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/0013

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 information on interaction with other medicinal products, in particular regarding co-administration with non-adjuvanted subunit seasonal influenza vaccines of Focetria reflected in the product information was based on data from the mock-up H5N1 vaccine. The current pandemic is caused by an A/H1N1 viral strain. Therefore, the marketing authorisation holder (MAH) is conducting a clinical trial (study V111_04) to address the immunogenicity and safety of concomitant vaccination with H1N1 and seasonal influenza vaccines. The study was designed to assess the immunogenicity and safety of 2 injections of 7.5µg HA A/H1N1 2009 in adult and elderly subjects previously exposed to 2009/10 northern hemisphere (NH) formulation of seasonal influenza vaccine and in those not yet vaccinated.

The submission of the abridged clinical report of study V111_04, post day 1 fulfils one of the MAH's specific obligations (SOB 27.2). The MAH applied for a variation to update the product information to include the results of this study.

Clinical immunogenicity and safety

Study design

Study V111_04 is an ongoing, phase II, open label study to evaluate the immunogenicity, tolerability and safety of a MF59-adjuvanted, inactivated novel swine origin A/H1N1 monovalent subunit influenza virus vaccine (Focetria) in healthy subjects aged 18 years and above. The study is aimed to investigate concomitant and sequential administration of the H1N1 pandemic vaccine with seasonal influenza vaccines in adults aged 18-60 years and to obtain additional data in subjects above 60 years of age with history of seasonal vaccination.
Two dosages of pandemic H1N1 vaccine were used (half dose or full dose) in healthy subjects, however the 3.75_half MF59 group is not discussed in this report as this dose formulation is not authorised. For completeness, some results are presented.

The study included five groups:

1. Group Agr→Foc subjects from both the 18-60 years and ≥61 years age strata, had previously received in an earlier clinical study (V71_10S) a vaccination with Agrippal (seasonal formulation for 2009/10 for the Northern Hemisphere), in June or early July 2009.
2. Group Fluad→Foc, all aged ≥65 years, had previously received in an earlier clinical study (V70_09S) the adjuvanted seasonal vaccine Fluad (seasonal formulation for 2009/10 for the Northern Hemisphere), all in June 2009. In study V111_04, which commenced in late August 2009, both groups received 2 vaccinations with Focetria 3 weeks apart.
3. Group Foc; subjects who had not been previously vaccinated with a 2009/10 seasonal vaccine and received 2 vaccinations with Focetria 3 weeks apart.
4. Group Conc, all aged 18 to 60 years, received concomitant vaccination of Focetria in the deltoid muscle of the non-dominant arm and seasonal Agrippal in the other, followed by a second vaccination with Focetria 3 weeks later.
5. Group of subjects received a half-dose of Focetria concomitantly with Agrippal. This group is not discussed or analysed in this report

Immunogenicity was assessed at baseline (before the first vaccination) and 3 weeks afterwards. Safety was assessed until 3 weeks after the first vaccination.

Objectives

The study is designed to enable comparisons of:

1) H1N1 responses in subjects previously exposed to the 2009/10 NH formulation of Agrippal or Fluad, and in those not yet vaccinated

2) H1N1 responses in subjects receiving Agrippal concomitantly with the first Focetria vaccination

3) Responses to the seasonal strains in subjects receiving the first vaccination with Focetria concomitantly with Agrippal (i.e., group Conc only).

The safety of the study vaccine was assessed based on the number of subjects exposed and with reported local and systemic reactions, as well as the number of subjects with reported adverse events by vaccine and age groups. Immunogenicity and safety data after the first vaccination (i.e., up to day 22) are presented in this report.

Study population

The study population consisted of male and female healthy subjects aged ≥18 years who had not had H1N1sw influenza vaccination or documented H1N1sw influenza disease. Those with immunosuppressive conditions, including chronic use of oral or systemic steroids, were not included. Female subjects of reproductive potential, who must have used birth control measures for at least 2 months before study participation and committed to use birth control measures during at least the first 3 weeks after last study vaccination, were included.

The study is conducted in 419 healthy adult subjects, 264 between 18 and 60 years of age and 155 above 61 years of age. Subjects were allocated to 5 vaccine groups.

The table below show the different vaccine groups and the number of subjects enrolled per group.

Enrolled subjects per vaccine group

Group abbreviation used in this addendum	**Agr[a]→Foc[b]**	**Fluad→Foc**	**Foc**	**Conc[c]**	**NA[d]**
Group abbreviation used in V111_04 Clinical Study Report	**TIV → 7.5_fullMF59**	**AdjTIV→ 7.5_fullMF59**	**7.5_fullMF59**	**7.5_fullMF59 + TIV**	**3.75_halfMF59 + TIV**
18 to 60 years:	**N=50**	**N=0**	**N=71**	**N=71**	**N=72**
over 60 years	**N=49**	**N=46[e]**	**N=60**	**N=0**	**N=0**
Total	**N=99**	**N=46**	**N=131**	**N=71**	**N=72**

[a]Agrippal NH 2009-2010, [b]Focetria, [c]Concomitant administration of Focetria into deltoid muscle of non-dominant arm and Agrippal into deltoid muscle of dominant arm. [d]NA=not applicable; study group not discussed in this report. [e]All subjects ≥65 years of age.

The sample size per each arm was consistent with the requirements set for seasonal trials. The age of the various study groups was slightly different, and this could be expected especially in those with positive history of TIV. No subjects above 80 years of age were included.

The demographic and other baseline characteristics are shown below (concomitant administration is shown in bold; only adults 18-60 years of age were studied):

	adults 18-60 years				**adults over 60 years**		
Vaccine groups	**TIV→7.5_full MF59**	**7.5_fullMF59**	**7.5_full MF59 + TIV**	**3.75_halfMF59 + TIV**	**TIV→7.5_full MF59**	**AdjTIV→7.5_full MF59**	**7.5_fullMF59**
	N=50	**N=71**	**N=70**	**N=69**	**N=49**	**N=46**	**N=59**
Age:	46.5±9.7	40.7±12.1	**40.6±12.3**	38.8±12.2	69.2±7.3	72.8±5.9	70.5±7.5
Female (%)	33(66%)	40(56%)	**37(53%)**	38(55%)	27(55%)	19(41%)	26(44%)
Weight (kg):	74.80±13.97	69.03±15.34	**70.81±17.49**	68.68±14.98	74.05±12.70	75.54±12.35	73.38±10.96
Height (cm):	166.2±8.1	168.5±10.0	**169.9±9.5**	168.7±9.1	165.0±7.9	164.3±7.3	166.4±7.1
Female of Childbearing	22(44%)	28(39%)	**32(46%)**	32(46%)	0	0	0

Potential:							
Previous influenza Study:	50(100%)	0	**0**	0	49(100%)	46(100%)	0
Met Protocol Criteria:	50(100%)	71(100%)	**70(100%)**	69(100%)	49(100%)	46(100%)	59(100%)

Categorical parameters: N(%), non-categorical parameters: Mean±Std

Results

Immunogenicity

The populations analysed were the full analysis set (FAS). Nearly all enrolled subjects (96 to 100% across vaccine and all age groups) were included in the immunogenicity analysis at day 22. In particular, for the concomitant group 7.5_fullMF59, the full analysis population was 99% (N=70).

The table below shows the overall results for the full analysis set (FAS) for haemagglutination inhibition (HI) against the pandemic A/H1N1 2009 strain at day 22. Geometric mean ratios (GMR), seroconversion and seroprotection are shown for the different groups (half dose not shown).

		Agr[a]→Foc[b]	Fluad→Foc	Foc	Conc[c]
18 to 60 years		**N=50**	**N=0**	**N=71**	**N=71**
GMR (95% CI)	Criterion: >2.5	**39** (21-70)	NA	**52** (36-77)	**48** (33-71)
Seroconversion (95% CI)	Criterion: >40%	47 (**94%**) (83-99)	NA	63 (**89%**) (79-95)	69 (**99%**) (92-100)
Seroprotection (95% CI)	Criterion >70%	48 (**96%**) (86-100)	NA	68 (**96%**) (88-99)	70 (**100%**) (95-100)
over 60 years		**N=49**	**N=46**	**N=60**	**N=0**
GMR (95% CI)	Criterion >2.0	**10** (4.52-24)	**7.94** (3.54-18)	**9.29** (5.34-16)	NA
Seroconversion (95% CI)	Criterion >30%	35 (**71%**) (57-83)	32 (**70%**) (54-82)	45 (**76%**) (63-86)	NA
Seroprotection (95% CI)	Criterion >60%	44 (**90%**) (78-97)	41 (**89%**) (76-96)	50 (**85%**) (73-93)	NA

[a]Agrippal NH 2009-2010, [b]Focetria, [c]Concomitant administration of Focetria into deltoid muscle of non-dominant arm and Agrippal into deltoid muscle of dominant arm.

The CHMP criteria (GMR > 2.5, Seroconversion > 40%, Seroprotection > 70%) were also met for the three seasonal strains at day 22, after concomitant vaccination with 7.5_fullMF59, as shown below.

		B_BRISBANE08		H1N1_BRISBANE07		H3N2_URUGUAY07	
		7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
		N=70	N=69	N=70	N=69	N=70	N=69
Seroprotection	day 1	12 (17%) (9-28)	16 (23%) (14-35)	29 (41%) (30-54)	33 (48%) (36-60)	31 (44%) (32-57)	30 (43%) (32-56)
	day 22	56 (80%) (69-89)	56 (81%) (70-90)	65 (93%) (84-98)	66 (96%) (88-99)	59 (84%) (74-92)	63 (91%) (82-97)
Seroconversion	day 22	40 (57%) (45-69)	40 (58%) (45-70)	40 (57%) (45-69)	44 (64%) (51-75)	39 (56%) (43-68)	35 (51%) (38-63)
GMT/GMR	day 1	12 (9.89-15)	15 (12-18)	26 (19-35)	28 (20-38)	23 (16-32)	28 (20-40)
	day 22	54 (43-68)	67 (53-84)	149 (115-192)	163 (126-211)	137 (102-183)	128 (96-172)
	day 22 to day 1	4.44 (3.35-5.88)	4.6 (3.47-6.12)	5.77 (4.17-7.99)	5.83 (4.2-8.09)	6 (4.18-8.62)	4.54 (3.15-6.53)

Adults 18-60 years of age

At baseline (day 1), across all the vaccine groups, similar proportions of subjects were seroprotected (HI ≥ 1:40, 7% to 11%) except for the TIV→7.5_fullMF59 group, where 26% were seroprotected at baseline. Baseline geometric mean titres (GMTs) ranged between 8.04 and 11. Proportion with

detectable antibody tires against 2009 H1N1 at baseline across the study groups is reported below. Serology was performed on sera taken in August at the time of the Focetria administration.

Percentages of Subjects with HI ≥ 1:10 at baseline – FAS

Age Group	Agrippal 7.5µg_100	Fluad 7.5µg_100	7.5µg_100	7.5µg_100 with Agrippal	3.75µg _50 with Agrippal
18 - 60 years	26/50 (52%)	-	18/71(25%)	20/71(28%)	21/72 (29%)
61 years and over	30/49 (61%)	38/46 (83%)	38/59 (64%)	-	-

Results for FAS and HI assay are shown below.

Percentages (95%CI) of adults aged 18-60 years with seroconversion after the first vaccination

Vaccine groups	TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=71	N=70	N=69
Seroconversion Day 22	22 (92%) (73-99) N=24	51 (96%) (87-100) N=53	50 (100%) (93-100) N=50	45 (94%) (83-99) N=48
Significant Increase Day 22	25 (96%) (80-100) N=26	12 (67%) (41-87) N=18	19 (95%) (75-100) N=20	18 (86%) (64-97) N=21
Seroconversion or Significant Increase Day 22	47 (94%) (83-99)	63 (89%) (79-95)	69 (99%) (92-100)	63 (91%) (82-97)

Percentages (95%CI) of adults aged 18-60 years seroprotected after the first vaccination

Vaccine groups	TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=71	N=70	N=69
Day 1	13 (26%) (15-40)	5 (7%) (2-16)	8 (11%) (5-21)	5 (7%) (2-16)
Day 22	48 (96%) (86-100)	68 (96%) (88-99)	70 (100%) (95-100)	66 (96%) (88-99)

GMTs and GMRs (95%CI) in adults 18-60 years after first vaccination

Vaccine groups	TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV
	N=50	N=71	N=70	N=69
Day 1	11 (7.84-17)	8.04 (6.34-10)	9.49 (7.47-12)	8.55 (6.72-11)
Day 22	441 (259-750)	421 (301-591)	458 (326-643)	264 (188-372)
Day 22 to Day 1	39 (21-70)	52 (36-77)	48 (33-71)	31 (21-45)

Adults aged over 60 years

Across vaccine groups, from 7% to 15% subjects were seroprotected at baseline. Baseline GMTs ranged between 10 and 14.

After one vaccination with 7.5_fullMF59, all CHMP criteria were met against pandemic H1N1 antigen strain, regardless of whether subjects had been vaccinated previously with TIV, adjTIV or had not received the 2009/2010 seasonal vaccination. There were no clear or consistent tendencies for higher immune responses across the immunogenicity endpoints (seroconversion, seroprotection, and GMR) in any of the vaccine groups.

Percentages (95%CI) of adults aged over 60 years with seroconversion after the first vaccination

Vaccine groups	TIV→7.5_full MF59	AdjTIV→7.5_full MF59	7.5_fullMF59
	N=49	N=46	N=59
Seroconversion Day 22	15 (79%) (54-94) N=19	12 (75%) (48-93) N=16	14 (67%) (43-85) N=21
Significant Increase Day 22	20 (67%) (47-83) N=30	20 (67%) (47-83) N=30	31 (82%) (66-92) N=38
Seroconversion or Significant Increase Day 22	35 (71%) (57-83)	32 (70%) (54-82)	45 (76%) (63-86)

Percentages (95%CI) of adults over 60 years seroprotected after the first vaccination

Vaccine groups	TIV→7.5_full MF59	AdjTIV→7.5_full MF59	7.5_fullMF59
	N=49	N=46	N=59
Day 1	4 (8%) (2-20)	7 (15%) (6-29)	4 (7%) (2-16)
Day 22	44 (90%) (78-97)	41 (89%) (76-96)	50 (85%) (73-93)

GMTs and GMRs (95%CI) in adults over 60 years after first vaccination

Vaccine groups	TIV→7.5_full MF59	AdjTIV→7.5_full MF59	7.5_fullMF59
	N=49	N=46	N=59
Day 1	11 (6.04-19)	14 (7.87-24)	10 (7.2-15)
Day 22	111 (44-281)	108 (44-266)	98 (53-181)
Day 22 to Day 1	10 (4.52-24)	7.94 (3.54-18)	9.29 (5.34-16)

Safety

The safety analyses included 418 of the 419 enrolled subjects (264 adults aged 18-60 years and 154 adults over 60 years: one enrolled subject was not exposed to the vaccine). Safety data is only available up to day 22.

All subjects were instructed to complete a diary card to record local (i.e., ecchymosis, erythema, induration, swelling and pain at injection site) and systemic reactions (i.e., chills, malaise, myalgia, arthralgia, headache, sweating, nausea and fatigue), axillary temperature (fever was defined as an axillary temperature ≥38°C), and use of analgesic/antipyretic medications on the day of vaccination (after 6 hours) and each of the 6 days following vaccination. All other adverse events (AEs) including serious AEs (SAEs) were collected up to day 22. All SAEs and AEs necessitating a physician's visit or

consultation and/or leading to withdrawal from the study will be collected for the entire study duration.

The table below presents the number (%) of subjects reporting solicited local and systemic reactions after first vaccination (days 1-7).

Age strata	Adults 18-60 Yrs				Adults over 60 Yrs		
Vaccine groups	TIV→7.5_full MF59	7.5_fullMF59	7.5_full MF59 + TIV	3.75_halfMF59 + TIV	TIV→7.5_full MF59	adjTIV→7.5_full MF59	7.5_fullMF59
	N=50	N=71	N=71	N=72	N=49	N=46	N=59
Any	32 (64%)	55 (77%)	52 (73%)	51 (71%)	21 (43%)	10 (22%)	28 (47%)
Local	25 (50%)	45 (63%)	45 (63%)	41 (57%)	12 (24%)	5 (11%)	17 (29%)
Systemic	23 (46%)	45 (63%)	36 (51%)	36 (50%)	15 (31%)	8 (17%)	20 (34%)
Other	2 (4%)	11 (15%)	6 (8%)	9 (13%)	3 (6%)	1 (2%)	3 (5%)

The table below presents the number (%) of subjects with unsolicited AEs with onset within 21 days after first vaccination.

Age Strata	Adults 18-60 Yrs				Adults over 60 Yrs		
Vaccine Group	TIV→ 7.5_full MF59	7.5_full MF59	7.5_full MF59 + TIV	3.75_half MF59 + TIV	TIV→7.5 _full MF59	adjTIV→ 7.5_full MF59	7.5_full MF59
	N=50	N=71	N=71	N=72	N=49	N=46	N=59
Any AEs	3 (6%)	14 (20%)	15 (21%)	25 (35%)	6 (12%)	2 (4%)	10 (17%)
At least possibly related AEs	0	2 (3%)	4 (6%)	3 (4%)	3 (6%)	1 (2%)	3 (5%)
Serious AEs	0	0	0	1 (1%)	0	0	0
At least possibly related SAEs	0	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	1 (1%)	0	0	0

Adults 18 to 60 years

Solicited local reactions and systemic reactions to the pandemic vaccine were experienced by 64% (TIV →7.5_fullMF59 group) to 77% (7.5_fullMF59) of the vaccine groups (see table above). Percentages of subjects experiencing each local reaction to the pandemic and seasonal vaccines were similar, with the exception of pain (pain ranged from 39% to 44% after TIV and from 50% to 61% after the pandemic vaccinations). The most commonly reported local reaction was pain and, the most commonly reported systemic reactions were headache and fatigue. Local and systemic reactions were typically mild or moderate in severity and were of short duration. Severe local reactions were infrequent, with only 1% of the subjects reporting severe pain. No subject reported fever ≥38°C.

Other adverse events were experienced by between 6% (TIV→7.5_full MF59) and 35% of 18 to 60 year subjects (3.75_halfMF59 + TIV). At least possibly related AEs were reported by between 0% (TIV→7.5_full MF59) and 6% of subjects (7.5_full MF59 + TIV). Oropharyngeal pain was the most common adverse event overall (range, 1% to 7%) while injection site haemorrhage was the most common event that was judged at least possibly related to the study vaccine (range, 0% to 3%). Only one subject had a serious adverse event (influenza, 3.75_halfMF59+TIV). It onset on day 5, led to premature withdrawal from the study, and was judged as not related to the study vaccine. No other adverse event led to premature withdrawal from the study and no deaths were reported.

Number (%) of adults 18-60 years with any (and severe />100mm) local reaction to the pandemic vaccines within 7 days after first vaccination

Vaccine groups		Agr[a]→Foc[b]	Foc	Conc[c]	
		N=50	N=71	Foc Arm N=71	Agr Arm N=71
Ecchymosis	Any	3(6)	1(1)	5(7)	4(6)
	>100 mm	0	0	0	0
Erythema	Any	9(18)	5(7)	5(7)	7(10)
	>100 mm	0	0	0	0
Induration	Any	3(6)	7(10)	6(8)	4(6)
	>100 mm	0	0	0	0
Swelling	Any	4(8)	5(7)	7(10)	2(3)
	>100 mm	0	0	0	0
Pain	Any	25(50)	43(61)	43(61)	28(39)
	Severe	1(2)	1(1)	1(1)	0

[a]Agrippal NH 2009-2010, [b]Focetria, [c]Concomitant administration of Focetria into deltoid muscle of non-dominant arm and Agrippal into deltoid muscle of dominant arm. The number (N) in the header are the total number of subjects with documented reactions.

Number (%) of adults 18-60 years with any systemic reaction within 7 days after first vaccination

Vaccine groups		Agr[a]→Foc[b]	Foc	Conc[c]
		N=50	N=71	N=71
Chills	Any	3(6)	5(7)	4(6)
	Severe	0	0	0
Malayse	Any	8(16)	16(23)	11(15)
	Severe	0	1(1)	0
Myalgia	Any	7(14)	15(21)	14(20)
	Severe	0	0	0
Arthralgia	Any	6(12)	9(13)	10(14)
	Severe	0	0	0
Headache	Any	13(26)	26(37)	14(20)
	Severe	1(2)	4(6)	0
Sweating	Any	7(14)	15(21)	14(20)
	Severe	0	0	0
Fatigue	Any	8(16)	25(35)	23(32)
	Severe	0	2(3)	0
Nausea	Any	6(12)	12(17)	3(4)
	Severe	0	0	0
Fever (≥ 38C)	Yes	0	0	0
Other				
Analg. Antip. Used	Yes	2(4)	11(15)	6(8)
Body Temperature	<38 C	50(100)	71(100)	71(100)

[a]Agrippal NH 2009-2010, [b]Focetria, [c]Concomitant administration of Focetria into deltoid muscle of non-dominant arm and Agrippal into deltoid muscle of dominant arm. The number (N) in the header are the total number of subjects with documented reactions.

Adults over 60 years

Solicited local reactions and systemic reactions to the pandemic vaccine were experience by 22% (adjTIV→7.5_fullMF59) to 47% (7.5_fullMF59) of the vaccine groups. The most commonly reported local reaction was pain and the most common systemic reactions were headache and fatigue. Local and systemic reactions were typically mild or moderate in severity and were of short duration. No subject reported severe pain. No subject reported fever ≥38°C.

Other adverse events were experienced by between 4% (adjTIV→7.5_fullMF59) and 17% (7.5_fullMF59) of over 60 year subjects. At least possibly related adverse events were reported by between 2% (adjTIV→7.5_fullMF59) and 6% (TIV→7.5_full MF59) of these subjects. Arthralgia was the most common adverse event overall (range, 0% to 4%) while headache was the most common event that was judged at least possibly related to the study vaccine (range, 0% to 4%). No over 60 year subject withdrew from the study due to an adverse event. No serious adverse event and no death were reported in this age stratum.

Number (%) of adults over 60 years with any (and severe />100mm) local reaction to the pandemic vaccines within 7 days after first vaccination

Vaccine groups		**Agr[a]→Foc[b]**	**Fluad→Foc**	**Foc**
		N=49	**N=46**	**N=59**
Ecchymosis	Any	2(4)	1(2)	3(5)
	>100 mm	0	0	0
Erythema	Any	3(6)	3(7)	1(2)
	>100 mm	0	0	0
Induration	Any	4(8)	0	2(3)
	>100 mm	0	0	0
Swelling	Any	3(6)	0	2(3)
	>100 mm	0	0	0
Pain	Any	9(18)	2(4)	14(24)
	Severe	0	0	0

[a]Agrippal NH 2009-2010, [b]Focetria, The number (N) in the header are the total number of subjects with documented reactions.

Number (%) of adults over 60 years with any systemic reaction within 7 days after first vaccination

Vaccine groups		Agr[a]→Foc[b]	Fluad→Foc	Foc
		N=49	N=46	N=59
Chills	Any	3(6)	0	1(2)
	Severe	0	0	0
Malayse	Any	5(10)	1(2)	6(10)
	Severe	1(2)	0	0
Myalgia	Any	5(10)	2(4)	6(10)
	Severe	0	0	0
Arthralgia	Any	8(16)	0	8(14)
	Severe	0	0	0
Headache	Any	7(14)	3(7)	7(12)
	Severe	1(2)	0	0
Sweating	Any	6(12)	3(7)	7(12)
	Severe	0	0	0
Fatigue	Any	5(10)	2(4)	12(20)
	Severe	0	0	1(2)
Nausea	Any	1(2)	0	3(5)
	Severe	0	0	0
Fever (≥ 38C)	Yes	0	0	0
Other				
Analg. Antip. Used	Yes	3(6)	1(2)	3(5)
Body Temperature	<38 C	49(100)	46(100)	59(100)

[a]Agrippal NH 2009-2010, [b]Focetria, The number (N) in the header are the total number of subjects with documented reactions.

Previous vaccination with seasonal vaccine

In those groups who had not received a seasonal (NH 2009-10 formulation) vaccination before entering the study, similar percentages of subjects in both age groups reported AEs (other than local and systemic reactions reported above), regardless of their assessment of relatedness, within 21 days of vaccination with Focetria. Percentages of subjects reporting AEs were very similar for the group receiving Focetria concomitantly with seasonal Agrippal (the Conc group), and the Foc group, who received Focetria alone (see table below). Those groups who had received a seasonal (NH 2009-10 formulation) vaccination previously, tended to have lower percentages of reported AEs.

Across vaccination and age groups, between 2% to 6% of subjects experienced AEs judged as possibly or probably related to vaccination.

	Percentages of Subjects with AEs					
	Adults 18-60 years			Adults >60 years		
	Agr[a]→Foc[b]	Foc	Conc[c]	Agr→Foc	Fluad→Foc	Foc
	N=50	N=71	N=71	N=49	N=46	N=59
Any AEs	6%	20%	21%	12%	4%	17%
At least possibly related AEs	0	3%	6%	6%	2%	5%
Serious AEs	0	0	0	0	0	0
At least possibly related SAEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0

[a]Agrippal NH 2009-2010, [b]Focetria, [c]Concomitant administration of Focetria into deltoid muscle of non-dominant arm and Agrippal into deltoid muscle of dominant arm.

Changes to the Product Information

The proposed changes to sections 4.5 and 5.1 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 PL was updated accordingly. Annex II was amended to reflect the fulfilment of specific obligations.

Overall discussion and benefit risk assessment

The results of study V111_04 up to day 22 were presented. In adults aged 18 to 60 years the immune responses to one vaccination of 7.5µg H1N1 antigen formulated with 100% MF59 (Focetria) met all three CHMP criteria for the pandemic H1N1 strain when administered concomitantly with unadjuvanted licensed seasonal influenza vaccine (2009/2010 season) in subjects who had not received a previous (2009/2010 season) seasonal influenza vaccine. In addition, the licensed unadjuvanted seasonal vaccine met all three CHMP criteria for all three seasonal strains in previously unvaccinated adults' subjects suggesting that it can be administered concomitantly with the pandemic vaccine. Additionally, when administered alone or several weeks after the unadjuvanted seasonal influenza vaccine, Focetria met all three CHMP criteria for 18 to 60 year subjects.

In adults over 60 years of age, all three CHMP criteria were met by the 7.5µg H1N1 antigen formulated with 100% MF59 regardless of whether it was administered alone or several weeks after the licensed adjuvanted or unadjuvanted seasonal influenza vaccine.

In both age strata there was no indication that the reactogenicity profiles were affected by sequential or concomitant administration of the pandemic and seasonal vaccines.

Results in adults aged 18 to 60 years indicate that Focetria may be administered concomitantly with seasonal influenza vaccine. Results in adults also indicated that previous administration of adjuvanted or non-adjuvanted seasonal vaccines and Focetria does not interfere with the immune response to Focetria. The product information was updated to reflect these findings.