European Medicines Agency

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ASSESSMENT REPORT FOR FOCETRIA

Common name:
pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/2009 (H1N1)v like strain (X-181A)

Procedure No. EMEA/H/C/000710/II/0010

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

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Introduction

Focetria is a pandemic H1N1v vaccine. The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 29/09/09 (EMEA/H/C/710/PU/05).
The current posology of Focetria was based on data from the mock-up vaccines, largely represented by vaccines containing the avian derived H5N1 antigen, scarcely immunogenic in humans. The marketing authorisation holder (MAH) submitted a type II variation based on study V87P13 with the aim of updating Focetria's product information to take into account the extended H5N1 safety data information available. Study V87P13 is a phase 3, randomised, controlled, observer-blind, multicentre study to evaluate the safety, tolerability and immunogenicity of two doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59[1], in adult and elderly subjects. The MAH submits an interim safety data analysis taking into account only adverse events (AEs) collected during the 64 days following the enrolment. The MAH had already committed to provide the final study report which will include a 6-months follow up of the enrolled subjects.

Clinical safety

Study design

Study V87P13 was designed to evaluate the safety, tolerability and immunogenicity of 2 doses of a monovalent A/H5N1 influenza vaccine adjuvanted with MF59 (AdjPanH5N1), each containing 7.5 µg of A/Vietnam/1194/2004 (H5N1 Clade 1) antigen administered 3 weeks apart.

The study was performed at multiple study sites, in a population of healthy subjects aged 18 to 60 years and over 60 years of age. Overall, subjects were enrolled and randomised at a 4:1 ratio within each age group to receive the study vaccinations listed in the table below.

Study Groups and Relative Vaccinations

Study Day	Adults		Elderly	
	NonAdjSeasonal/ AdjPanH5N1	Placebo/ AdjSeasonal	NonAdjSeasonal/ AdjPanH5N1	Placebo/ AdjSeasonal
day 1	NonAdjSeasonal	Placebo	NonAdjSeasonal	Placebo
day 22 (-2/+14)	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
day 43 (-2/+14)	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal

AdjPanH5N1: Adjuvanted pandemic H5N1 (Fluad-H5N1); AdjSeasonal: Adjuvanted seasonal (Fluad) ; NonAdj Seasonal: Non Adjuvanted seasonal (Agrippal)

Subjects were enrolled into two age stratifications: 3372 adults (18 to 60 years) and 275 elderly (>60 years). A total of 3371 subjects were vaccinated according to the randomisation list (2692 received AdjPanH5N1 and 679 received AdjSeasonal).
Elderly subjects were enrolled first. At day 1, subjects were randomised at a 4:1 ratio to receive a single 0.5 ml IM injection of the trivalent inactivated subunit vaccine NonAdjSeasonal (Groups 1 and 3), or placebo (Groups 2 and 4), followed by two 0.5 ml IM injections, administered three weeks apart (day 22 and day 43), of the MF59-adjuvanted monovalent A/H5N1 influenza vaccine (AdjPanH5N1) or the MF59-adjuvanted trivalent inactivated subunit vaccine (AdjSeasonal), according to the study group. NonAdjSeasonal was used to provide also elderly and adult subjects enrolled in the Groups 1 and 3, respectively, with a seasonal influenza vaccine. Placebo was used to maintain the blind approach (3 consecutive injections in each vaccination group).

[1] Due to the different names given to the products during clinical development, in the present report the following names refer to the same formulation (antigen quantity and adjuvant amount): Fluad-H5N1, AdjPanH5N1, H5N1 mock-up vaccine and Focetria (H5N1). The non adjuvanted vaccine is referred to as the seasonal subunit vaccine Agrippal or NonAdjSeasonal.

Most of the enrolled subjects completed the study and the premature withdrawals were <5% and balanced across both the vaccine groups within each age stratification. The common reasons for premature withdrawals were withdrawal of consent, subjects being lost to follow-up and protocol deviation. All details from AEs occuring in subjects which prematurely withdrew will be provided with the final study report.

It was noted that the exclusion criteria included also several condition that are characteristics of the elderly population e.g. diabetes, arteriosclerosis, chronic obstructive pulmonary disease (COPD), hepatic disease, renal disease, congestive heart failure, obesity.

In order to provide a comprehensive picture of safety observed with mock-up vaccines, a pooled analysis of safety data for the H5N1 mock up vaccine from several studies conducted from 2006 to present in adults 18 years and above will be provided. The complete analysis is expected with the final report. It is expected that study V87P13, which had a secondary objective to compare the safety and tolerability profiles of 7.5µg Focetria (H5N1) and of the MF59- adjuvanted seasonal vaccine, will contributed for most of the data off the pooled analysis. Further information on the statistical significance of the comparison will also be available with the final report.

Objectives

The primary safety objectives were:
• To assess the safety and tolerability profile of two doses of MF59-adjuvanted A/Vietnam/1194/2004 (H5N1 Clade 1) influenza vaccine (AdjPanH5N1), each containing 7.5 µg of H5N1 antigen.
• To contribute to an integrated safety database of approximately 3400 subjects exposed to AdjPanH5N1, capable of detecting rare adverse events in adult subjects, i.e. those occurring at a frequency of ≤0.1%, and uncommon adverse events in elderly, i.e. those occurring at a frequency of ≤1% according to the EMEA guideline CHMP/VWP/263499/2006.

There was also a secondary safety objective:
• To evaluate the safety and tolerability profile of AdjPanH5N1 compared with a MF59-adjuvanted interpandemic trivalent influenza vaccine (AdjSeasonal).

The study had two immunogenicity objectives, which are out of the scope of the present variation and so they will be assessed after the submission of the report at the end of the study. The MAH is committed to provide this report.

Results:

A total of 3372 adults were enrolled and randomised in this age cohort, 3371 of them were vaccinated according to the randomisation list (2692 received AdjPanH5N1 and 679 received AdjSeasonal). Subjects who provided AdjPanH5N1 or AdjSeasonal post-vaccination safety data were included in at least one safety analysis of these two vaccines.
Within the three weeks after each vaccination there were 22 serious adverse events (SAEs) (<1%) reported for 19 adults (11 adults following either AdjPanH5N1 vaccination, 2 adults following either AdjSeasonal vaccination, 4 adults after the NonAdjSeasonal vaccination and 2 adults after the placebo vaccination). Two adult subjects (AdjPanH5N1 and NonAdjSeasonal) experienced possibly or probably related serious adverse events (anaphylactic reaction and muscle weakness). The event of muscle weakness will be followed up in light of the prolongued persistence of the reaction.
One female adult subject (AdjPanH5N1) experienced imminent abortion, which in the opinion of the investigator was not related to the study vaccine. However, since this event occurred about 3 weeks after the vaccination this cannot be confirmed on the basis of the evidence provided. Further information is expected with the final report.
In total, 10 adult subjects withdrew prematurely from the study due to an AE following either of the two AdjPanH5N1 or AdjSeasonal vaccinations (5 subjects [<1%] from the AdjPanH5N1 group and 5 subjects [1%] from the AdjSeasonal group). This compares with 6 (<1%) subjects who withdrew prematurely due to an AE after the initial NonAdjSeasonal vaccination and 5 (1%) subjects who withdrew after the placebo.

No death was reported up to day 64.

A total of 275 elderly subjects were enrolled and randomised to receive either AdjPanH5N1 (219 subjects) or AdjSeasonal vaccination (56 subjects) and were included in the safety set.
There were five reports of SAEs (<1%) for four elderly subjects (1 elderly following either AdjPanH5N1 vaccination, 2 elderly following either AdjSeasonal vaccination, 1 elderly after the NonAdjSeasonal vaccination). Two elderly subjects experienced possibly or probably related serious adverse events (bronchial hyperreactivity and pneumonia in one subject [AdjSeasonal] and leukocytoclastic vasculitis in another subject [NonAdjSeasonal]). Only one subject prematurely withdrew from the study following an AE after either AdjPanH5N1 vaccination. One subject withdrew due to an AE following the initial NonAdjSeasonal vaccine and one subject prematurely withdrew after the initial placebo vaccination. No deaths were reported up to day 64.

As the administration of NonAdjSeasonal could confound both the safety evaluation of AdjPanH5N1 alone and the comparison between AdjPanH5N1 and AdjSeasonal additional analyses were provided.
The reactogenicity profile of AdjPanH5N1 was generally lower than the AdjSeasonal vaccine. This finding is in line with previous observations in clinical trials and is probably related to the lower antigen content of the H5N1 vaccine (7.5µg) compared with the seasonal one (45 µg) given that the adjuvant content was identical.
Looking at the reactogenicity profile within each vaccine group, the AdjPanH5N1 vaccine when given for the first time (2nd vaccination) had a slightly higher reactogenicity profile when compared to the second administration (3rd vaccination) in both age groups. A similar phenomenon of lower reactogenicity after the subsequent dose was observed for the control group (AdjSeasonal), also reporting slightly decreased reactogenicity rates after the third vaccination.
Only a slight underreporting (differences between second and third vaccinations of 1-17% of any solicited reaction across all vaccine and age groups) seemed to have occurred. If these differences are due to the introduction of a first vaccination or simply reflect the phenomenon of lower reporting after each subsequent dosing cannot be answered without a third control arm. According to MAH, due to ethical and logistical reasons at the time of the study design and set-up it was not possible to include an additional control arm (two doses of AdjPanH5N1 without the first vaccination with NonAdjSeasonal), which would have been the only measure to control the potential confounding effect of the first vaccination with NonAdjSeasonal. However, as this potential underreporting affects both vaccine groups in an equal way, the comparative assessment of the AdjPanH5N1 and AdjSeasonal and therefore the overall interpretability of the results is not affected. Regarding unsolicited AEs no significant differences were observed in the reporting rates after subsequent dosing.

Solicited reactions

Adults
After first injection a higher percentage of subjects reported solicited local and systemic reactions in the NonAdjSeasonal group when compared to the group of subjects receiving placebo (69% vs. 50% respectively). Solicited reactions were more frequent in the AdjSeasonal than in the AdjPanH5N1 vaccine group. There was a consistent trend towards a reduction of the percentage of subjects with solicited reactions reported after a second consecutive dose of AdjPanH5N1 andAdjSeasonal vaccines.

Elderly:
In the elderly group, the percentage of subjects reporting any solicited reactions was higher in the NonAdjSeasonal vaccine group than in the placebo group after the first vaccination (54% vs 45%). After first and second vaccination with either AdjPanH5N1 or seasonal AdjSeasonal vaccines, there was a general tendency towards a decrease in percentage of subjects reporting local, systemic and other reactions. The two vaccine groups showed similar percentages of subjects with solicited reactions reported.
The percentage of subjects with solicited reactions after receiving the AdjPanH5N1 vaccination was similar or lower than that for those receiving the AdjSeasonal vaccination. In the elderly 44% of those in the AdjPanH5N1 group and 55% in the AdjSeasonal group had solicited reactions after third vaccination.

The table below provides a summary of the solicited reactions reported by injection and study group.

Overview of subjects with solicited reactions, by injections

	Number (%) of Subjects With Solicited Reactions			
Age Group	**Adults**		**Elderly**	
Vaccine Group	**Group 1**	**Group 2**	**Group 3**	**Group 4**
After 1st vaccination (Days 1-7)	**NonAdjSeasonal N=2688**	**Placebo N=678**	**NonAdjSeasonal N=219**	**Placebo N=56**
Any	1858 (69%)	339 (50%)	118 (54%)	25 (45%)
Local	1456 (54%)	202 (30%)	84 (38%)	15 (27%)
Systemic	1207 (45%)	229 (34%)	66 (30%)	18 (32%)
Other	338 (13%)	65 (10%)	18 (8%)	4 (7%)
After 2nd vaccination (Days 22-28)	**AdjPanH5N1 N=2607**	**AdjSeasonal N=657**	**AdjPanH5N1 N=214**	**AdjSeasonal N=54**
Any	1770 (68%)	507 (77%)	113 (53%)	30 (56%)
Local	1532 (59%)	452 (69%)	89 (42%)	22 (41%)
Systemic	1134 (43%)	343 (52%)	71 (33%)	17 (31%)
Other	246 (9%)	106 (16%)	16 (7%)	4 (7%)
After 3rd vaccination (Day 43-49)	**AdjPanH5N1 N=2559**	**AdjSeasonal N=639**	**AdjPanH5N1 N=212**	**AdjSeasonal N=53**
Any	1413 (55%)	385 (60%)	94 (44%)	29 (55%)
Local	1200 (47%)	342 (54%)	66 (31%)	21 (40%)
Systemic	844 (33%)	206 (32%)	55 (26%)	16 (30%)
Other	185 (7%)	45 (7%)	16 (8%)	3 (6%)

The table below shows the percentage of subjects with each (and severe) local reactions

	Injection 1		Injection 2		Injection 3	
	NonAdjSeasonal	Placebo	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
Adults	**N= 2686**	**N=677**	**N=2606**	**N=656**	**N=2556**	**N=638**
Erythema	29 (<1) [a]	16 (0)	17 (0)	23 (<1) [a]	17 (0) [b]	20 (<1) [a]
Induration	19 (0) [a]	5 (0)	14 (<1)	21 (0) [a]	13 (0) [a]	16 (0) [a]
Swelling	14 (0) [a]	5 (0)	11 (<1) [a]	18 (<1) [a] N=655	9 (0) [a]	15 (0) [a]
Ecchymosis	7 (<1) [a]	7 (0)	6 (0) [a]	8 (0) [a]	4 (0) [a]	6 (0)
Pain	35 (<1)	13 (<1)	51 (1) [a]	61 (2)	38 (<1)	45 (0) [a]
Elderly	**N=219**	**N=56**	**N=214**	**N=54**	**N=212**	**N=53**
Erythema	29 (0)	14 (0)	15 (0)	19 (0)	10 (0)	13 (0)
Induration	12 (0)	5 (0)	9 (0)	7 (0)	2 (0)	15 (0)
Swelling	5 (0)	4 (0)	7 (0)	9 (0)	3 (0)	2 (0)
Ecchymosis	5 (0)	13 (0)	6 (0)	4 (0)	5 (0)	11 (0)
Pain	11 (0)	0 (0)	30 (0)	24 (0)	22 (<1)	30 (0)

[a]One subject's data was missing; [b] Two subjects' data were missing.

The table below shows the percentage of subjects with each (and severe) systemic reactions

	Injection 1		Injection 2		Injection 3	
	NonAdjSeasonal	Placebo	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
Adults	**N=2686**	**N=677**	**N=2606**	**N=656**	**N=2555**	**N=639**
Chills	11 (<1)	9 (<1)	8 (<1)	14 (1)	7 (<1)	8 (<1)
Malaise	10 (<1)	8 (1)	9 (1)	17 (1)[a]	6 (1)	7 (<1)
Myalgia	20 (<1)	10 (<1)	26 (<1)	37 (2)	19 (<1)	21 (0)
Arthralgia	5 (<1)	3 (<1)	4 (<1)	9 (<1)[a]	4 (<1)	5 (0)
Headache	23 (1)	17 (1)	18 (1)	23 (2)[a]	14 (1)	12 (<1)
Sweating	6 (<1)	5 (<1)	6 (<1)	8 (1)[a]	4 (<1)	3 (<1)
Nausea	6 (<1)	5 (1)	5 (<1)	8 (<1)[a]	3 (<1)	4 (<1)
Fatigue	22 (1)	18 (1)	17 (1)	24 (2)[a]	14 (1)	13 (1)
Fever ≥ 38C (≥ 40 C)[a]	1 (0)	<1 (0)	1 (0)[a]	2 (<1)	<1 (0)[b]	<1 (0)
Stay Home	1	1	1	3	1	<1
Analgesic Antipyretic Medication Use	12	9	9	15	7	7
Elderly	**N=219**	**N=56**	**N=214**	**N=54**	**N=212**	**N=53**
Chills	8 (<1)	14 (0)	9 (0)	11 (0)	8 (<1)	9 (0)
Malaise	4 (0)	4 (0)	7 (0)	6 (0)	6 (<1)	6 (2)
Myalgia	13 (1)	5 (0)	20 (0)	17 (0)	13 (<1)	19 (0)
Arthralgia	4 (<1)	4 (0)	3 (0)	4 (0)	5 (<1)	6 (0)
Headache	10 (0)	18 (2)	12 (1)	13 (0)	10 (0)	6 (0)
Sweating	2 (0)	7 (0)	3 (0)	2 (0)	2 (0)	2 (0)
Nausea	2 (1)	4 (0)	4 (0)	4 (0)	3 (0)	2 (2)
Fatigue	6 (1)	14 (2)	8 (<1)	9 (0)	8 (<1)	8 (2)
Fever ≥ 38C (≥ 40 C)[a]	1 (0)	0 (0)	0 (0)	0 (0)	<1 (0)	2 (0)
Stay Home	<1	0	<1	0	1	2
Analgesic Antipyretic Medication Use	8	7	7	7	8	4

[a]One subject's data was missing; [b] Two subjects' data were missing.
(≥40)[a] indicates severe reaction.

Unsolicited reactions

Adults

The most commonly affected system organ classes (SOCs) after first and second injections of AdjPanH5N1 and AdjSeasonal vaccines was infections and infestations, followed by musculoskeletal, connective tissue and bone disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, gastrointestinal disorders, and nervous system disorders.

The most common adverse event reported in adults within 21 days of any injection was nasopharyngitis (7% in AdjPanH5N1 and 8% in AdjSeasonal vaccine group). Upper respiratory tract infections were reported by 6% of adult subjects in the AdjPanH5N1 vaccine group and 5% in AdjSeasonal vaccine group. Other adverse events were reported in ≤ 5% of subjects, were generally balanced between the vaccine groups, and were caused by expected adverse events in this population or known side effects to influenza vaccination.

Elderly:
The most commonly affected SOCs after first and second injections of AdjPanH5N1 and AdjSeasonal vaccines was infections and infestations, followed by musculoskeletal, connective tissue and bone disorders, respiratory, thoracic and mediastinal disorders, general disorders and administration site conditions, gastrointestinal disorders, and nervous system disorders. The most common adverse event reported by elderly subjects within 21 days of each injection were upper respiratory tract infection (4% in AdjPanH5N1 and 9% in AdjSeasonal vaccine group), headache (3% in AdjPanH5N1 and 6% in AdjSeasonal vaccine group) and rhinitis (2% in AdjPanH5N1 and 6% in AdjSeasonal vaccine group). Other adverse events were reported in < 5% of subjects, were generally balanced between the vaccine groups, and were caused by expected adverse events in this population or known side effects to influenza vaccination.

The table below provides a summary of the unsolicited AEs by injection and study group.

Overview of unsolicited AEs by injection

Type of Reaction	**Number (%) of Subjects With Adverse Event**			
Age Group	**Adults**		**Elderly**	
Vaccine Group	**Group 1**	**Group 2**	**Group 3**	**Group 4**
After 1st vaccination	**NonAdjSeasonal N=2688**	**Placebo N=678**	**NonAdjSeasonal N=219**	**Placebo N=56**
Any AEs	851 (32)	198 (29)	54 (25)	13 (23)
At least possibly related AEs	318 (12)	67 (10)	17 (8)	6 (11)
After 2nd vaccination	**AdjPanH5N1 N=2607**	**AdjSeasonal N=657**	**AdjPanH5N1 N=214**	**AdjSeasonal N=54**
Any AEs	690 (26)	174 (26)	51 (24)	18 (33)
At least possibly related AEs	231 (9)	76 (12)	17 (8)	9 (17)
After 3rd vaccination	**AdjPanH5N1 N=2559**	**AdjSeasonal N=639**	**AdjPanH5N1 N=212**	**AdjSeasonal N=53**
Any AEs	548 (21)	146 (23)	38 (18)	7 (13)
At least possibly related AEs	155 (6)	42 (7)	12 (6)	4 (8)

Summary of Adverse Events
One case of anaphylaxis was reported. Two cases each were reported for convulsions and eye swelling, corresponding to a frequency of rare. A total of 19 cases of urticaria were reported in the two different cohorts (adults and elderly), corresponding to an uncommon frequency. The frequency of headache, myalgia, injection site swelling, injection site pain, injection site induration, injection site redness, malaise, fatigue and shivering (chills) was reviewed as there was an increase in the reporting of these adverse events. Influenza like illnesses occurred uncommonly. Several cases of nausea were reported commonly. The product information was updated to reflect this.

The tables below provide a summary of AEs that occurred in 1% or more of the population after either AdjPanH5N1 or AdjSeasonal vaccination in adults and a summary of all treatment emergent adverse events that occurred in 1% or more of the population after either AdjPanH5N1 or AdjSeasonal vaccination in elderly.

Summary of Adverse Events After Any AdjPanH5N1 or AdjSeasonal Vaccination by ≥1% of subjects in adults

Preferred Term	Number (%) of Subjects with Adverse Events			
	All AEs		At Least Possibly Related AEs	
	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
	N=2611	N=658	N=2611	N=658
Nasopharyngitis	172 (7%)	50 (8%)	45 (2%)	18 (3%)
Upper Respiratory Tract Infection	157 (6%)	35 (5%)	38 (1%)	5 (1%)
Headache	121 (5%)	23 (3%)	33 (1%)	3 (<1%)
Rhinitis	81 (3%)	27 (4%)	21 (1%)	7 (1%)
Oropharyngeal Pain	85 (3%)	24 (4%)	47 (2%)	8 (1%)
Gastroenteritis	50 (2%)	13 (2%)	6 (<1%)	0
Sinusitis	41 (2%)	13 (2%)	9 (<1%)	2 (<1%)
Injection Site Haemorrhage	31 (1%)	12 (2%)	30 (1%)	12 (2%)
Cough	45 (2%)	9 (1%)	14 (1%)	3 (<1%)
Diarrhoea	45 (2%)	11 (2%)	15 (1%)	4 (1%)
Back Pain	41 (2%)	11 (2%)	2 (<1%)	0
Fatigue	43 (2%)	10 (2%)	30 (1%)	7 (1%)
Bronchitis	31 (1%)	8 (1%)	4 (<1%)	0
Pyrexia	22 (1%)	8 (1%)	4 (<1%)	2 (<1%)
Arthralgia	27 (1%)	7 (1%)	11 (<1%)	4 (1%)
Influenza	11 (<1%)	7 (1%)	2 (<1%)	0
Myalgia	24 (1%)	5 (1%)	9 (<1%)	3 (<1%)
Abdominal Pain Upper	18 (1%)	6 (1%)	5 (<1%)	2 (<1%)
Ecchymosis	15 (1%)	6 (1%)	14 (1%)	6 (1%)
Migraine	20 (1%)	6 (1%)	2 (<1%)	1 (<1%)
Musculoskeletal Pain	20 (1%)	3 (<1%)	7 (<1%)	0
Injection Site Pruritus	12 (<1%)	5 (1%)	12 (<1%)	5 (1%)
Lymphadenopathy	4 (<1%)	5 (1%)	3 (<1%)	5 (1%)
Pain In Extremity	15 (1%)	5 (1%)	5 (<1%)	2 (<1%)
Dysmenorrhoea	18 (1%)	3 (<1%)	1 (<1%)	0
Vertigo	16 (1%)	4 (1%)	6 (<1%)	4 (1%)
Abdominal Pain	7 (<1%)	4 (1%)	2 (<1%)	0
Dizziness	5 (<1%)	4 (1%)	1 (<1%)	2 (<1%)
Ear Infection	2 (<1%)	4 (1%)	0	0
Hyperhidrosis	8 (<1%)	4 (1%)	7 (<1%)	3 (<1%)
Hypertension	3 (<1%)	4 (1%)	0	1 (<1%)
Pharyngitis	9 (<1%)	4 (1%)	1 (<1%)	1 (<1%)
Toothache	10 (<1%)	4 (1%)	1 (<1%)	0
Vertebral Injury	12 (<1%)	4 (1%)	0	0
Nausea	15 (1%)	2 (<1%)	3 (<1%)	2 (<1%)
Malaise	14 (1%)	3 (<1%)	7 (<1%)	3 (<1%)
Neck Pain	14 (1%)	1 (<1%)	7 (<1%)	1 (<1%)

Summary of All Treatment Emergent Adverse Events After Any AdjPanH5N1 or AdjSeasonal Vaccination by ≥1% of Subjects in Elderly

Preferred Term	Number (%%) of Subjects with Adverse Events			
	All AEs		At Least Possibly Related AEs	
	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
	N=214	N=54	N=214	N=54
Upper Respiratory Tract Infection	8 (4%)	5 (9%)	2 (1%)	2 (4%)
Headache	7 (3%)	3 (6%)	0	2 (4%)
Rhinitis	4 (2%)	3 (6%)	1 (<1%)	1 (2%)
Cough	2 (1%)	2 (4%)	1 (<1%)	2 (4%)
Diarrhoea	0	2 (4%)	0	2 (4%)
Dyspepsia	1 (<1%)	2 (4%)	1 (<1%)	1 (2%)
Nasopharyngitis	7 (3%)	0	0	0
Oropharyngeal Pain	6 (3%)	1 (2%)	4 (2%)	1 (2%)
Injection Site Haemorrhage	5 (2%)	1 (2%)	5 (2%)	1 (2%)
Gastroenteritis	4 (2%)	0	0	0
Abdominal Pain Upper	0	1 (2%)	0	1 (2%)
Bronchial Hyperreactivity	0	1 (2%)	0	1 (2%)
Chest Pain	0	1 (2%)	0	0
Dry Mouth	0	1 (2%)	0	0
Ecchymosis	3 (1%)	1 (2%)	3 (1%)	1 (2%)
Enteritis	0	1 (2%)	0	0
Erectile Dysfunction	0	1 (2%)	0	0
Fatigue	2 (1%)	1 (2%)	1 (<1%)	0
Humerus Fracture	0	1 (2%)	0	0
Hyperhidrosis	0	1 (2%)	0	0
Injection Site Erythema	2 (1%)	1 (2%)	2 (1%)	1 (2%)
Insomnia	0	1 (2%)	0	1 (2%)
Otitis Externa	0	1 (2%)	0	0
Pneumonia	0	1 (2%)	0	1 (2%)
Rhinorrhoea	0	1 (2%)	0	1 (2%)
Sensation Of Foreign Body	0	1 (2%)	0	0
Thermal Burn	0	1 (2%)	0	0
Toothache	1 (<1%)	1 (2%)	0	0
Tremor	0	1 (2%)	0	1 (2%)
Urticaria	0	1 (2%)	0	1 (2%)
Back Pain	3 (1%)	0	0	0
Migraine	3 (1%)	0	0	0
Vertigo	3 (1%)	0	1 (<1%)	0
Arthralgia	2 (1%)	0	2 (1%)	0
Conjunctivitis	2 (1%)	0	0	0
Herpes Simplex	2 (1%)	0	0	0

Preferred Term	Number (%%) of Subjects with Adverse Events			
	All AEs		At Least Possibly Related AEs	
	AdjPanH5N1	AdjSeasonal	AdjPanH5N1	AdjSeasonal
	N=214	N=54	N=214	N=54
Influenza	2 (1%)	0	0	0
Nasal Congestion	2 (1%)	0	0	0
Pain In Extremity	2 (1%)	0	0	0
Sinusitis	2 (1%)	0	0	0

Among the "at least possible related AEs" there is in AdjPanH5N1 a percentage of adults subjects with some adverse events higher than in AdjSeasonal. However, the number of subjects involved was very small and further details on these differences will be available with the final report, which the MAH is committed to provide.

Serious adverse events

In the following tables the listing of serious adverse events in adults 18-60 years and elderly subjects is presented.

Listing of Serious Adverse Events Occurring up to Day 64 in 18 to 60 year old subjects

Preferred Term	Onset (Day)	Duration (days)	Outcome	Hospitalisation	Relatedness
Pleurisy	5	17	Recovered	Yes	None
Pyelonephritis	28	4	Recovered	Yes	None
Pyelonephritis Acute	68	34	Recovered	Yes	None
Stress Cardiomyopathy	12	7	Recovered	Yes	None
Cerebral Infarction	74	16	Recovered	Yes	None
Subarachnoid Haemorrhage	70	15	Recovered	Yes	None
Cholecystitis Acute	30	14	Recovered	Yes	None
Pneumonia	35	9	Recovered	Yes	None
Anaphylactic Reaction	48	<1	Recovered	No	Probably Related
Anxiety Disorder	40	28	Recovered	Yes	None
Muscular Weakness	31		Ae Persist	No	Possibly Related
Biliary Colic	22	<1	Recovered	Yes	None
Cholelithiasis	23	3	Recovered	Yes	None
Hyperventilation	28	<1	Recovered	Yes	None
Inguinal Hernia	32	29	Recovered	Yes	None
Depression	5		Unk/Lostfu	Yes	None
Imminent Abortion	47	2	Recovered	Yes	None
Vertigo	56	2	Recovered	Yes	None
Abdominal Pain Lower	59	1	Recovered	Yes	None
Gastroenteritis	70	5	Recovered	Yes	None
Uterine Leiomyoma	60	3	Recovered	Yes	None
Rectal Haemorrhage	10	7	Recovered	Yes	None

Listing of Serious Adverse Events Occurring up to Day 64 in Over 60 Year Old subjects

Preferred Term	Onset (Day)	Duration (days)	Outcome	Hospitalisation	Relatedness
Humerus Fracture	35	143	Recovered	Yes	None
Haemorrhoid Operation	59	1	Unk/Lostfu	Yes	None
Bronchial Hyperreactivity	50	2	Recovered	No	Possibly Related
Pneumonia	50	7	Recovered	No	Possibly Related
Leukocytoclastic Vasculitis	18		Ae Persist	No	Possibly Related

A compiled listing of SAE will be provided with the final report, as presently these data are not available.

Changes to the Product Information

The proposed changes to section 4.8 of the summary of product characteristics (SPC) were reviewed and initially not agreed with. A revision of the wording was submitted taking into account the results of the assessment and this was agreed with by the CHMP. The package leaflet (PL) was updated accordingly. Several minor corrections and clarifications were introduced in the product information and these were agreed with by the CHMP.

Overall discussion and benefit risk assessment

The present study was aimed to evaluate the safety and tolerability of 2 doses of the monovalent AdjPanH5N1, each dose containing 7.5 µg of A/Vietnam/1194/2004 antigen antigen in approximately 2600 adults and 210 elderly. The study was to contribute to an integrated AdjPanH5N1 safety database from clinical trials of approximately 3400 exposed subjects, the sample size that would be sufficient to detect rare adverse events in adults (at ≤0.1% frequency) and elderly (at ≤1% frequency).

After two injections, both AdjPanH5N1 and AdjSeasonal vaccines were well tolerated. Solicited local and systemic reactions were mostly mild or moderate in severity. The percentage of solicited reactions was higher in the NonAdjSeasonal group than in the placebo group after first vaccination. The percentage was higher after the second dose than the third. Overall, the safety profile of the AdjPanH5N1 did not seem to be significantly affected by the prior vaccination with the seasonal subunit vaccine.
The most frequent local solicited reactions after AdjPanH5N1 was pain in both adults and elderly, whilst the most frequent systemic reaction was myalgia. A high number of AEs concerning the infections and infestations SOC was observed. These should be monitored and reported in the final report. Anaphylaxis was considered as a SAE probably related to the study vaccine. Two cases of convulsions were reported (one in first vaccination, which cannot be thus attributed to Focetria (H5N1). Two cases of eye swelling were also reported. Since in both cohorts malaise and shivering occurred with an incidence ≥10% these AE should be considered as very common. Several local reactions (injection site redness, swelling, pain and induration) and headache were also very commonly reported. Urticaria was uncommonly reported (19 cases, 18 in the adult cohort and 1 in the elderly), and none considered as serious. Influenza like illnesses should be reported as an uncommon AE since it occurred with a frequency of 0.6%. Nausea was commonly reported. The product information was updated to reflect the available safety information.