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/0011

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 current pandemic is caused by an A/H1N1 viral strain. Immune response to the pandemic virus is expected to be higher than that observed with viruses of non-human sources so far used in the mock-up vaccines.
The marketing authorisation holder (MAH) is conducting a H1N1 clinical trial (study V111_02) to assess the effect of the full dose compared to half dose and to non-adjuvated vaccine in adults and of the two Focetria dosages in elderly. Based on available safety and immunogenicity from this study, the MAH applied for a change in the posology for recommendation of a single dose and of a half dose (0.25 ml).

Clinical immunogenicity and safety

Study design

Study V111_02 is an ongoing randomised, single-blind, dose-ranging study. The study is run in seven study sites in three EU Countries. It started with the first subject enrolled on 24/08/09 and the last subject day 22 visit was completed on 28/09/09.
Three candidate vaccines were compared in this study to evaluate preferred formulation, dose and schedule:
• 3.75 µg H1N1 antigen and half adjuvant MF59 (3.75_halfMF59)
• 7.5 µg H1N1 antigen and full adjuvant MF59 (7.5_fullMF59)
• 15 µg H1N1antigen without MF59 (15_noMF59)

The vaccines formulation per group is shown below.

Group	Vaccine formulation			Volume for Injection
	Antigen content	MF59 content		
3.75_halfMF59	3.75 µg	4.875 µg	50% (half)	0.25 mL
7.5_fullMF59	7.5 µg	9.75 µg	100% (full)	0.5 mL
15_noMF59	15 µg	-	0% (no)	0.5 mL

The MAH proposed a sample size of 228 subjects per vaccination group (456 in total) claiming 82% power to reject the null hypothesis, if the real ratio of GMTs is 0.93 (differences in term of mean log10 HI is -0.03), considering a common standard deviation of 1.0 (calculated as the upper limit of 80% CI in previous studies), and a one-sided alpha level of 0.025. The non-inferiority margin was set to 0.5 however in the present preliminary analyses non-inferiority evaluation was not performed.

The subjects enrolled were healthy meeting eligibility criteria. In total 661 subjects were enrolled, of which 410 were aged 18 to 60 years and 251 were aged over 60 years (see table below). In both adults 18 to 60 years and adults over 60 years, 96% to 99% subjects completed the day 22 visit. For those who did not complete the day 22 visit, the major reasons for withdrawal was inappropriate enrolment, generally due to screening failure.

	18 to 60 years		Over 60 years	
	Planned	Actual	Planned	Actual
3.75_halfMF59	120	137	120	126
7.5_fullMF59	120	138	120	125
15_noMF59	120	135	-	-

Objectives

The primary objectives were: to identify the preferred vaccine formulation (with and without adjuvant, MF59), dosage (of antigen and adjuvant) and schedule (one or two administrations) of the egg-derived H1N1sw monovalent vaccine in healthy adults based on CHMP criteria and pairwise statistical comparisons for immunogenicity, and safety & tolerability.

The secondary objectives were:
• To evaluate immunogenicity of a booster dose of the egg-derived H1N1sw monovalent influenza vaccine administered 12 months after the primary course with respect to CHMP criteria.
• To evaluate the non-inferiority of the post-vaccination (Day 43) hemagglutination inhibition (HI) geometric mean titer (GMT) of the half dose (3.75 µg of HA + half MF59) of the egg-derived H1N1sw monovalent vaccine to the corresponding GMTs of the full dose (7.5 µg of HA + full MF59) of the egg-derived H1N1sw monovalent vaccine, after two doses administered 3 weeks apart in the pooled adult and elderly population.

In both adults 18 to 60 years and adults over 60 years, 96% to 99% subjects completed the day 22 visit. For those who did not complete the day 22 visit, the major reasons for withdrawal was inappropriate enrolment, generally due to screening failure.

Population definition:

(a) All randomised set
All subjects enrolled in this study and randomised irrespective of whether they have been vaccinated or not.

(b) Full analysis set (FAS) Immunogenicity: all subjects in the All randomised set who:
▫ actually received a study vaccination, and
▫ provided at least one evaluable serum sample both before and after baseline
In case of vaccination not done according to randomisation, subjects were analysed as randomised in the FAS.

(c) Per protocol set (PPS) Immunogenicity: all subjects in the FAS who:
▫ receive all the relevant doses of vaccine correctly, and
▫ provide evaluable serum samples at the relevant time points, and
▫ have no major protocol violation as pre-specified in the Analysis Plan
A major deviation was defined as a protocol deviation that is considered to have a significant impact on the immunogenicity result of the subject.

(d) Exposed Set: all subjects in the all randomised set who actually received a study vaccination.

Demographics

The table below shows the demographics and other baseline characteristics of all enrolled subjects.

	18 to 60 years			Over 60 years	
	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59	3.75_ halfMF59	7.5_ fullMF59
	N=137	N=138	N=135	N=126	N=125
Age (Yrs):	38.4±11.5	38.5±11.9	38.7±11.1	68.0±5.2	67.0±4.6
% Male:	69 (50%)	74 (54%)	68 (50%)	71 (56%)	62 (50%)
Ethnic Origin:					
Asian	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Caucasian	135 (99%)	136 (99%)	133 (99%)	126 (100%)	124 (100%)
Other	2 (1%)	2 (1%)	1 (<1%)	0 (0%)	0 (0%)
Weight (kg):	74.±15	79±18	77±16	79±16	78±15
Height (cm):	173±9	174±9.6	173±10	170±9	169±8
Body Mass Index:	24.56±4.20	25.50±5.19	25.63±4.38	27.33±4.92	27.13±4.39
Female of Childbearing Potential:	50 (74%)	52 (81%)	48 (72%)	0 (0%)	0 (0%)
Negative Pregnancy Test	51 (98%)	52 (98%)	48 (98%)	-	-
Previous seasonal Influenza Vaccination:	69 (50%)	70 (51%)	67 (50%)	107 (85%)	107 (86%)
Met Entry Criteria:	135 (99%)	134 (97%)	133 (99%)	125 (99%)	124 (99%)

At baseline most subjects of all vaccination groups (85 of 132 for the 3.75_halfMF59; 82 of 132 for the 7.5_fullMF59; and 81 of 131 for the 15_noMF59 vaccination group) were seropositive (HI≥1:10). After first vaccination, at day 22, the CHMP criterion for 18 to 60 year adults was met, with the highest response being in the 7.5_fullMF59 group.

At baseline, more than half the subjects (181/246 subjects) had detectable titers. GMTs were similar between the two vaccination groups.

Results

Immunogenicity data assessed by hemagglutination inhibition (HI) and microneutralisation (MN) assays of serum samples collected up to day 22 (range 18-22) are presented in this section. The CHMP criteria for the evaluation of pandemic vaccines were used to assess the immune response.

IMMUNE HI RESULTS AFTER ONE DOSE (DAY 22) ADULTS AND ELDERLY (FAS)

HI Results after one dose	Focetria (V111_02)		
	3.75µg	7.5µg	15µg
ADULTS 18 - 60 yrs	N=132	N=132	N=131
Median Age (Yrs)	38	40	39
Seroprotection Rate (required: >70%)	77%	96%	84%
Geometric Mean Ratio (required: >2.5)	7.04	18	9.43
Seroconversion + Sign. Increase Rate (required: >40%)	64%	88%	69%
ELDERLY >60 yrs	N=124	N=122	
Median Age (Yrs)	67	66	
Seroprotection Rate (required: > 60%)	56%	72%	
Geometric Mean Ratio (required: >2.0)	2.2	4	
Seroconversion + Sign. Increase Rate (required: >30%)	25%	43%	

Pairwise comparisons of GMTs at day 22 between vaccination groups indicated that the immune response to the 3.75_halfMF59 vaccine was less than that to the 7.5_fullMF59 vaccine, and similar to that of the 15_noMF59 vaccine. The response to 7.5_fullMF59 vaccine was superior to both the 3.75_halfMF59 and 15_noMF59 vaccine. The 3.75_halfMF59 and 15_noMF59 vaccine induced similar responses.

Pairwise comparisons of seroprotection at day 22 between vaccination groups indicated that the immune response to the 7.5_fullMF59 vaccine was superior to both the 3.75_halfMF59 and 15_noMF59 vaccine. The 3.75_halfMF59 and 15_noMF59 vaccine inducted similar responses.

A pairwise comparison of GMTs at day 22 between vaccination groups indicated that the immune response to the 3.75_halfMF59 vaccine was inferior to that of the 7.5_fullMF59 vaccine.

The biological functionality of antibodies measured by HI assay was further assessed by MN assay (shown below)

IMMUNE MN RESULTS AFTER ONE DOSE (DAY 22). ADULTS AND ELDERLY

Microneutralization after one dose	Focetria (V111_02)		
	3.75µg	7.5µg	15µg
ADULTS 18 - 60 yrs	N=132	N=132	N=130
MN 1:40 Rate	89%	98%	85%
MN 1:80 Rate	72%	93%	74%
MN 1:160 Rate	53%	80%	63%
Geometric Mean Ratio	21	42	21
4-fold increase Rate	90%	95%	79%
ELDERLY >60 yrs	N=124	N=123	
MN 1:40 Rate	50%	68%	
MN 1:80 Rate	32%	47%	
MN 1:160 Rate	22%	37%	
Geometric Mean Ratio	4.88	11	
4-fold increase Rate	48%	74%	

Overall, the assessment showed a robust response in all the vaccination groups in adults aged 18 to 60 years and confirmed the results observed by HI assay. GMTs were low at baseline and increased

21 to 42-fold after vaccination. Likewise, the percentages with MN titer ≥ 40 increased from a low baseline (16% to 18%) to 85% to 98%. From 79% to 95% subjects demonstrated at least 4-fold increases in MN titers after vaccination. Overall, the highest MN response was observed after administration of the 7.5_fullMF59.

It is noted that half dose of Focetria induced an immune response comparable to the 15 µg of unadjuvated vaccine (with 4 times less antigen quantity), however the results clearly point out that the full dose of Focetria provides the best response in adults and elderly among the assessed formulations. In elderly the three CHMP criteria are not met with the half dose. It should also be noted that the results from this trial provide hints on the suggested advantage of the administration of one dose of non-adjuvated vaccine, which is lower compared to the full adjuvated dose and similar to the adjuvanted half dose.
Although non-inferiority statistical analysis is not presented, satisfactory immunogenicity is shown for the full dose. In contrast with the data previously provided with the mock-up vaccine H5N1, the results from the V111_02 study suggest that one full dose of Focetria H1N1 may be able to induce a satisfactory immune response, meeting the CHMP criteria for adults.
No specific threshold for protection has been defined for MN assay, however the results obtained confirm the immunogenicity profile observed with HI.

Results by baseline antibody titre

In all three vaccination groups, 307 adults aged 18 to 60 years were not seroprotected while 88 subjects were seroprotected at the baseline.
In both vaccination groups, 184 adults aged over 60 years were not seroprotected while 62 subjects were seroprotected at the baseline.

In order to assess the effect of pre-existing immunity the proportion of subjects showing seroconversion or significant increase following immunisation was computed in seronegative and seropositive subjects. The following tables shows the proportion of seroconverted subjects with baseline HI titres below 1:10 (to be considered seronegative at baseline) and the proportion of serocoverters among those with a baseline HI titres equal or above 1:10 (seropositive) .

Adults 18-60 years
In the seronegative adults 18-60 years, the proportions were 74%, 98% and 80% in the three study groups (3.75 µg, 7.5 µg and 15 µg, respectively).

Percentage of Subjects with Seroconversion or Significant Increase in HI Titers and Vaccine Group Differences by Seropositive and Not at Baseline in Adults - FAS

A/California/7/2009 (H1N1)v
Age Group : ADULTS 18-60 YRS Baseline HI (H1N1)v Titer : < 1:10

	Vaccine Group				Vaccine Group Differences		
	3.75ug_50	7.5ug_100	15ug_0		3.75ug_50 - 7.5ug_100	3.75ug_50 - 15ug_0	7.5ug_100 - 15ug_0
Seroconversion Day 22 to Day 1							
Number	35	49	40				
Percentage	74%	98%	80%	Difference	-24%	-6%	18%
95% Conf Int	60%-86%	89%-100%	66%-90%	95% Conf Int	-37%- -10%	-22%- 11%	6%- 30%
N	47	50	50				
Significant Increase Day 22 to Day 1							
Number							
Percentage				Difference			
95% Conf Int				95% Conf Int			
N	0	0	0				
Seroconv. or Sign. Increase Day 22 to Day 1							
Number	35	49	40				
Percentage	74%	98%	80%	Difference	-24%	-6%	18%
95% Conf Int	60%-86%	89%-100%	66%-90%	95% Conf Int	-37%- -10%	-22%- 11%	6%- 30%
N	47	50	50				

Similar data for seropositive subjects at the baseline is reported below, showing that 59%, 82%, and 62% of subjects in the three study arms (3.75 µg, 7.5 µg and 15 µg, respectively) had significant increase in the antibody titres at day 22.

Percentage of Subjects with Seroconversion or Significant Increase in HI Titers and Vaccine Group Differences by Seropositive and Not at Baseline in Adults - FAS

A/California/7/2009 (H1N1)v
Age Group : ADULTS 18-60 YRS Baseline HI (H1N1)v Titer : >= 1:10

	Vaccine Group				Vaccine Group Differences		
	3.75ug_50	7.5ug_100	15ug_0		3.75ug_50 - 7.5ug_100	3.75ug_50 - 15ug_0	7.5ug_100 - 15ug_0
Seroconversion Day 22 to Day 1							
Number							
Percentage				Difference			
95% Conf Int				95% Conf Int			
N	0	0	0				
Significant Increase Day 22 to Day 1							
Number	50	67	50				
Percentage	59%	82%	62%	Difference	-23%	-3%	20%
95% Conf Int	48%-69%	72%-89%	50%-72%	95% Conf Int	-36%- -9%	-18%- 12%	6%- 33%
N	85	82	81				
Seroconv. or Sign. Increase Day 22 to Day 1							
Number	50	67	50				
Percentage	59%	82%	62%	Difference	-23%	-3%	20%
95% Conf Int	48%-69%	72%-89%	50%-72%	95% Conf Int	-36%- -9%	-18%- 12%	6%- 33%
N	85	82	81				

The responses were also evaluated with the MN assay. Detailed analyses took into consideration the distribution of MN responses at day 22 stratified according to the baseline titres assessed with the MN assay and is reported in the two tables below. In adults 18-60 years with negative MN assay at baseline 98% of recipients of a full dose of Focetria showed post-immunisation titers measured in MN ≥ 1:40. The corresponding proportion for recipients of half dose of Focetria was 84% and for recipients of non-adjuvated vaccine was 76%.

Percentage of Subjects with MN Titers >= 1:40 and Vaccine Group Differences in Adults - FAS

A/California/7/2009 (H1N1)v
Age Group : ADULTS 18-60 YRS Baseline MN (H1N1)v Titer : < 1:10

	Vaccine Group				Vaccine Group Differences		
	3.75ug_50	7.5ug_100	15ug_0		3.75ug_50 - 7.5ug_100	3.75ug_50 - 15ug_0	7.5ug_100 - 15ug_0
Day 1							
Number	0	0	0				
Percentage	0%	0%	0%	Difference			
95% Conf Int	0%-4%	0%-4%	0%-4%	95% Conf Int			
N	88	91	82				
Day 22							
Number	74	89	62				
Percentage	84%	98%	76%	Difference	-14%	8%	22%
95% Conf Int	75%-91%	92%-100%	65%-84%	95% Conf Int	-22%- -5%	-4%- 21%	12%- 32%
N	88	91	82				

Higher proportions at MN assay were observed for subjects positive at baseline with values ranging between 98% and 100%.

Percentage of Subjects with MN Titers >= 1:40 and Vaccine Group Differences in Adults - FAS

A/California/7/2009 (H1N1)v
Age Group : ADULTS 18-60 YRS Baseline MN (H1N1)v Titer : >= 1:10

	Vaccine Group				Vaccine Group Differences		
	3.75ug_50	7.5ug_100	15ug_0		3.75ug_50 - 7.5ug_100	3.75ug_50 - 15ug_0	7.5ug_100 - 15ug_0
Day 1							
Number	21	19	24				
Percentage	48%	46%	50%	Difference	1%	-2%	-4%
95% Conf Int	32%-63%	31%-63%	35%-65%	95% Conf Int	-20%- 23%	-23%- 18%	-24%- 17%
N	44	41	48				
Day 22							
Number	43	40	48				
Percentage	98%	98%	100%	Difference	0%	-2%	-2%
95% Conf Int	88%-100%	87%-100%	93%-100%	95% Conf Int	-6%- 7%	-7%- 2%	-7%- 2%
N	44	41	48				

Elderly >61years

The following table shows the seroconversion rate by study groups in subjects above 60 years of age and seronegative at the baseline. Seroconversion as measured by HI was 56% in the recipients of 7.5ug vaccine and 37% in subjects who received half the dose.

Percentage of Subjects with Seroconversion or Significant Increase in HI Titers and Vaccine Group Differences by Seropositive and Not at Baseline in Elderly - FAS

A/California/7/2009 (H1N1)v
Age Group : ELDERLY >= 61 YRS Baseline HI (H1N1)v Titer : < 1:10

	Vaccine Group		Vaccine Group Differences	
	3.75ug_50	7.5ug_100		3.75ug_50 - 7.5ug_100
Seroconversion Day 22 to Day 1				
Number	14	15		
Percentage	37%	56%	Difference	-19%
95% Conf Int	22%-54%	35%-75%	95% Conf Int	-43%- 6%
N	38	27		
Significant Increase Day 22 to Day 1				
Number				
Percentage			Difference	
95% Conf Int			95% Conf Int	
N	0	0		
Seroconv. or Sign. Increase Day 22 to Day 1				
Number	14	15		
Percentage	37%	56%	Difference	-19%
95% Conf Int	22%-54%	35%-75%	95% Conf Int	-43%- 6%
N	38	27		

The significant increase in antibody titres observed in elderly seropositive at the baseline is observed in a proportion of 39% in the recipients of the full dose and a proportion of 20% in recipients of half dose, as shown below.

Percentage of Subjects with Seroconversion or Significant Increase in HI Titers and Vaccine Group Differences by Seropositive and Not at Baseline in Elderly - FAS

A/California/7/2009 (H1N1)v
Age Group : ELDERLY >= 61 YRS Baseline HI (H1N1)v Titer : >= 1:10

	Vaccine Group		Vaccine Group Differences	
	3.75ug_50	7.5ug_100		3.75ug_50 - 7.5ug_100
Seroconversion Day 22 to Day 1				
Number				
Percentage			Difference	
95% Conf Int			95% Conf Int	
N	0	0		
Significant Increase Day 22 to Day 1				
Number	17	37		
Percentage	20%	39%	Difference	-19%
95% Conf Int	12%-30%	29%-49%	95% Conf Int	-32%- -6%
N	86	95		
Seroconv. or Sign. Increase Day 22 to Day 1				
Number	17	37		
Percentage	20%	39%	Difference	-19%
95% Conf Int	12%-30%	29%-49%	95% Conf Int	-32%- -6%
N	86	95		

The data in elderly subjects from the MN assay were also reported for seronegative and seropositive subjects respectively (see tables below). Results showed that 59% of seronegative subjects at baseline recipients of the full dose are seroprotected according to percentages achieving 1:40 titers. In seropositive subjects at baseline the seroprotection rate was 97%.

Percentage of Subjects with MN Titers >= 1:40 and Vaccine Group Differences in Elderly - FAS

A/California/7/2009 (H1N1)v
Age Group : ELDERLY >= 61 YRS Baseline MN (H1N1)v Titer : < 1:10

	Vaccine Group		Vaccine Group Differences	
	3.75ug_50	7.5ug_100		3.75ug_50 - 7.5ug_100
Day 1				
Number	0	0		
Percentage	0%	0%	Difference	
95% Conf Int	0%-4%	0%-4%	95% Conf Int	
N	91	93		
Day 22				
Number	34	55		
Percentage	37%	59%	Difference	-22%
95% Conf Int	27%-48%	48%-69%	95% Conf Int	-36%- -8%
N	91	93		

Percentage of Subjects with MN Titers >= 1:40 and Vaccine Group Differences in Elderly - FAS

A/California/7/2009 (H1N1)v
Age Group : ELDERLY >= 61 YRS Baseline MN (H1N1)v Titer : >= 1:10

	Vaccine Group		Vaccine Group Differences	
	3.75ug_50	7.5ug_100		3.75ug_50 - 7.5ug_100
Day 1				
Number	15	11		
Percentage	45%	37%	Difference	9%
95% Conf Int	28%-64%	20%-56%	95% Conf Int	-15%- 33%
N	33	30		
Day 22				
Number	28	29		
Percentage	85%	97%	Difference	-12%
95% Conf Int	68%-95%	83%-100%	95% Conf Int	-26%- 2%
N	33	30		

Results by age sub-groups

The serological response was also evaluated in adults stratified by age, as shown below.

IMMUNE HI RESULTS AFTER ONE DOSE (DAY 22). ADULTS 18-39 AND 40-60 (FAS)

HI Results after one dose	Focetria (V111_02)		
	3.75µg	7.5µg	15µg
ADULTS 18 - 39 yrs	N=72	N=64	N=68
Median Age (Yrs)	28	26.5	28.5
Seroprotection Rate (CHMP criteria 18-60: >70%)	86%	100%	87%
Geometric Mean Ratio (CHMP criteria 18-60: >2.5)	12	37	13
Seroconversion + Sign. Increase Rate (CHMP criteria 18-60: >40%)	76%	95%	72%
ADULTS 40 - 60 yrs	N=60	N=68	N=63
Median Age (Yrs)	49	48	48
Seroprotection Rate (CHMP criteria 18-60: >70%)	65%	93%	81%
Geometric Mean Ratio (CHMP criteria 18-60: >2.5)	4.36	12	8.79
Seroconversion + Sign. Increase Rate (CHMP criteria 18-60: >40%)	50%	81%	65%

Although the sample size was very small the results of HI assay stratified by age-group among adults showed a marked difference in the response as for adults above 40 years the immune response resulted to be lower than in younger adults and not meeting all CHMP criteria with the half-dose. Results obtained with MN assay were slightly more reassuring but confirmed the difference in response.

IMMUNE MN RESULTS AFTER ONE DOSE (DAY 22) ADULTS 18-39 AND AFTER 40-60 (FAS)

Microneutralization after one dose	Focetria (V111_02)		
	3.75µg	7.5µg	15µg
ADULTS 18 - 39 yrs	N=72	N=64	N=67
MN 1:40 Rate	96%	100%	87%
MN 1:80 Rate	85%	100%	82%
MN 1:160 Rate	65%	89%	70%
Geometric Mean Ratio	30	54	24
4-fold increase Rate	93%	95%	82%
ADULTS 40 - 60 yrs	N=60	N=68	N=63
MN 1:40 Rate	80%	96%	83%
MN 1:80 Rate	57%	87%	65%
MN 1:160 Rate	38%	71%	56%
Geometric Mean Ratio	15	33	19
4-fold increase Rate	87%	94%	76%

The following tables summarise the data on the effect of seropositivity at pre-immunisation by age-groups. Pooled summary of seroprotection and GMR are reported. Taking into account CHMP criterion percentage seroconversion or significant increase (SC) is not reached for elderly subjects (>60 years) exposed to half dosage of vaccine and ≥71 year patients with baseline HI ≥1:10.

Percentage of Subjects Showing Seroconversion or Significant Increase at Day 22 in Adults and Elderly - FAS

Cohort		3.75_50			7.5_100			15_0		
		Baseline HI≥1:10	Baseline HI<1:10	All	Baseline HI≥1:10	Baseline HI<1:10	all	Baseline HI≥1:10	Baseline HI<1:10	All
Adults	18-39 ys	74%	80%	76%	91%	100%	95%	66%	83%	72%
	40-50 ys	43%	62%	50%	84%	93%	87%	57%	83%	68%
	51-60 ys	35%	78%	50%	59%	100%	70%	57%	63%	59%
	Total	59%	74%	64%	82%	98%	88%	62%	80%	69%
Elderly	61-70 ys	21%	35%	26%	44%	57%	47%			
	≥71 ys	16%	43%	23%	22%	50%	26%			
	Total	20%	37%	25%	39%	56%	43%			

CHMP criterion: Percentage seroconversion or significant increase (SC) should exceed 40% (adults) and 30% (elderly).
Please note: For subjects with HI≥1:10 at baseline SC is equivalent to significant increase (at least 4-fold to baseline); for subjects with HI<1:10 at baseline SC is equivalent to seroconversion (at least a titer of 1:40).

Geometric Mean Ratios at Day 22 in Adults and Elderly - FAS

Cohort		3.75_50			7.5_100			15_0		
		Baseline HI≥1:10	Baseline HI<1:10	All	Baseline HI≥1:10	Baseline HI<1:10	all	Baseline HI≥1:10	Baseline HI<1:10	All
Adults	18-39 ys	8.3	17	12	17	56	37	6.8	26	13
	40-50 ys	2.2	7.8	4.9	9.4	23	15	6.3	16	10
	51-60 ys	2.9	42	3.8	3.8	70	7.3	4.3	9.5	6.6
	Total	4.8	18	7.0	10	65	18	5.8	28	9.4
Elderly	61-70 ys	1.9	2.1	2.4	3.7	5.5	4.5			
	≥71 ys	1.4	4.7	1.8	2.6	8.6	3.4			
	Total	1.7	3.9	2.2	3.1	9.6	4			

CHMP criterion: GMR > 2.5 in adults and > 2.0 elderly.

Percentage of Subjects Showing HI ≥ 1:40 at Day 22 in Adults and Elderly - FAS

Cohort		3.75_50			7.5_100			15_0		
		Baseline HI≥1:10	Baseline HI<1:10	All	Baseline HI≥1:10	Baseline HI<1:10	all	Baseline HI≥1:10	Baseline HI<1:10	All
Adults	18-39 ys	89%	80%	86%	100%	100%	100%	89%	83%	87%
	40-50 ys	81%	62%	74%	100%	93%	98%	87%	83%	85%
	51-60 ys	41%	78%	54%	76%	100%	83%	79%	63%	73%
	Total	78%	74%	77%	95%	98%	96%	86%	80%	84%
Elderly	61-70 ys	69%	35%	58%	81%	57%	75%			
	≥71 ys	53%	43%	50%	65%	50%	63%			
	Total	65%	37%	56%	77%	56%	72%			

CHMP criterion: Percentage HI ≥ 1:40 should exceed 70% (adults) and 60% (elderly).

The presence of subjects already seropositive before the trial complicates the analysis, however such setting is similar to the conditions to be expected when the vaccine will be used. During extended vaccination programs a higher proportion of already seropositive subjects should be expected. The degree of clinical protection of these seroprotected subjects at baseline is unknown, however additional benefit provided by vaccination should be pursued.

In subjects with pre-vaccination antibody titres the half dose doses did not meet all the CHMP criteria in adult subgroups. In the elderly seronegative subjects at baseline do not meet all the criteria with the half and full doses.

Results by effect of history of influenza vaccination

In all three vaccination groups about half of the adults aged 18 to 60 years were previously immunised (204 subjects-immunised versus 191 subjects-not immunised) with at least one seasonal influenza vaccine.

After the first vaccination, in the subgroup not previously immunised with influenza seasonal vaccination, three out of three CHMP criteria were met by all three vaccines while in the subgroup of subjects who had been previously vaccinated all three CHMP criteria were met only by the 7.5_fullMF59 and 15_noMF59 groups. The CHMP GMR and seroconversion criteria were met by the 3.75_halfMF59 group, with seroprotection being marginally missed (69%).

After the first vaccination, in the subgroup who had not previously received influenza seasonal vaccination, there was more increase in titers across three vaccination groups (GMR 12 to 32), as compared with the subgroup that had been previously vaccinated (GMR 5.13 to 14).

A possible explanation for the greater immune response in the subset not previously vaccinated is that the average age was lower that that of the subset who were previously vaccinated and no adjustment in the analyses was performed.

In the two vaccination groups (3.75_halfMF59 and 7.5_fullMF59) in the elderly (subjects above 60 years of age), most of the subjects were previously immunised (210 subjects-immunised versus 36 subjects not immunised) with at least one seasonal influenza vaccine.

After the first vaccination, in the subgroup which had not previously received influenza vaccines, both 3.75_halfMF59 and 7.5_fullMF59 groups met all the CHMP criteria. In the subgroup which had previously received seasonal influenza vaccination all three CHMP criteria were met by the 7.5_fullMF59 group. None of the CHMP criteria were met by 3.75_halfMF59 group. After the first vaccination, in the subgroup who had not previously received influenza seasonal vaccination, there was more increase in titers (GMR 4.31 and 5.33), as compared with the subgroup that had been previously vaccinated (GMR 1.89 and 3.78).

As for the 18 to 60 year age group, subjects who had been previously immunised were older than the subgroup that had not been previously immunised.

The table below summarises the results.

IMMUNE HI RESULTS AFTER ONE DOSE (DAY 22). ADULTS AND ELDERLY BY PREVIOUS INFLUENZA VACCINATION (FAS)

	Focetria (V111_02)		
Subjects with Previous Flu vaccine (at any time)	3.75µg	7.5µg	15µg
ADULTS 18 - 60 yrs	N=68	N=70	N=76
Median Age (Yrs)	*41*	*44*	*43*
Seroprotection Rate (required: >70%)	69%	94%	77%
Geometric Mean Ratio (required: >2.5)	5.13	14	7.56
Seroconversion + Sign. Increase Rate (required: >40%)	51%	79%	61%
ELDERLY >60 yrs	N=105	N=105	
Median Age (Yrs)	*67*	*66*	
Seroprotection Rate (required: > 60%)	51%	70%	
Geometric Mean Ratio (required: >2.0)	1.89	3.78	
Seroconversion + Sign. Increase Rate (required: >30%)	21%	42%	
Subjects without a Previous Flu vaccine (at any time)			
ADULTS 18 - 60 yrs	N=64	N=62	N=65
Median Age (Yrs)	*33.5*	*35*	*35*
Seroprotection Rate (required: >70%)	84%	98%	91%
Geometric Mean Ratio (required: >2.5)	12	32	15
Seroconversion + Sign. Increase Rate (required: >40%)	78%	98%	77%
ELDERLY >60^ yrs	N=19	N=17	
Median Age (Yrs)	*64*	*64*	
Seroprotection Rate (required: > 60%)	84%	82%	
Geometric Mean Ratio (required: >2.0)	4.31	5.33	
Seroconversion + Sign. Increase Rate (required: >30%)	47%	47%	

Subgroup analyses suggest a better immune response in subjects who had not previously received influenza seasonal immunisation than subjects who had been previously immunised and the immune response decreased by age group with immune responses being the highest for the 18 to 39 year old.

Results by body mass index (BMI)
Additional subanalyses on the effect of BMI were presented as subjects with BMI > 30 have been indicated as at risk subjects to be offered vaccination by many health authorities.
The subanalyses showed that the immune response is inversely proportional to BMI and lower for the recipients of the half dose of Focetria.

Discussion on immunogenicity
The demographic and other baseline characteristics were balanced among the three vaccine groups of the 18 to 60 year age stratum and between the two vaccine groups of the over 60 year age stratum. Nearly all enrolled subjects (96% to 98% across vaccine and age groups) were included in the immunogenicity analysis.

The presence of subjects already seropositive before the trial complicated the analysis, although such observation is not fully unexpected as the trial was conducted during the late summer when a large circulation of H1N1 was already reported. It has to be noted also that the proportion of subjects positive at baseline was higher in adults than in elderly. This observation matches with the reported epidemiological pattern for the pandemic so far in EU where reported cases were for the vast majority young adults. It is also likely that the source of positivity at baseline is different among adults and elderly, being the first one due to recent infections and for the second to residual cross-protection from the past. It is unknown if there is any biological difference in quality and the effect of pre-immunisation titres.
Detailed analyses on the data provided were reported in order to support the inference on the effects of vaccination of seropositive and seronegative subjects. However, in this situation the true efficacy of the vaccination is best estimated from the effect in seronegative subjects to be considered representative of the naïve population exposed to the pandemic. The data provided showed that positivity at baseline is affecting the amount of the immune response after one dose of Focetria. Of note, baseline serostatus obtained with the two assays HI and MN showed slightly higher seropositivity with HI versus MN.

In adults after the first vaccination, all three CHMP criteria were met both by the subjects who were seropositive and seronegative at baseline in the 7.5_fullMF59 group and across age strata. Therefore the data provided suggests the use of one full dose in adults 18-60 may be sufficient in this patient population, as 98% of naïve subjects (seronegative at baseline with HI assay) seroconverted 22 days following immunisation. Lower proportions were observed for recipients of half dose vaccine (74%) or unadjuvanted vaccine (80%). The MAH claim for a reduced posology for half the dose (0.25 ml) instead of full dose (0.5 ml) in adults was based on the advantage of a potential increased number of vaccinated subjects with the same amount of vaccine production but was not supported by the results observed. The results showed that the half dose of Focetria in adults provided lower immune response than the full dose adjuvanted and similar to the non-adjuvanted vaccine. The Committee also noted that the future investigations of the company regarding the use of a different posology (e.g., 0.25 ml vs 0.5 ml) for various population subgroups may be a source of errors and additional procedures and systems should be developed in order to record the volume injected.

The proportion of elderly subjects with pre immunisation antibody was not higher than that observed in adults. The proportion of seronegative subjects who are seroprotected following one full dose of Focetria was 56%, not meeting the CHMP criterion of seroprotection (60%), while 77% of seropositive subjects showed seroprotection. The seconversion rate in the seropositive subjects was only 39%. The lack of adequate seroprotection in the seronegative subjects older than 60 did not provide adequate reassurance on vaccine efficacy after one single dose of Focetria in this population. Results from the MN assay showed that 59% of seronegative subjects at baseline recipients of the full dose are seroprotected according to percentages achieving 1:40 titers. In seropositive subjects at baseline the seroprotection rate was 97%. The results from MN are in line with the results obtained

with HI assay. However, the lower baseline serostatus detected by MN versus HI would still underline the need of assay validation and, as general comment, the need of assay standardisation. The validation reports for the HI and MN assays are expected. Serological samples will also be analysed by OMCL laboratories. The MAH committed to provide these in accordance with appropriate timelines.

In summary, the HI response data on the full 7.5 µg dose in healthy adults 18-60 years provided good seroprotection rates of 93% -100% in subjects with baseline HI titres <10. The three CHMP criteria were reached for all age groups and regardless of baseline serostatus and of any other subject characteristics (e.g., age, history of previous vaccination, etc).
In the elderly CHMP criteria are met in the overall analyses. However such result is obtained with the contribution of subjects seropositive at baseline and the CHMP criteria following one dose were not met in subjects seronegative at the baseline. Therefore there is a need to assess the value of a second dose for this age group. Following this consideration the CHMP considered prudent at the present time to remain with the 2-dose recommendation for elderly subjects, to ensure optimal protection.

Based on previous experience with H5N1 and on the robust immune response achieved in young adults with H1N1 as shown in this report, the observation gathered for adult subjects are likely to be relevant also for adolescents in the age group 9-17 years and therefore the adult posology could be considered for immunisation of adolescents. As far as children of lower age are concerned results from an ongoing study are to be awaited for confirming posology.

Safety
The safety analyses included all enrolled subjects except twelve 18 to 60 year (4 subjects from each vaccination group) and 4 over 60 year subject who were not vaccinated (2 subjects from each group). Similar percentages of adults received the first vaccination among the vaccination groups

Safety variables assessed after each vaccination

Vaccination	Variables	Duration post vaccination	Study days
First Vaccination	**Solicited local and systemic reactions[a]**	**1 week**	**1 – 7**
	All unsolicited AEs (incl SAEs, AEs that led to withdrawal of the subject, and prescription medication, and solicited reactions ongoing past day 7).	**3 weeks**	**1 – 21**
Second vaccination	Solicited local and systemic reactions[a]	1 week	22 – 28
	All unsolicited AEs (as above)	3 weeks	22 – 42
	Only SAEs, onset of chronic disease, AEs that led to withdrawal of the subject and prescription medication	3 weeks post second to 1 year	43 – 365
Booster vaccination	Solicited local and systemic reactions[a]	1 week	366 - 372
	All unsolicited AEs (as above)	3 weeks	367 - 388
	Only SAEs, onset of chronic disease, AEs that led to withdrawal of the subject and prescription medication	3 weeks to 6 months post booster	389 - 546

[a] Local (ecchymosis, erythema, induration, swelling, pain at injection site) and systemic reactions: (headache, arthralgia, chills, fatigue, malaise, myalgia, nausea, sweating, and fever) were summarized according to the Brighton collaboration case definition (Bonheffers et al, Vaccine 2009; 27: 2282-2288)

Adults 18-60 years
After the first vaccination, higher percentages of 18 to 60 year adults in the adjuvanted vaccination groups reported solicited local and systemic reactions (58% and 69% for the 3.75_halfMF59 and 7.5_fullMF59 groups, respectively) than in the unadjuvanted vaccination group (52%;). Most reactions were local reactions, which were most frequent in the 7.5_fullMF59 group (55%) and lowest in the 15_noMF59 group (22%). Although systemic reactions were reported less frequently than local reactions they were also most common in the 7.5_fullMF59 group.

There were no reports of severe local reactions and most of the local reactions had onset within one or two days of vaccination with only 1% to 2% of subjects reporting any of local reactions on day 7.

The table below provide a summary of local and systemic reactions reported.

Numbers (and percents) of 18 to 60 year old adults with any (and severe/>100 mm) local or systemic reaction within 7 days after first vaccination: Safety population

		3.75_ halfMF59	7.5_ fullMF59	15_ NoMF59
		N=133	N=134	N=131
Local Reactions	Ecchymosis (mm)	6 (5%)	8 (6%)	7 (5%)
	>100mm	0	0	0
	Erythema (mm)	17 (13%)	13 (10%)	10 (8%)
	>100mm	0	0	0
	Induration (mm)	11 (8%)	17 (13%)	3 (2%)
	>100mm	0	0	0
	Swelling (mm)	6 (5%)	11 (8%)	8 (6%)
	>100mm	0	0	0
	Pain	45 (34%)	64 (48%)	21 (16%)
	Severe	0	0	0
Systemic Reactions	Chills	3 (2%)	1 (1%)	1 (1%)
	Severe	1 (1%)	0	0
	Malaise	13 (10%)	12 (9%)	13 (10%)
	Severe	2 (2%)	0	1 (1%)
	Myalgia	23 (17%)	26 (19%)	10 (8%)
	Severe	0	0	0
	Arthralgia	9 (7%)	9 (7%)	3 (2%)
	Severe	0	0	0
	Headache	31 (23%)	29 (22%)	31 (24%)
	Severe	3 (2%)	1 (1%)	3 (2%)
	Sweating	12 (9%)	13 (10%)	12 (9%)
	Severe	1 (1%)	1 (1%)	0
	Fatigue	27 (20%)	28 (21%)	43 (33%)
	Severe	2 (2%)	1 (1%)	2 (2%)
	Nausea	4 (3%)	6 (4%)	6 (5%)
	Severe	1 (1%)	0	1 (1%)
	Fever (≥ 38C)	1 (1%)	1 (1%)	0
	≥ 40°C	0	0	0
	Stayed Home	1 (1%)	0	1 (1%)
	Analg. Antipyr. Med.Used	13 (10%)	12 (9%)	9 (7%)

Adults over 60 years

In adults over 60 years there was a tendency for higher percentages of subjects reporting pain and swelling, but not the other local reactions, in the 7.5_fullMF59 than 3.75_halfMF59 group after the first vaccination. The most commonly reported local reactions were also pain and erythema in both the vaccination groups. No severe local reactions were reported.

Overall frequencies of the systemic reactions were similar in both vaccination groups.

Fatigue, headache, and sweating were the most commonly reported solicited systemic reactions by adults of over 60 years, with severe reactions being infrequent. No subjects reported severe fever (≥40°C) and most subjects did not take analgesics/antipyretics nor stayed at home.

The table below provide a summary of local and systemic reactions reported.

Number of over 60 year adults with any (and severe/>100 mm) local or systemic reactions within 7 days after first vaccination: Safety Set

		3.75_ halfMF59	7.5_ fullMF59
		N=124	N=123
Local Reactions	Ecchymosis (mm)	8(6%)	3(2%)
	>100mm	0	0
	Erythema (mm)	13(10%)	12(10%)
	>100mm	0	0
	Induration (mm)	3(2%)	7(6%)
	>100mm	0	0
	Swelling (mm)	3(2%)	7(6%)
	>100mm	0	0
	Pain	12(10%)	23(19%)
	Severe	0	0
Systemic Reactions	Chills	3(2%)	3(2%)
	Severe	0	0
	Malaise	9(7%)	10(8%)
	Severe	1(1%)	1(1%)
	Myalgia	13(10%)	11(9%)
	Severe	0	0
	Arthralgia	7(6%)	6(5%)
	Severe	0	0
	Headache	17(14%)	14(11%)
	Severe	0	1(1%)
	Sweating	13(10%)	14(11%)
	Severe	2(2%)	1(1%)
	Fatigue	24(19%)	20(16%)
	Severe	2(2%)	1(1%)
	Nausea	6(5%)	1(1%)
	Severe	0	0
	Fever (≥ 38C)	0	1(1%)
	≥ 40C	0	0
	Stayed Home	2(2%)	1(1%)
	Analg. Antipyr. Med.Used	4(3%)	4(3%)

Discussion on safety

The safety analyses included 99% of the exposed subjects (N= 645; 398 adults aged 18-60 years and 247 adults over 60 years).
Local and systemic reactions were typically mild or moderate in severity and were of short duration (generally resolving within the 7-day time window). Severe local reactions were infrequent, with none of the subjects in either age group reporting severe pain. Severe systemic reactions were also infrequent. No subject reported fever ≥ 40°C. The proportion of subjects with unsolicited adverse events (AEs) was balanced among vaccination groups. AEs were generally mild or moderate in severity and were of short duration. Unsolicited AEs that were judged by the investigator to be at least

possibly related to vaccination were balanced among the vaccine groups reported and caused by ongoing local and systemic reactions or other known side effects of vaccination.
No deaths occurred. One serious adverse event was reported which was judged unrelated to the study vaccine. There was one premature withdrawal due to an AE after first vaccination (arthralgia, possibly related) which onset on day 8 and lasted 10 days.

The results are in line with the profile of Focetria. In adults recipients, half dose showed a reduced local reactogenicity (43% vs 55%), but comparable systemic reactogenicity (46% vs 49%). In elderly the differences were even lower (22% vs 28%). The use of the half dose formulation may be related to a small reduction in reactogenicity, however the recommended dose is 0.5 ml.

Changes to the Product Information

The proposed changes to section 4.2, 4.4, 4.8 and 5.1 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. Annex II was amended to reflect the fulfilment of specific obligations.

Overall discussion and benefit risk assessment

The interpretation of results from the V111_02 study is complicated by the high number of subjects with evidence of immunity at the baseline and the actual effect of the immunisation is better estimated by the analyses restricted to the immune response developed by subjects seronegative at the baseline.
With this approach, taking into consideration data obtained after one dose of Focetria H1N1 in adults and elderly the CHMP criteria are met in adults, but not in the elderly and therefore results from the effect of the second dose are considered necessary in order to review the posology for this age group.

Previous observations obtained with Focetria H5N1 had shown that in adults one dose should be given and a second dose should preferably be given. However, results with Focetria 7.5 ug H1N1 (0.5 ml) from the present study with a single adjuvanted H1N1 7.5µg dose suggest that adequate immune response is observed after the first dose in healthy adults. Based on these data, inclusion of advice regarding the possibility of using a single dose in adults aged 18-60 years is deemed appropriate in the SPC. The observation gathered for adult subjects are likely to be relevant also for adolescents in the age group 9-17 years and therefore the adult posology could be considered for immunisation of adolescents.

Administration of half dose of Focetria was shown to induce immune responses lower than the full dose and affected by background conditions of the vaccine recipients (the response was lower in those aged above 40 years, in those with history of previous influenza vaccination, in those with antibodies at the baseline, in those with BMI >30). A reduced local reactogenicity (43% vs 55%), but comparable systemic reactogenicity (46% vs 49%) was observed in adults receiving the half dose. In elderly the differences were even lower (22% vs 28%). The Committee considered there is no relevant advantage in terms of safety with the 0.25 ml vs 0.5 ml, and that the immunogenicity was not as satisfactory as with the full dose. Based on the results and in view of the various situations in which the vaccine is going to be used in the field and that vaccination is first recommended to at risk population with underlying health conditions the proposal to accept a posology with half dose of Focetria was not accepted.