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/0009

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).
Assessment of data on the effect of a booster dose and on persistence of protection was conducted as part of a commirment to submit results of study V87P1. The marketing authorisation holder (MAH) now applies for an update of the product information to include reference to persistence of antibodies data from the initial H5N1 mock-up file[1].

Clinical

Study V87P1[2] was a phase 2, randomised, controlled, observer-blind, multicentre study designed to evaluate the safety and immunogenicity of two doses (day 0 and day 21), administered three weeks apart, and a six months booster dose (subset) of two MF59 adjuvanted influenza vaccine containing 7.5 µg or 15 µg of H5N1 influenza antigen, in adults, including the elderly.

Study ID Country Year	**Study Objectives**	**Study Design: Randomisation, Control, Blinding**	**Test Products: Dosage Regimen; Route of Administration**	**Number of Healthy Subjects Enrolled and Age**	
V87P1 Italy 2006/2007	Immunogenicity, persistence of immune response and safety of 2 or 3 injections of 7.5/15 µg H5N1 mock-up vaccine. Non-inferiority of 7.5 to15 µg HA (A/H5N1)	Phase 2, Randomised (1:1), Controlled, Observer-blind Multicentre	H5N1 mock-up vaccine : 7.5 µg H5N1 mock-up vaccine: 15 µg IM	18-60 years ≥61 years	7.5µg: 157 15µg: 156 7.5µg: 87 15µg: 86

[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, H5N1 mock-up vaccine and Focetria (H5N1).
[2] For more information on the study design and initial results of this pivotal study, please refer to the published scientific discussion in the european public assessment report.

Results

A total of 486 subjects were enrolled, 313 aged 18-60 years (adults) and 173 aged 61 years and over (elderly). A subset of subjects received a six month booster dose. The primary immunogenicity objective was to assess immunogenicity of H5N1 influenza antigen as measured by HI assay after primary vaccinations with H5N1 mock-up influenza vaccine.
The results presented in this section were analysed in the per-protocol (PP) population, and are discussed for the 7.5 µg dose for the elderly only, as per the scope of this variation application.

The table below shows the antibody persistence 6 months after primary vaccination with Focetria (H5N1), per protocol population.

		H5N1 (A/Vietnam Strain)	
		Adults (18-60 years) N=116	**Elderly (≥61 years) N=66**
HI	GMT[b] day 202 pre-booster (95% CI)	12 (9.63-16)	23 (15-37)
	GMR[c] day 202/day 43 (95% CI)	0.15 (0.11-0.2)	0.33 (0.24-0.46)[e]
	% SP[d] day 202 pre-booster (95% CI)	28 (20-37)	50 (37-63)
SRH	GMA[f] day 202 pre-booster (95% CI)	8.06 (6.67-9.75)	6.96 (5.26-9.2)
	GMR day 202/day 43 (95% CI)	0.22 (0.18-0.26)	0.24 (0.18-0.32)
	% SP day 202 pre-booster (95% CI)	26 (18-35)	24 (15-36)
MN	GMT day 202 pre-booster (95% CI)	35 (29-42)	33 (24-46)
	GMR day 202/day 43 (95% CI)	0.29 (0.23-0.35)	0.43 (0.33-0.56)
	% ≥1:40 day 202 pre-booster (95% CI)	44 (35-53)	44 (32-57)

[a] PP population = all randomised subjects who received all vaccinations correctly, provided evaluable serum samples before and after baseline and with no major protocol violations. [b] GMT= geometric mean titer; [c] GMR = geometric mean ratio; [d] SP = seroprotection, is defined as HI titers ≥40 or SRH area ≥25 mm^2; [e] N=64; [f] GMA= geometric mean area

Haemagglutination inhibition (HI) assay persistence results

In the elderly, 50% of subjects in the 7.5 µg group were seroprotected before the booster (day 202). Approximately 3 weeks after primary vaccination, GMTs against the A/Vietnam/1194/2004-like (H5N1) influenza antigen in the elderly for the 7.5 µg group were 66. There was a decrease in titers at day 202 (GMTs: 23), where GMRs over day 43 was 0.33.

The antibody persistence by HI assay is shown below (PP population).

Responses to 7.5 and 15 µg FLUAD-H5N1 and 7.5 vs. 15 Vaccine Group Ratios - Titers With 95 CIs (%)							
		Adults (18-60 yrs)			Elderly (> 60 yrs)		
		7.5 µg N=116	15 µg N=122	7.5 vs. 15	7.5 µg N=66	15 µg N=55	7.5 vs. 15
Post-2nd (day 43)	GMT (day 43)	83 (59-115)	75 (54-105) N=119	1.1 (0.69-1.75)	66 (42-103) N=64	69 (42-113) N=51	0.97 (0.52-1.8)
Persistence Primary Vaccination (day 202)	GMT (day 202)	12 (9.63-16)	17 (13-21)	0.75 (0.53-1.07)	23 (15-37)	31 (19-51)	0.76 (0.4-1.42)
	GMR[a]	0.15 (0.11-0.2)	0.22 (0.16-0.28) N=119	0.7 (0.47-1.03)	0.33 (0.24-0.46) N=64	0.41 (0.29-0.6) N=51	0.8 (0.5-1.27)
		N=69	N=76		N=35	N=22	
Post-booster (day 223)	GMT (day 223)	124 (82-187)	105 (70-156)	1.18 (0.67-2.08)	128 (80-203) N=34	201 (118-341)	0.64 (0.32-1.25)
Persistence Booster (day 382)	GMT (day 382)	27 (18-41)	29 (20-42)	0.96 (0.56-1.65)	36 (20-68)	71 (34-145)	0.52 (0.21-1.29)
	GMR[b]	0.22 (0.16-0.31)	0.27 (0.19-0.38)	0.81 (0.5-1.31)	0.3 (0.19-0.49) N=34	0.35 (0.2-0.6)	0.87 (0.43-1.75)

Single radial haemolysis (SRH) assay persistence results

Twenty four percent of the elderly subjects in the 7.5 µg group were seroprotected before the booster (day 202). Approximately 3 weeks after the booster, the SRH GMA against the A/Vietnam/1194/2004-like (H5N1) influenza antigen in these elderly subjects was 33. Six months after the booster (day 382), decreases in GMA were observed, with GMR over day 223 of 0.38.

The antibody persistence by SRH assay is shown below (PP population).

Responses to 7.5 and 15 µg FLUAD-H5N1 and 7.5 vs. 15 Vaccine Group Ratios - Titers With 95 CIs (%)							
		Adults (18-60 yrs)			Elderly (> 60 yrs)		
		7.5 µg N=116	15 µg N=122	7.5 vs. 15	7.5 µg N=66	15 µg N=55	7.5 vs. 15
Post-2nd (day 43)	GMA (day 43)	37 (32-44)	35 (30-41)	1.05 (0.84-1.31)	29 (22-38)	31 (23-41)	0.94 (0.65-1.36)
Persistence Primary Vaccination (day 202)	GMA (day 202)	8.06 (6.67-9.75)	9.11 (7.56-11)	0.89 (0.68-1.15)	6.96 (5.26-9.2)	11 (8.04-15)	0.64 (0.43-0.94)
	GMR[a]	0.22 (0.18-0.26)	0.26 (0.21-0.31)	0.84 (0.65-1.1)	0.24 (0.18-0.32)	0.36 (0.26-0.48)	0.68 (0.46-0.99)
		N=69	N=76		N=35	N=22	
Post-booster (day 223)	GMA (day 223)	41 (34-49)	41 (35-49)	0.99 (0.78-1.27)	33 (24-47)	44 (30-65)	0.76 (0.46-1.25)
Persistence Booster (day 382)	GMA (day 382)	17 (13-21)	17 (14-21)	0.97 (0.7-1.35)	13 (8.42-19)	25 (16-39)	0.51 (0.28-0.91)
	GMR[b]	0.41 (0.33-0.5)	0.41 (0.34-0.51)	0.98 (0.74-1.3)	0.38 (0.27-0.52)	0.56 (0.39-0.81)	0.67 (0.42-1.06)

Microneutralization (MN) assay persistence results

Forty four percent of elderly subjects in the H5N1 mock-up vaccine 7.5 µg group had an MN titer ≥40 before the booster. Approximately 3 weeks after the booster (day 223), GMTs against the A/Vietnam/1194/2004-like (H5N1) influenza antigen in these elderly subjects was 154. Six months after the booster (day 382), decreases in GMTs were observed, with GMRs over day 223 of 0.17.

The antibody persistence by MN assay is shown below (PP population).

Responses to 7.5 and 15 µg FLUAD-H5N1 and 7.5 vs. 15 Vaccine Group Ratios - Titers With 95 CIs (%)							
		Adults (18-60 yrs)			Elderly (> 60 yrs)		
		7.5 µg N=116	15 µg N=122	7.5 vs. 15	7.5 µg N=66	15 µg N=55	7.5 vs. 15
Post-2nd (day 43)	GMT (day 43)	121 (99-149)	96 (78-117)	1.27 (0.95-1.69)	78 (56-108)	88 (62-127)	0.88 (0.56-1.39)
Pre-booster (day 202)	GMT (day 202)	35 (29-42)	45 (37-55)	0.77 (0.59-1.01)	33 (24-46)	47 (33-67)	0.71 (0.46-1.1)
	GMR [a]	0.29 (0.23-0.35)	0.47 (0.38-0.58)	0.61 (0.46-0.81)	0.43 (0.33-0.56)	0.53 (0.4-0.71)	0.81 (0.56-1.16)
Post-booster (day223)		N=69	N=76		N=35	N=22	
	GMT (day 223)	211 (169-264)	213 (172-263)	0.99 (0.73-1.35)	154 (103-230)	206 (129-327)	0.75 (0.41-1.35)
Persistence Booster (day 382)	GMT (day 382)	34 (26-44)	35 (27-44)	0.98 (0.7-1.38)	25 (17-39)	46 (28-75)	0.55 (0.3-1.02)
	GMR [b]	0.16 (0.14-0.19)	0.16 (0.14-0.19)	0.99 (0.78-1.25)	0.17 (0.13-0.21)	0.22 (0.17-0.29)	0.74 (0.52-1.04)

Changes to the Product Information

The proposed changes to section 5.1 of the SPC (summary of product characteristics) to reflect that limited data on persistence of antibodies in elderly immunised with the H5N1 mock-up vaccine showed that up to 50% of the subjects were seroprotected at six months, were agreed with by the CHMP.

Overall discussion and benefit risk assessment

Study V78P1 was aimed to compare the two initial formulations of vaccines including different amount of H5N1 antigen (7.5 vs 15 µg). As the authorised formulation was 7.5 µg the results were discussed regarding this study group.
The overall study had been already submitted as a commitment and this variation procedure focused on the evaluation of the persistence of circulating antibodies and on the effect of the booster dose six months apart from the second dose.

At day 202, 50% of elderly subjects were seroprotected with HI titres >= 40. The MN results showed a seroprotection of 44% in elderly subjects, which was consistent with the HI data.
Overall the results of the study presented support the inclusion of the statement regarding antibody persistence in the elderly population in the product information of the Focetria A/H1N1 pandemic vaccine.