observed lower limit ≥ 60% was larger than 99%.

The protocol defined the following populations (using the MAH's standard definitions):

- Total Vaccinated cohort
- According-To-Protocol (ATP) cohort for analysis of safety
- According To Protocol (ATP) cohort for analysis of immunogenicity

An interim analysis on the first 100 enrolled subjects was planned at Day 7 in order to provide a safety evaluation and was conducted by a GSK Internal Safety Monitoring Board. Data collected up to Day 21 after the first vaccination was also made available to the Board to detect potential early safety signals (and stop enrolment at this point until the safety analysis was performed). This interim analysis actually concerned review of Grade 3 solicited symptoms in 20% per study group at Day 7.

The decision whether to stop or continue was to be postponed until the analysis at Day 7 for those subjects who had already been vaccinated had been carried out. After the analysis at Day 7 the Board could halt further enrolment and/or vaccination in a given group.

The main analysis was to be performed when all data on HI immune responses and safety up to D51 became available. A further analysis would be performed on immune responses and safety (SAEs) obtained between Day 51 and Day 180. Additional analyses will be performed on safety and immunogenicity data obtained at Month 12 and Month 24 from subjects in Belgium.

Results

There were 437 subjects enrolled and vaccinated as shown below:

Number of subjects enrolled in the study as well as the number excluded from the ATP analyses with reasons for exclusion

	Total			7.5/NoAS		3.8/NoAS		7.5/AS		3.8/AS	
Title	n	s	%	n	s	n	s	n	s	n	s
Total enrolled cohort	437										
Total vaccinated cohort	437		100	52		61		159		165	
Administration of vaccine(s) forbidden in the protocol (code 1040)	3	3		0	0	0	0	1	1	2	2
Randomisation failure (code 1050)	1	1		0	0	0	0	1	1	0	0
Study vaccine dose not administered according to protocol (code 1070)	9	9		4	4	0	0	3	3	2	2
ATP safety cohort	424		97.0	48		61		154		161	
Initially seropositive or initially unknown antibody status (code 2020)	15	15		3	3	5	5	4	4	3	3
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	4	4		0	0	1	1	0	0	3	3
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	10	15		1	1	1	2	5	6	3	6
Essential serological data missing (code 2100)	0	15		0	3	0	5	0	4	0	3
ATP immunogenicity cohort	395		90.4	44		54		145		152	

Of the 12 subjects eliminated from the ATP safety cohort (one other was erroneously eliminated but was counted as eliminated in the table, which counts 13 eliminated), 3 received concomitant vaccination forbidden by the protocol and 9 did not receive vaccine doses according to protocol.

Of the 29 subjects eliminated from the ATP immunogenicity cohort (some had more than one reason to be eliminated), 15 had unknown pre-vaccination antibody status, 4 did not comply with the vaccination schedule and 15 were non-compliant with the blood sampling schedule.

As the percentage of subjects excluded from the ATP cohort for immunogenicity was > 5% (*i.e.* 9.6%) the analyses for immunogenicity were also performed on the Total Vaccinated Cohort. However, the results were very similar to those for the ATP Immunogenicity Cohort and therefore only the ATP cohort data are presented and discussed in this assessment report.

The overall range of ages at the time of vaccination was 61-89 years. The mean age was similar across all four groups ranging from 69.7 and 70.8 years. The overall male-female subject ratio was 1.18 (54.2%:45.8%) and 97% (424 subjects) were of Caucasian/European heritage with 3% (13 subjects) of Arabic/north African heritage.

HI responses

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

The **seropositivity rates** against **A/Vietnam** increased significantly at D21 and at D42 compared to D0 in the adjuvanted vaccine groups and at D42 compared to Day 0 in the group that received 7.5 µg HA alone. At D42 the seropositivity rates were significantly higher in the adjuvanted groups (93.4% and 97.9%) compared to the non-adjuvanted groups (72.7% and 66.7%). The **GMTs** increased significantly in the adjuvanted groups at D21 (50.0-69.4) and at D42 (126.8-237.3) but there were only small increments in the non-adjuvanted groups. At D42 the GMT was significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

The **seropositivity rates** against **A/Indonesia** at D21 were higher in the adjuvanted groups (23.7% and 33.1% versus 3.7% and 11.4% in the non-adjuvanted groups). At D42 the rates in the adjuvanted groups increased significantly compared to D21 (54.6% and 74.5%) and were significantly higher than in the non-adjuvanted groups (13.0% and 18.2%). The **GMTs** increased significantly compared to Day 0 after each vaccination dose only in the adjuvanted groups. At D42 the GMT and the seropositivity rate were significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

Based on **GMTs** a clear adjuvant effect was demonstrated at D42 for HI responses in the single injection and double injection groups against A/Vietnam and A/Indonesia. There was also a dose effect between the two adjuvanted groups at D42 for HI responses to both strains. In contrast there was no significant dose effect between the two non-adjuvanted groups.

Study 010 extended into study 021 to assess the persistence of the immune response and rates of SAEs up to D180. The MAH provided HI antibody responses against A/Indonesia/2005/05 and A/Vietnam/1194/2004 in all groups at Day 180. At 6 months after the primary vaccination the proportion of subjects seropositive for HI antibody against both strains was still higher in the adjuvanted vaccine groups compared to the unadjuvanted HA groups. However, the difference was notable only for antibody against A/Vietnam.

By D180 the GMT values had decreased compared to Day 42 but were higher in the adjuvanted vaccine groups (see below). Again, the difference was notable only for antibody against A/Vietnam. In addition, the GMT for HI against A/Vietnam was higher in the group that had received a double dose of vaccine at each of D0 and D21 although the 95% CI overlapped.

Seropositivity rates and GMTs of H5N1 HI antibodies against the vaccine strain A/Vietnam/1194/2004 (H5NI) (ATP cohort for immunogenicity)

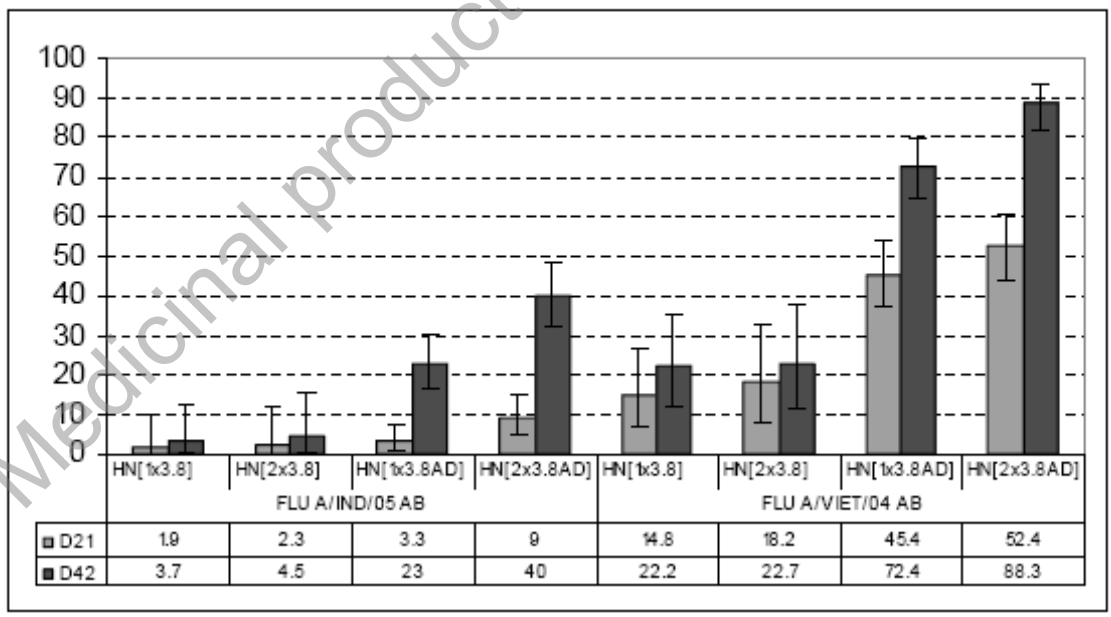
				GMT				
					95% CI			
Antibodies against	Group	Timing	N	value	LL	UL	Min	Max
A/Vietnam	7.5/NoAS	PRE	44	8.8	6.6	11.8	<10.0	640.0
		PII(D42)	44	25.3	16.0	40.1	<10.0	640.0
		PII(D180)	44	13.1	8.9	19.2	<10.0	320.0
	3.8/NoAS	PRE	54	9.7	7.3	13.0	<10.0	453.0
		PI(D21)	54	16.8	11.7	24.0	<10.0	640.0
		PII(D42)	54	22.7	15.1	34.1	<10.0	1280.0
		PII(D180)	50	11.0	24.3	<10.0	640.0	
	7.5/AS	PRE	145	10.2	8.4	12.5	<10.0	1280.0
		PI(D21)	145	69.4	52.1	92.3	<10.0	5120.0
		PII(D42)	145	237.3	191.9	293.6	<10.0	14480.0
		PII(D180)	131	53.5	41.9	68.4	<10.0	5120.0
	3.8/AS	PRE	152	11.3	9.2	13.9	<10.0	5120.0
		PI(D21)	152	50.0	38.1	65.6	<10.0	3620.0
		PII(D42)	152	126.8	99.4	161.7	<10.0	5120.0
		PII(D180)	140	38.5	30.0	49.5	<10.0	1810.0

A/Indonesia	7.5/NoAS	PRE	44	5.0	5.0	5.0	<10.0	<10.0
		PI(D21)	44	5.6	5.0	6.3	<10.0	40.0
		PII(D42)	44	6.3	5.2	7.6	<10.0	113.0
		PII(D180)	44	5.2	4.8	5.5	<10.0	20.0
	3.8/NoAS	PRE	54	5.2	4.9	5.5	<10.0	20.0
		PI(D21)	54	5.3	4.8	5.9	<10.0	80.0
		PII(D42)	54	6.1	5.1	7.4	<10.0	226.0
		PII(D180)	50	5.5	4.8	6.4	<10.0	160.0
	7.5/AS	PRE	145	5.1	5.0	5.2	<10.0	14.0
		PI(D21)	145	8.6	7.3	10.1	<10.0	1810.0
		PII(D42)	145	24.4	19.9	30.0	<10.0	1280.0
		PII(D180)	131	8.6	7.5	9.9	<10.0	320.0
	3.8/AS	PRE	152	5.1	5.0	5.1	<10.0	14.0
		PI(D21)	152	6.9	6.2	7.7	<10.0	160.0
		PII(D42)	152	13.7	11.3	16.4	<10.0	320.0
		PII(D180)	140	6.6	6.0	7.3	<10.0	80.0

7.5/NoAS = H5N1/[2x3.8µg HA]; 3.8/NoAS = H5N1/[1x3.8µg HA]; 7.5/AS = H5N1/[2x3.8µg HA/AS03]; 3.8/AS = H5N1/[1x3.8µg HA/AS03]; N = number of subjects with available results; 95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit; MIN/MAX = Minimum/Maximum; PRE = Pre-vaccination at Day 0; PI (D21) = Post-vaccination at Day 21; PII (D42) = Post-vaccination at Day 42, PII (D180) = Post-vaccination at Day 180

The **seroconversion rates** (SCR) against **A/Vietnam** were >30% in the two adjuvanted vaccine groups at D21 (45.4% and 52.4%) and increased significantly again at D42 (72.4% and 88.3%) with an advantage in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group. The 30% SCR threshold was not reached in the non-adjuvanted groups. Against **A/Indonesia** the threshold was reached only in the group that received 7.5 µg HA + AS03 and only at D42.

Seroconversion rates for H5N1 HI antibodies against A/Vietnam /1194/2004 and A/Indonesia/5/2005 (ATP cohort for immunogenicity)

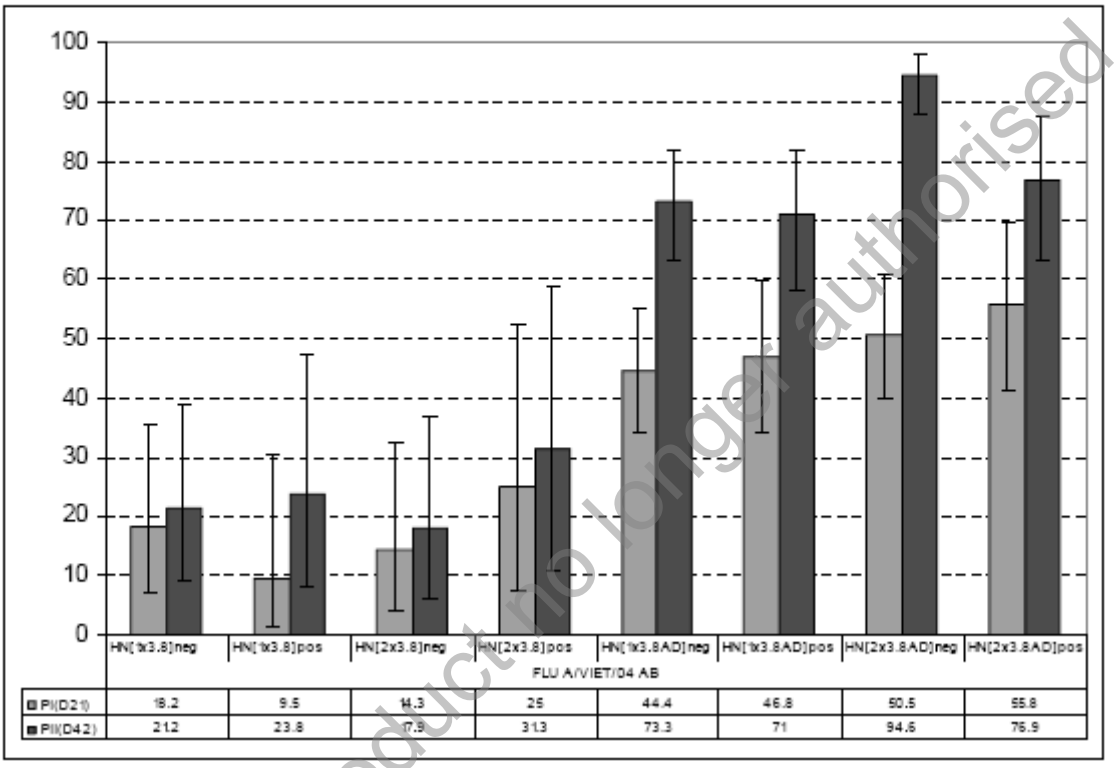


D21	1.9	2.3	3.3	9	14.8	18.2	45.4	52.4
D42	3.7	4.5	23	40	22.2	22.7	72.4	88.3

As seen with GMTs, the SCRs showed a clear adjuvant effect and a dose effect between the two adjuvanted groups at D42 for HI responses to both strains. Higher response against A/Vietnam/194/2004 was also observed in the adjuvanted groups at Day 180. The CHMP criteria for SCR was met in the 3.8/AS and 7.5/AS groups at D180. In contrast there was no dose effect between the two non-adjuvanted groups.

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

Seroconversion rates for H5N1 HI antibodies against A/Vietnam/1194/2004 strain by initial sero-status (ATP cohort for immunogenicity)



	HN[1x3.8]neg	HN[1x3.8]pos	HN[2x3.8]neg	HN[2x3.8]pos	HN[1x3.8AD]neg	HN[1x3.8AD]pos	HN[2x3.8AD]neg	HN[2x3.8AD]pos
PI(D21)	18.2	9.5	14.3	25	44.4	46.8	50.5	55.8
PII(D42)	21.2	23.8	17.9	31.3	73.3	71	94.6	76.9

The **seroconversion factors** (SCF) exceeded 2.0 against **A/Vietnam** in three of the four groups at D21 and by all groups at D42. Values were higher in the adjuvanted vaccine groups and significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group. The threshold was only reached against **A/Indonesia** in the adjuvanted groups at D42 and again there was an advantage for the higher HA dose.

Seroconversion factor for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 (ATP cohort for immunogenicity)

				SCF		
					95% CI	
Antibodies against	Group	Timing	N	Value	LL	UL
A/Vietnam/04 AB	7.5/NoAS	PI(D21)	44	2.4	1.7	3.4
		PII(D42)	44	2.9	2.0	4.1
	3.8/NoAS	PI(D21)	54	1.7	1.3	2.3
		PII(D42)	54	2.3	1.6	3.3
	7.5/AS	PI(D21)	145	6.8	5.3	8.6
		PII(D42)	145	23.2	18.5	29.0
	3.8/AS	PI(D21)	152	4.4	3.5	5.5
		PII(D42)	152	11.2	8.9	14.1
A/Indonesia/5/05	7.5/NoAS	PI(D21)	44	1.1	1.0	1.3
		PII(D42)	44	1.3	1.0	1.5
	3.8/NoAS	PI(D21)	54	1.0	0.9	1.1
		PII(D42)	54	1.2	1.0	1.4
	7.5/AS	PI(D21)	145	1.7	1.4	2.0
		PII(D42)	145	4.8	3.9	5.9
	3.8/AS	PI(D21)	152	1.4	1.2	1.5
		PII(D42)	152	2.7	2.2	3.2

When analysed according to initial serostatus to A/Vietnam, the threshold was reached by all groups at D42 except in the initially seropositive subset that received non-adjuvanted 3.8 µg HA.

Seroconversion factor (SCF) for H5N1 HI antibodies against A/Vietnam/1294/2004 strain at each post-vaccination time-point Day 21 and Day 42 (Initially seronegative cohort, ATP cohort for immunogenicity)

				SCF		
					95% CI	
Antibodies against	Group	Timing	N	Value	LL	UL
A/Vietnam	7.5/NoAS	PI(D21)	28	2.1	1.3	3.4
		PII(D42)	28	2.6	1.6	4.3
	3.8/NoAS	PI(D21)	33	1.9	1.3	2.9
		PII(D42)	33	2.7	1.6	4.5
	7.5/AS	PI(D21)	93	8.0	5.9	11.0
		PII(D42)	93	39.7	31.5	50.0
	3.8/AS	PI(D21)	90	5.1	3.7	6.9
		PII(D42)	90	16.0	11.7	22.0

Seroconversion factor (SCF) for H5N1 HI antibodies against A/Vietnam/1294/2004 strain at post-vaccination time-points Day 21 and Day 42 (Initially seropositive cohort, ATP cohort for immunogenicity)

				SCF		
					95% CI	
Antibodies against	Group	Timing	N	Value	LL	UL
A/Vietnam	7.5/NoAS	PI(D21)	16	2.9	1.6	5.2
		PII(D42)	16	3.4	1.9	6.2
	3.8/NoAS	PI(D21)	21	1.4	1.1	2.0
		PII(D42)	21	1.9	1.2	2.9
	7.5/AS	PI(D21)	52	5.0	3.5	7.2
		PII(D42)	52	8.9	6.3	12.5
	3.8/AS	PI(D21)	62	3.6	2.7	4.8
		PII(D42)	62	6.7	4.9	9.1

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

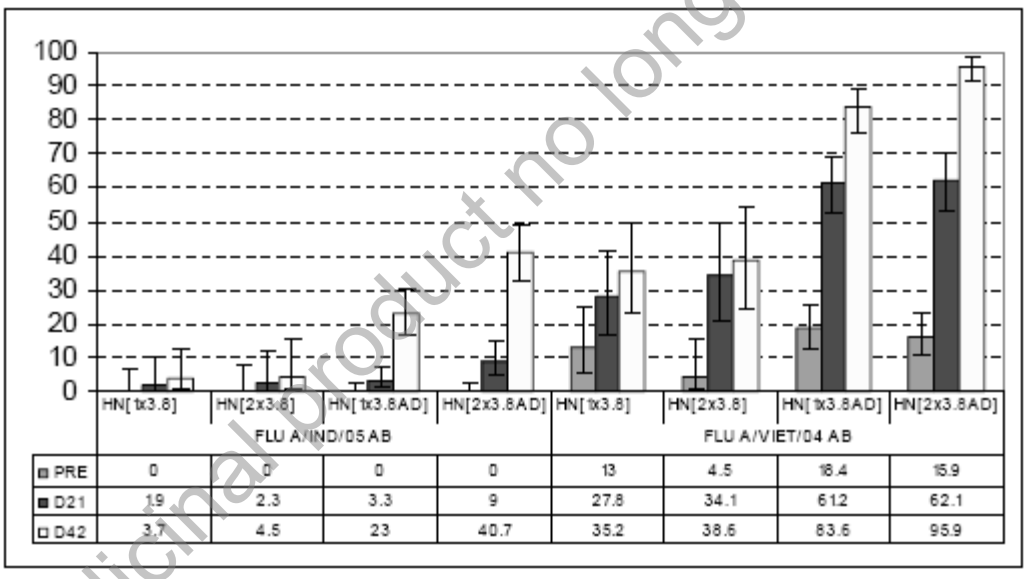
As shown in the first figure below, the **seroprotection rates** (SPRs) were >60% against **A/Vietnam** at D21 in both adjuvanted groups (61.2% and 62.1%) with further significant increases at D42 (83.6% and 95.9%). The threshold was not met in the non-adjuvanted groups. The SPRs against **A/Indonesia**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

The second figure below shows the SPRs against **A/Vietnam** according to initial sero-status.

In the initially seropositive subset there were significant increases at D21 in the adjuvanted groups and the double dose non-adjuvanted group (85.5%, 82.7% and 68.8%, respectively). In the single dose non-adjuvanted group the rate reached 42.9%. There were only modest increments between D21 and D42 in these groups.

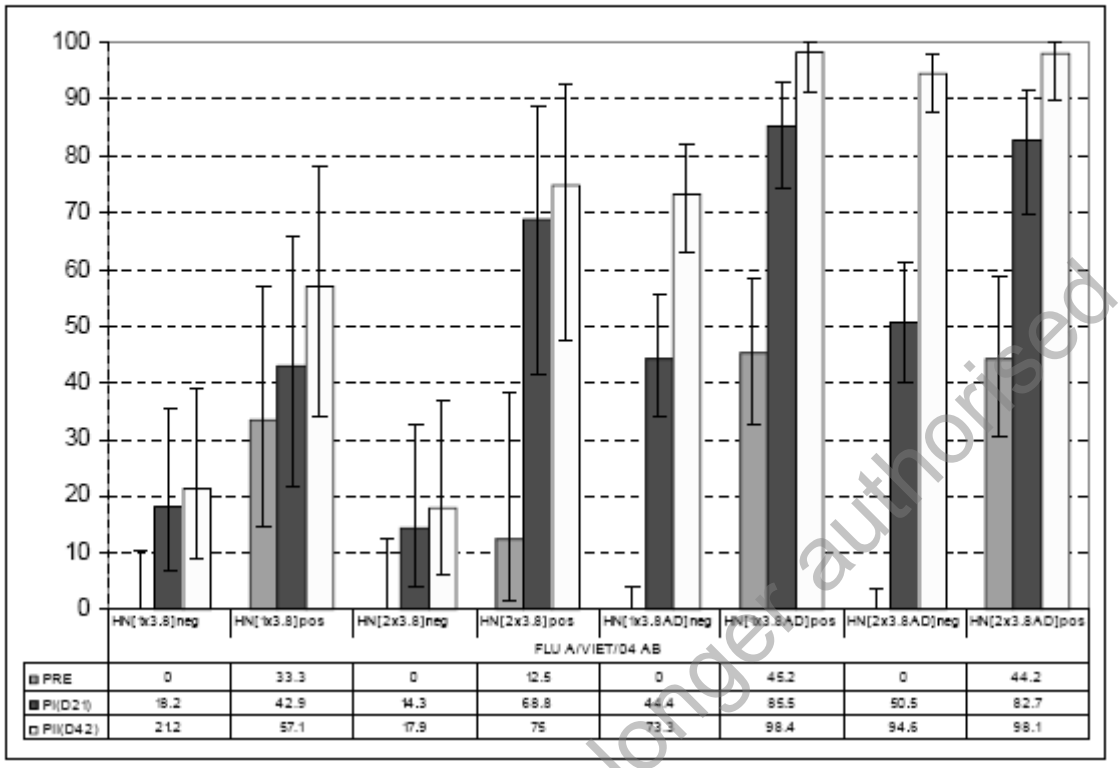
In the initially seronegative subset the D21 SPRs were 14.3% - 50.5%. At D42 the threshold was reached in the two adjuvanted vaccine groups (73.3% and 94.6%) and the rate was significantly higher in the 7.5 µg HA + AS03 group compared to the 3.8 µg HA + AS03 group.

Seroprotection rates for H5N1 HI antibodies against A/Vietnam/1194/2004 and A/Indonesia/5/2005 strains (ATP cohort for immunogenicity)



	HN[1x3.8]	HN[2x3.8]	HN[1x3.8AD]	HN[2x3.8AD]	HN[1x3.8]	HN[2x3.8]	HN[1x3.8AD]	HN[2x3.8AD]
PRE	0	0	0	0	13	4.5	18.4	15.9
D21	1.9	2.3	3.3	9	27.8	34.1	61.2	62.1
D42	3.7	4.5	23	40.7	35.2	38.6	83.6	95.9

Seroprotection rates for H5N1 HI antibodies against A/Vietnam/1194/2004 strain by initial sero-status (ATP cohort for immunogenicity)



	HN[1x3.8]neg	HN[1x3.8]pos	HN[2x3.8]neg	HN[2x3.8]pos	HN[1x3.8AD]neg	HN[1x3.8AD]pos	HN[2x3.8AD]neg	HN[2x3.8AD]pos
PRE	0	33.3	0	12.5	0	45.2	0	44.2
PII(D21)	18.2	42.9	14.3	68.8	44.4	85.5	50.5	82.7
PII(D42)	21.2	57.1	17.9	75	73.3	98.4	94.6	98.1

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

Neutralising antibody responses

Neutralising antibody titres were measured at D0 and D42 against A/Indonesia/5/2005 only and in a subset of subjects from the adjuvanted groups.

In this older population a high proportion of subjects were already seropositive for NA to A/Indonesia before vaccination (65.5% and 58.5%). Nevertheless at D42 the rates had increased to 94.3% and 100%). The D0 GMTs were similar and increased significantly at D42 as shown below. The 7.5 µg HA + AS03 group showed a higher GMT and greater percentage with titres of 1:40 and 1:80 compared to the 3.8 µg HA + AS03 group.

Seropositivity rates and geometric means titres (GMTs) of neutralising antibody titres against A/Indonesia/5/2005 strain at Days 0 and 42 (ATP cohort for immunogenicity)

				≥ 28 (1:dil)				GMT				
						95% CI			95% CI			
Antibody against	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
A/Indonesia	7.5/AS	PRE	82	48	58.5	47.1	69.3	39.7	32.0	49.3	<28.0	360.0
		PII(D42)	82	82	100	95.6	100	169.6	144.7	198.9	28.0	2840.0
	3.8/AS	PRE	87	57	65.5	54.6	75.4	44.2	36.0	54.1	<28.0	226.0
		PII(D42)	87	82	94.3	87.1	98.1	107.5	88.9	130.0	<28.0	2260.0

Supplement 29 Percentage of subjects that reached NT antibody titre of 1:40 a,d 1:80 against A/Indonesia/5/2005 strain at Day 0,42 (ATP cohort for immunogenicity)

				>=40				>=80			
						95%				95%	
Antibodies against	Group	Timing	N	n	%	LL	UL	n	%	LL	UL
A/Indonesia	7.5/AS	PRE	82	44	53.7	44.0	63.1	26	31.7	23.3	41.2
		PII(D42)	82	81	98.8	94.3	99.9	74	90.2	83.1	95.1
	3.8/AS	PRE	87	47	54.0	44.7	63.2	30	34.5	26.0	43.7
		PII(D42)	87	76	87.4	79.9	92.7	58	66.7	57.4	75.0

At D42 the SCR was higher in the double dose group.

Seroconversion rate (SCR) for neutralising antibody response against A/Indonesia/5/2005 strain at Day 42 (ATP cohort for immunogenicity)

				SCR			
						95% CI	
Antibodies against	Group	Timing	N	n	%	LL	UL
A/Indonesia	7.5/AS	PII(D42)	82	40	48.8	37.6	60.1
	3.8/AS	PII(D42)	87	25	28.7	19.5	39.4

The NA response against A/Indonesia/5/2005 observed six months after the primary vaccination series paralleled the HI responses in the adjuvanted groups.

Cell-mediated immune response

Antigen-specific Th1 CD4 T-cell responses were elicited in all study groups but were of lower amplitude in the two non-adjuvanted groups compared to the adjuvanted groups. There were marked increases at D42 in the adjuvanted groups only.

CD8 T-cells responses were nearly absent in all the study groups.

At Day 180, the level of Th1 CD4 T-cell response against A/Vietnam/1194/2004 had decreased from D42 but was higher in the adjuvanted vaccine groups. No CD8 T cell response was observed in any group at this time-point.

Stratified analysis (61-70, 71-80, >80 years of age)
A breakdown of subjects by age in the entire study was provided covering pre- and post-vaccination serological findings by age sub-groups.

The impact of age on immunogenicity was evaluated in terms of the HI antibody response against both A/Vietnam/1194/2007 and A/Indonesia/05/2005. The breakdown of HI responses by age analysis was further stratified by serostatus, especially in the above 80 years, to account for seropositivity for HI antibody to A/Vietnam/1194/2004.

A trend of increased seropositivity with age against A/Vietnam/1194/2004 was observed, especially for subjects aged above 80 years where about 60% of subjects were seropositive at baseline in each treatment group, noting that the denominators were small. In contrast the pre-vaccination seropositivity rates for HI against A/Indonesia/05/2005 were negligible across the different groups and no effect of age was evident.

Geometric mean titres
The pre-vaccination GMTs of HI antibody against A/Vietnam/1194/2004 were low and were not different across age groups (range from 7.0 - 14.1).

At Day 42 HI GMTs for A/Vietnam/1194/2004 did not vary much across age groups in subjects vaccinated with 1x3.8AD and aged up to 80 years but a much lower GMT was observed in those aged > 80 years. The age-related effect was more apparent in the groups that received two doses of vaccine at each of D0 and D21, for whom GMTs were anyway higher as was noted previously for the entire study population.

As already observed for the whole study population, higher GMTs levels were observed in all age groups at Day 42 in those who received 2x3.8AD (101.9 - 305.9). In addition in subjects vaccinated with 2x3.8AD there was a clear trend for decreasing GMTs from 65 years of age onwards.

The HI GMTs against A/Indonesia/05/2005 at Day 42 were much lower. Nevertheless, there was a trend for a decrease with age irrespective of the vaccination schedule.

A stratified analysis showed that subjects which were seropositive before vaccination developed higher GMTs against A/Vietnam/1094/2004 after vaccination. There were too few subjects in the A/Indonesia/05/2005 arm to interpret the findings.

Seroprotection rates
The CHMP criterion for SPR in this age group (>60%) was met in the two adjuvanted groups against A/Vietnam/1194/2004 in every age group at Day 42 irrespective of the HA dose injected. However, the 60% rate was only just exceeded by subjects aged > 80 years who received a single dose of vaccine at D0 and D21.

In general baseline serostatus did not have major impact on the percentages that met the SPR threshold. Nevertheless, in most of the age groups, subjects who were seropositive before vaccination achieved higher SPRs against A/Vietnam/1194/2004 after vaccination with either 1x3.8AD or 2x3.8AD.

All age sub-groups meet the CHMP criterion at Day 42 regardless of baseline serostatus except for those aged > 80 years who were seronegative at baseline and received a single dose at D0 and at D21. None of these five subjects was seroprotected even at D42.

In line with the overall analysis of the study already presented the >60% SPR threshold for HI antibody against A/Indonesia/05/2005 was not met by any of the sub-groups at Day 42. The SPRs tended to decrease with age from 70 years onwards and were slightly higher at Day 42 after vaccination with 2x3.8AD compared to 1x3.8AD

Seroconversion rates
The CHMP criterion for SCR in this age group (>30%) was met against A/Vietnam/1194/2004 in every age group at Day 42 irrespective of the HA dose injected. However, rates were lowest in subjects aged > 80 years whether one or two doses were given at each of D0 and D42. This suggests a reduced ability to respond to vaccination with increasing age.

Baseline serostatus did not seem to have much impact on the ability to meet the SCR threshold. All age sub-groups meet the criterion at Day 42 regardless of baseline with the exception that none of the five subjects aged > 80 years who were seronegative before vaccination and received 1x3.8AD seroconverted.

The >30% SCR threshold for HI antibody against A/Indonesia/05/2005 was met at Day 42 in subjects aged up to 80 years who were vaccinated with 2x3.8AD while no subject in the 1x3.8AD sub-groups met the SCR criterion.

Discussion on clinical efficacy
Study 010 demonstrated overall that the current vaccine (i.e. 3.8 µg HA + AS03) administered at D0 and again at D21 elicited HI antibody responses directed against homologous virus at D42 that met the three CHMP criteria applicable to subjects aged > 60 years and also met the criteria applicable to subjects aged from 18-60 years. In addition, all three criteria were met at D42 regardless of baseline

serostatus and two were met at D21 in the subset that was seronegative at baseline (the exception was the SPR).

However, the data obtained at D42 indicated a numerical advantage for administration of two doses at D0 and another two doses at D21 when compared to the recommended regimen. This overall advantage for double doses was mainly driven by results in the previously seronegative sub-population.

It was also noted that:

- Two administrations of adjuvanted vaccine (whether a single or double dose was given) were necessary to fully meet the CHMP criteria in previously seronegative subjects aged > 60 years
- Two administrations of 3.8 µg HA + AS03 at D0 and D21 gave responses at D42 that were better than seen at D21 after administration of 7.5 µg HA + AS03
- Comparison of the D21 results between the two adjuvanted vaccine dose groups did not show a significant advantage for a double dose at D0 versus a single dose at D0.

The additional analyses of HI data to D42 by age strata and by baseline serostatus demonstrated that:

- The pre-vaccination seropositivity rate increased with age for HI antibody against A/Vietnam/1194/2004 particularly in the subjects aged > 80 years whereas baseline seropositivity rates were low in each age stratum against A/Indonesia/05/2005.

- Overall HI antibody responses against A/Vietnam at D42 in each age sub-group met all CHMP criteria for subjects aged > 60 years regardless whether or not a double dose of HA was given. However, there was a clear trend for lower HI responses with increasing age, especially in those aged > 80 years.

- Further analyses by baseline serostatus showed an almost complete lack of response to a single dose at each of D0 and at D21 in the very few subjects aged > 80 years who were seronegative at baseline and in sharp contrast with the results for those aged > 80 years who were seropositive at baseline.

- The risk of being seronegative at baseline decreases with increasing age and baseline serostatus would not be determined either in a pre-pandemic or pandemic situation. Based on study 010 about half of subjects aged > 80 years are at high risk of failing to develop a seroprotective HI response when vaccinated according to the current SPC.

- In subjects aged < 80 years the seroprotection rates by age sub-groups were slightly lower with a single dose compared to a double dose at D42 but the SPR criterion even for younger subjects was met (i.e. rates exceeded 70%) regardless of baseline serostatus.

- NA against A/Vietnam to D42 showed very high baseline antibody levels but there was a good response to vaccination. At Day 42, a trend for a higher SCR was observed in the 7.5/AS group compared to the 3.8/AS group. However, percentages of subjects that reached NA titres of 1:40 and 1:80 were comparable between adjuvanted dose groups.

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

CLINICAL SAFETY

Study 010

The H5N1-010 experimental design included four groups: 3.8/AS (180 subjects), 3.8/NoAS: (60 subjects), 7.5/AS (180 subjects) and 7.5/NoAS" (60 subjects). One hundred and sixty five (165) subjects > 60 years received the proposed dose of 3.8 µg/AS03, whereas 159 subjects received a double dose of 7.5 µg/AS03 in the safety cohort.

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

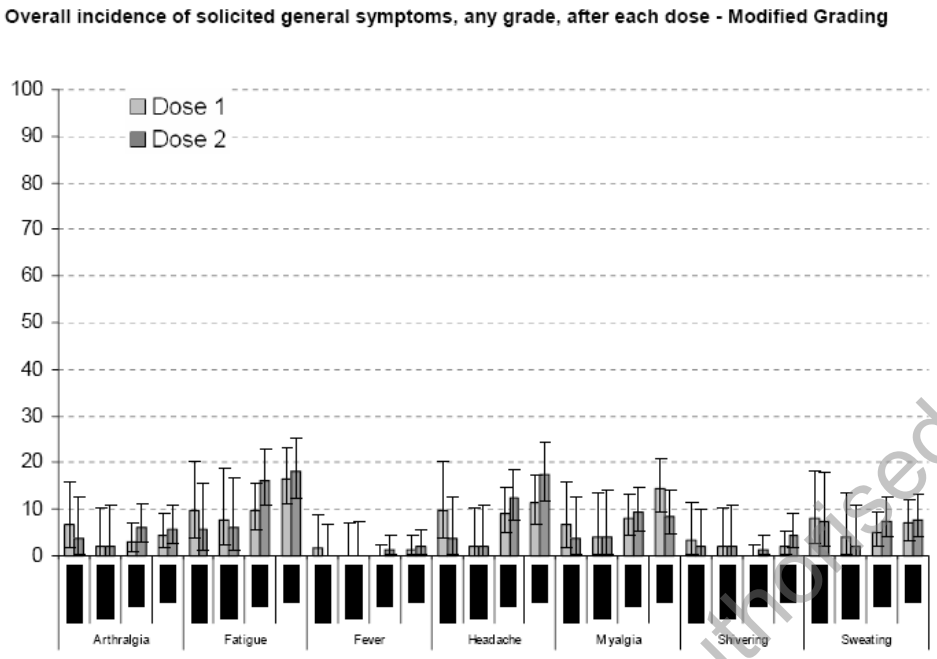
Rates of reporting local symptoms of pain, redness and swelling were significantly higher in the 3.8 µg HA + AS03 group than in the 3.8 µg HA alone group. Pain and redness also occurred at a significantly higher rate in the group given 7.5 µg HA + AS03 compared to the group that received 7.5 µg HA alone.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

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

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

As shown in the figure below:

- Fatigue was the most frequently reported general symptom in the adjuvanted vaccine groups (12.9% to 17.3% compared to 7-8% in the non-adjuvanted vaccine groups) but rates of Grade 3 fatigue were < 2%.
- Headache was reported in 10.8% to 14.4% compared to 2-7% in respective groups but the rates for Grade 3 headache were < 1%.
- Myalgia was also more frequently reported in the adjuvanted vaccine groups (8.6% to 11.5% compared to 4-5%) but rates of Grade 3 myalgia were < 1.5%.
- Rates of other general symptoms, including fever, were low but usually higher in the adjuvanted vaccine groups.



Unsolicited adverse events (AEs) were reported by 88/437 subjects of which 11 reported at least one grade 3 unsolicited AE and 22 reported at least one unsolicited AE considered to be causally related to vaccination. The overall incidences of unsolicited AEs and unsolicited AEs considered related to vaccination were not different between the adjuvanted and non-adjuvanted groups (based on overlapping 95% CIs).
There were 5 SAEs reported by 4 subjects up to the initial D51 data lock point. These were clearly intercurrent illnesses unrelated to vaccination, none was fatal and all were resolved. SAEs were reported between Day 52 and Day 180 with a data lock point of 15 December, 2008. During this period 13 subjects reported a total of 13 SAEs up to the data lock point. Of these SAEs; two were unresolved, six were resolved and five were fatal. The five fatalities concerned a cerebrovascular accident (2), congestive cardiac failure (2) and ventricular fibrillation. Overall (from D0 onwards) 18 SAEs were reported by 16 subjects in this study.

In general, the results of the biochemical analysis were within the normal range except that up to 28.2% showed elevated blood urea nitrogen values.

There were eight non-fatal adverse events during the extended safety follow-up period. None of these SAEs were assessed by the investigators as related to the vaccination.

Discussion on clinical safety

There were very few Grade 3 solicited and unsolicited AEs reported and no differences were observed between groups.

There were no new concerns or unexpected findings in the safety data obtained from this older population.

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

RISK MANAGEMENT PLAN

The risk management plan (RMP) for Pandemrix had been previously assessed through a follow-up measure. A revised version (version 5) was provided to incorporate additional information relevant to use in subjects aged > 60 years. However, the revised RMP differed from the previous versions submitted in October 2008 only in minor textual amendments. Data from study H5N1-010 relevant to the elderly variation were included in the previous versions of the RMPs and the discussion of these data remains the same in the new versions with no new safety concerns identified.

BENEFIT RISK ASSESSMENT

Benefits

The immunogenicity data are sufficient to support approval of Pandemrix for use from the age of 18 years onwards. This conclusion reflects CHMP's previous discussion on extrapolation of data generated with A/Vietnam vaccine in the elderly to Prepandrix containing A/Indonesia. In this regard, while baseline seropositivity rates are lower against A/Indonesia study 010 clearly demonstrated that the CHMP criteria were met regardless of baseline serostatus except for subjects aged > 80 years.

Risks

The assessment has to be made based on safety and immunogenicity data, including fulfilment of the three CHMP criteria that are applied to seasonal influenza vaccines. The data cannot necessarily predict protection against pandemic influenza.

The additional safety data do not raise any new concerns for use of AS03-adjuvanted vaccine in subjects aged > 60 years.

The AS03-adjuvanted vaccine is commonly or very commonly associated with a range of local and systemic adverse reactions but these are not often of severe intensity and the safety profile does not preclude the use of the vaccine in subjects aged > 60 years.

Balance

The data specific to use in subjects aged > 60 years support a favourable risk-benefit relationship.

Conclusion

The benefit-risk relationship is favourable for use in subjects aged > 60 years during a declared pandemic.

CONCLUSION

On 29 May 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the summary of product characteristics, annex II and package leaflet, subject to the additional commitments undertaken.