European Medicines Agency
Evaluation of Medicines for Human Use

London, 17 December 2009
Doc. Ref: EMA/CHMP/842825/2009

TYPE II VARIATION ASSESSMENT REPORT
(Safety/Efficacy variations)

EMEA/H/C/000710/II/0018

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

Indication (brief): prophylaxis of influenza (pandemic situation)

MAH: NOVARTIS VACCINES AND DIAGNOSTICS S.R.L.

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

I. SCIENTIFIC DISCUSSION

I.1. 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 reflected in the product information was based initially on data from the mock-up H5N1 vaccine and data from clinical trials with the H1N1 vaccine strain. The marketing authorisation holder (MAH) continues with the programme of H1N1 studies to fulfil the specific obligations agreed and results are submitted at regular timepoints. In this framework, the CHMP assessed the interim analysis including immunogenicity and safety data as available up to 27 November 2009 for the study V111_03 in children and adolescentsin the context of SOB 28.1. Based on the assessment of the data, the Committee considered that a type II variation should be submitted to update the product information (PI). The MAH provided the abridged study report of study V111_03 post day 1 on 16 December 2009. The submission of the report fulfils one of the MAH's specific obligations as outlined in Annex II to this opinion. This report will be the subject of an additional assessment.

Furthermore Section 4.8 is updated at the request of the CHMP following the evaluation of the simplified periodic safety update report 1 (sPSUR 1) (reporting period 5 October 2009 – 02 November 2009) and sPSUR 2 (reporting period 03 November – 30 November 2009) to include adverse drug Reactions reported for Focetria in post marketing surveillance.

I.2 Clinical immunogenicity and safety

Study design

Study V111_03 is an ongoing, randomised, single-blind, dose-ranging study in infants, children and adolescents from 6 months to 17 years of age aimed to evaluate immunogenicity, safety and tolerability of different formulations of adjuvanted and non-adjuvanted egg-derived, inactivated novel swine origin A/H1N1 monovalent subunit influenza virus vaccine in healthy subjects.

The study includes 4 cohorts and recruitment started in parallel for subjects of cohorts 1-3 (17-9 years of age, 9-3 years of age, 3-1 year of age, respectively). Enrolment of the subjects in cohort 4 (children aged 6 to 11 months) started after 7-day safety and reactogenicity data of the first dose administered to the first 120 subjects enrolled in cohorts 1, 2 and 3 was assessed by an independent Data Monitoring Committee (DMC).

Two doses of vaccine were administered intramuscularly (IM) three weeks apart. After approximately 12 months from the first vaccination, all subjects will receive a third vaccine dose (booster). All subjects will be analysed for safety and immunogenicity. Subjects will be followed until approximately 6 months after the last (booster) dose, for safety assessment.

The vaccination groups were defined as noted below:

3.75ug_50:	3.75µg HA[1] H1N1sw	+half dose MF59	(group A)
7.5ug_100	7.5µg HA H1N1sw	+full dose MF59	(group B)
15ug_0	15µg HA H1N1sw	without MF59	(group C)

Immunogenicity analyses were based on the full analysis set (FAS) and subjects were analysed as randomised. Measurements were made against CHMP criteria as determined by hemagglutination inhibition (HI). The MAH also presented data for measures of immunogenicity as determined by microneutralisation (MN).

[1] HA = haemagglutinin

Objectives

The primary objective of the study is to identify the preferred vaccine formulation (with or without MF59), dosage (1/2 vs 1 dose of antigen and adjuvant) and schedule (one or two administrations) of the egg-derived H1N1sw monovalent vaccine in healthy children and adolescents based on CHMP criteria and pairwise statistical comparisons for immunogenicity, safety and tolerability.

Secondary objectives include the evaluation of 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; and the evaluation of the non-inferiority of the post-vaccination (day 43) 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 children population.

Safety objectives include the evaluation of safety and tolerability of the egg-derived H1N1sw monovalent vaccine for 3 weeks after first and second vaccination and up to 6 months after the last (booster) vaccination.

Study population

The study population included healthy males and females aged 6 months to 17 years on the day of enrollment. The demographic characteristics of the different cohorts were presented and no major difference was detected across vaccination groups.

The number of subjects available for the analysis of immunogenicity and safety is shown in the table below.

Table 1

Age Cohort	Panel	Day	Vaccine Group		
			3.75ug_50	7.5ug_100	15ug_0
9-17 years	Enrolled**		**95**	**95**	**N/A**
	IMM	22 (HI)	94	94	N/A
		43 (HI)	82	82	N/A
		22 (MN)	95	94	N/A
		43 (MN)	75	68	N/A
	L&S	Post 1st	94	95	N/A
		Post 2nd	94	94	N/A
	AE*		94	95	N/A
3-8 years	Enrolled		**88**	**88**	**44**
	IMM	22 (HI)	87	85	43
		43 (HI)	49	41	22
		22 (MN)	87	82	42
		43 (MN)	33	30	14
	L&S	Post 1st	89	87	44
		Post 2nd	88	84	43
	AE*		85	85	43
12-35 mo	Enrolled		**79**	**76**	**40**
	IMM	22 (HI)	46	41	21
		43 (HI)	8	9	4
		22 (MN)	40	36	18
		43 (MN)	1	1	0
	L&S	Post 1st	75	72	38
		Post 2nd	48	42	25
	AE*		37	33	19
6-11 mo	Enrolled		**23**	**24**	**N/A**
	IMM	22 (HI)	13	10	N/A
		43 (HI)	2	3	N/A
		22 (MN)	12	10	N/A
		43 (MN)	1	0	N/A
	L&S	Post 1st	22	23	N/A
		Post 2nd	15	11	N/A
	AE*		9	12	N/A

IMM=Immunogenicity; L&S=Local & systemic reactions for 7 days post vaccination; AE=Adverse events
* Most adverse events relate to the period post 1st vaccination. Exposure times differed.
** Available in database at cut-off for data inclusion (27 November 09)

IMM=

immunogenicity; L&S=local & systemic reactions for 7 days post vaccination; AE=adverse events
* most adverse events relate to the period post 1st vaccination. Exposure times differed.
** available in database at cut-off for data inclusion (28 October 2009)

The data provided were used for the interim assessment of the effect of vaccination at day 22 and day 43 in cohorts 1 (children and adolescents aged 9-17 years of age) and cohort 2 (children aged 3-8 years of age). Data for the younger subjects (cohorts 3 and 4) are incomplete due to the slow enrollment of subjects in these age groups.

In the age-group 9-17 years the results from the second dose are almost complete, while data for only half of the children in the age-group 3-8 at day 43 are reported. In the age-groups 12-35 months and 3-8 years a small group of subjects has received the non-adjuvated vaccine. Partial data are reported.

Data are considered insufficient in the younger cohorts, while data for cohort 1 and 2 was considered sufficient. Results for cohorts other than 1 and 2 are sometimes reported for completeness.

Results

Immunogenicity

The frequency and percentage (including 2-tailed 95% confidence interval) of subjects with HI Titer ≥ 1:40, seroconversion or significant increase and geometric mean titers (GMT) at day 1, 22, and 43 and the geometric mean ratios (GMR) (day 22/day 1, day43/day 1) are provided below for cohorts 1 and 2. Analyses are shown for the FAS population.

Seroprotection (HI)

Table 2: Percentages of Subjects with HI Titer ≥ 1:40 - FAS

		3.75ug_50	7.5ug_100	15ug_0
COHORT 1(9-17 YRS)		**N=94**	**N=94**	**N/A**
	Day 1	10 (11%) (5-19)	13 (14%) (8-22)	N/A
	Day 22	90 (96%) (89-99)	91 (97%) (91-99)	N/A
	Day 43	82 (100%) (96-100) N=82	81 (99%) (93-100) N=82	N/A
COHORT 2(3-8 YRS)		**N=87**	**N=85**	**N=43**
	Day 1	9 (10%) (5-19)	13 (15%) (8-25)	9 (21%) (10-36)
	Day 22	84 (97%) (90-99)	85 (100%) (96-100)	26 (60%) (44-75)
	Day 43	49 (100%) (93-100) N=49	41 (100%) (91-100) N=41	21 (95%) (77-100) N=22
COHORT 3(12-35 MON)		**N=46**	**N=41**	**N=21**
	Day 1	5 (11%) (4-24)	8 (20%) (9-35)	4 (19%) (5-42)
	Day 22	44 (96%) (85-99)	40 (98%) (87-100)	8 (38%) (18-62)
	Day 43	8 (100%) (63-100) N=8	9 (100%) (66-100) N=9	3 (75%) (19-99) N=4
COHORT 4(6-11 MON)		**N=13**	**N=10**	**N/A**
	Day 1	1 (8%) (0-36)	1 (10%) (0-45)	N/A
	Day 22	11 (85%) (55-98)	10 (100%) (69-100)	N/A
	Day 43	2 (100%) (16-100) N=2	3 (100%) (29-100) N=3	N/A

Source: Table 14.2.1.3

Table shows : N(%) and 2-tailed 95% CI

Seroconversion or significant increase

Table 3: Percentages of Subjects with Seroconversion of Significant Increase - FAS

		3.75ug_50	7.5ug_100	15ug_0
COHORT 1 (9-17 YRS)		**N=94**	**N=94**	**N/A**
	Seroconversion or Significant Increase Day 22 to Day 1	84 (89%) (81-95)	89 (95%) (88-98)	N/A
	Seroconversion or Significant Increase Day 43 to Day 1	76 (93%) (85-97) N=82	79 (96%) (90-99) N=82	N/A
COHORT 2 (3-8 YRS)		**N=87**	**N=85**	**N=43**
	Seroconversion or Significant Increase Day 22 to Day 1	83 (95%) (89-99)	84 (99%) (94-100)	25 (58%) (42-73)
	Seroconversion or Significant Increase Day 43 to Day 1	49 (100%) (93-100) N=49	41 (100%) (91-100) N=41	19 (86%) (65-97) N=22
COHORT 3 (12-35 MON)		**N=46**	**N=41**	**N=21**
	Seroconversion or Significant Increase Day 22 to Day 1	44 (96%) (85-99)	40 (98%) (87-100)	7 (33%) (15-57)
	Seroconversion or Significant Increase Day 43 to Day 1	8 (100%) (63-100) N=8	9 (100%) (66-100) N=9	3 (75%) (19-99) N=4
COHORT 4 (6-11 MON)		**N=13**	**N=10**	**N/A**
	Seroconversion or Significant Increase Day 22 to Day 1	11 (85%) (55-98)	9 (90%) (55-100)	N/A
	Seroconversion or Significant Increase Day 43 to Day 1	2 (100%) (16-100) N=2	3 (100%) (29-100) N=3	N/A

Source: Table 14.2.1.4

Table shows : n/N (%) and 2-tailed 95% CI

Table 4: Geometric Mean Titers and Geometric Mean Ratio (GMR) by Vaccine Group - FAS

		3.75ug_50	7.5ug_100	15ug_0
COHORT 1(9-17 YRS)		**N=94**	**N=94**	**N/A**
	Day 1	12 (8.62-16)	12 (8.88-17)	N/A
	Day 22	503 (348-729)	718 (496-1041)	N/A
	Day 22 to Day 1	43 (28-66)	59 (38-91)	N/A
	Day 43	721 (555-937) N=82	972 (748-1265) N=82	N/A
	Day 43 to Day 1	58 (39-86) N=82	85 (57-127) N=82	N/A
COHORT 2(3-8 YRS)		**N=87**	**N=85**	**N=43**
	Day 1	8.23 (5.78-12)	9.63 (6.67-14)	11 (6.92-16)
	Day 22	212 (139-324)	281 (181-435)	88 (53-146)
	Day 22 to Day 1	26 (17-38)	29 (19-44)	8.39 (5.25-13)
	Day 43	703 (477-1034) N=49	667 (435-1021) N=41	202 (123-330) N=22
	Day 43 to Day 1	83 (52-132) N=49	72 (43-119) N=41	22 (12-39) N=22
COHORT 3(12-35 MON)		**N=46**	**N=41**	**N=21**
	Day 1	6.53 (3.62-12)	10 (5.48-20)	11 (5.64-23)
	Day 22	208 (107-403)	294 (143-604)	45 (21-99)
	Day 22 to Day 1	32 (18-57)	28 (15-54)	4 (1.99-8.02)
	Day 43	410 (201-834) N=8	558 (295-1052) N=9	389 (155-979) N=4
	Day 43 to Day 1	159 (75-339) N=8	37 (19-73) N=9	14 (5.2-37) N=4
COHORT 4(6-11 MON)		**N=13**	**N=10**	**N/A**
	Day 1	9.81 (3.73-26)	13 (4.07-39)	N/A
	Day 22	149 (59-374)	354 (121-1034)	N/A
	Day 22 to Day 1	15 (6.53-35)	28 (10-76)	N/A

GMR (HI) are shown below for all cohorts according to seropositivity at baseline (< 1:10 or ≥ 1:10, respectively).

Seroprotection (HI)

Table 5: Percentages of Subjects with HI Titer ≥ 1:40 for Subjects Seronegative (HI < 1:10) at Baseline - FAS

		3.75ug_50	7.5ug_100	15ug_0
COHORT 1(9-17 YRS)		**N=60**	**N=54**	**N/A**
	Day 22	57 (95%) (86-99)	51 (94%) (85-99)	N/A
	Day 43	50 (100%) (93-100) N=50	47 (100) (89-100) N=48	N/A
COHORT 2(3-8 YRS)		**N=71**	**N=59**	**N=30**
	Day 22	68 (96%) (88-99)	59 (100%) (94-100)	16 (53%) (34-72)
	Day 43	39 (100%) (91-100) N=39	30 (100%) (88-100) N=30	15 (94%) (70-100) N=16
COHORT 3(12-35		**N=40**	**N=30**	**N=15**
	Day 22	38 (95%) (83-99)	30 (100%) (88-100)	3 (20%) (4-48)
	Day 43	8 (100%) (63-100) N=8	4 (100%) (40-100) N=4	1 (50%) (1-99) N=2
COHORT 4(6-11 MON)		**N=10**	**N=8**	**N/A**
	Day 22	8 (80%) (44-97)	8 (100%) (63-100)	N/A
	Day 43	2 (100%) (16-100) N=2	3 (100%) (29-100) N=3	N/A

Source: Table 14.2.1.9
Table shows : N(%) and 2-tailed 95% CI

Table 6: GMR (HI)

GMT and GMR at day 22 and 43 by baseline and study groups							
Age Cohort	Day	Vaccine Group					
		3.75ug_50		7.5ug_100		15ug_0	
		<1:10	>=10	<1:10	>=10	<1:10	>=10
6-11 months	GMT 22	99	320	231	453		
	GMR 22/1	20	5.7	45	4.8		
	GMT 43	718	-	2032	-		
	GMR 43/1	121	-	406	-		
12-35 months	GMT 22	195	605	225	428	20	324
	GMR 22/1	39	12	45	7.7	4.1	3.8
	GMT 43	576	-	302	2463	141	1955
	GMR 43/1	115	-	60	64	28	32
3-8 years	**GMT 22**	**194**	**343**	**218**	**383**	**50**	**154**
	GMR 22/1	**39**	**7.1**	**44**	**13**	**10**	**4.8**
	GMT 43	786	629	733	580	175	225
	GMR 43/1	156	21	147	20	35	13
9-17 years	**GMT 22**	**368**	**602**	**457**	**957**		
	GMR 22/1	**72**	**16**	**90**	**27**		
	GMT 43	690	698	790	1134		
	GMR 43/1	135	18	155	35		

The CHMP criteria were met with both formulations of the adjuvated vaccines. At day 22 GMR were higher in subjects seronegative at baseline. Subjects seropositive at baseline show higher GMR following the administration of the full dose of Focetria. However the clinical meaning of these observations is unclear. Seroconversion or significant increase in antibody titres was systematically higher in recipients of full dose of Focetria. The second dose added further benefit.

Presence of functional antibodies induced by vaccination was assessed in a subgroup of study subjects. Results of MN were provided and are shown below.

Table 7: Percentage of Subjects with MN Titer ≥ 1:40 by Baseline Positivity (<1:10 vs ≥1:10) by Age Cohort - FAS - Seropositivity Determined by HI Test

		HI < 1:10			HI ≥ 1:10		
		3.75ug_50	**7.5ug_100**	**15ug_0**	**3.75ug_50**	**7.5ug_100**	**15ug_0**
COHORT 1 (9-17 YRS)		**N=33**	**N=31**	**N=0**	**N=27**	**N=27**	**N=0**
	Day 1	0 (0%) (0-11)	0 (0%) (0-11)		5 (19%) (6-38)	3 (11%) (2-29)	
	Day 22	32 (97%) (84-100)	30 (97%) (83-100)		26 (96%) (81-100)	27 (100%) (87-100)	
	Day 43	5 (100%) (48-100) N=5	4 (100%) (40-100) N=4		2 (100%) (16-100) N=2	1 (100%) (3-100) N=1	
COHORT 2 (3-8 YRS)		**N=18**	**N=17**	**N=9**	**N=6**	**N=6**	**N=2**
	Day 1	0 (0%) (0-19)	0 (0%) (0-20)	0 (0%) (0-34)	0 (0%) (0-46)	1 (17%) (0-64)	0 (0%) (0-84)
	Day 22	18 (100%) (81-100)	17 (100%) (80-100)	7 (78%) (40-97)	6 (100%) (54-100)	6 (100%) (54-100)	1 (50%) (1-99)
	Day 43						
COHORT 3 (12-35 MON)		**N=2**	**N=0**	**N=0**	**N=0**	**N=1**	**N=0**
	Day 1	0 (0%) (0-84)				0 (0%) (0-98)	
	Day 22	2 (100%) (16-100)				1 (100%) (3-100)	
	Day 43						

The MN titres by detectable titres in MN at baseline is shown below:

Table 8: Percentage of Subjects with MN Titer ≥ 1:40 by Baseline Positivity (<1:10 vs ≥1:10) by Age Cohort - FAS - Seropositivity Determined by MN Test

		MN < 1:10			MN ≥ 1:10		
		3.75ug_50	7.5ug_100	15ug_0	3.75ug_50	7.5ug_100	15ug_0
		N=50	N=51	N=0	N=11	N=7	N=0
COHORT 1 (9-17 YRS)	Day 1	0 (0%) (0-7)	0 (0%) (0-7)		6 (55%) (23-83)	3 (43%) (10-82)	
	Day 22	48 (96%) (86-100)	50 (98%) (90-100)		11 (100%) (72-100)	7 (100%) (59-100)	
	Day 43	6 (100%) (54-100) N=6	5 (100%) (48-100) N=5		1 (100%) (3-100) N=1		
		N=24	N=19	N=10	N=0	N=4	N=1
COHORT 2 (3-8 YRS)	Day 1	0 (0%) (0-14)	0 (0%) (0-18)	0 (0%) (0-31)		1 (25%) (1-81)	0 (0%) (0-98)
	Day 22	24 (100%) (86-100)	19 (100%) (82-100)	7 (70%) (35-93)		4 (100%) (40-100)	1 (100%) (3-100)
	Day 43						
		N=2	N=1	N=0	N=0	N=4	N=1
COHORT 3 (12-35 MON)	Day 1	0 (0%) (0-84)	0 (0%) (0-98)				
	Day 22	2 (100%) (16-100)	1 (100%) (3-100)				
	Day 43						

Table 9: Percentage of Subjects with MN Titer ≥ 1:160 by Baseline Positivity (<1:10 vs ≥1:10) by Age Cohort - FAS - Seropositivity Determined by MN Test

		MN < 1:10			MN ≥ 1:10		
		3.75ug_50	7.5ug_100	15ug_0	3.75ug_50	7.5ug_100	15ug_0
		N=50	N=51	N=0	N=11	N=7	N=0
COHORT 1 (9-17 YRS)	Day 1	0 (0%) (0-7)	0 (0%) (0-7)		3 (27%) (6-61)	2 (29%) (4-71)	
	Day 22	43 (86%) (73-94)	44 (86%) (74-94)		11 (100%) (72-100)	7 (100%) (59-100)	
	Day 43	6 (100%) (54-100) N=6	5 (100%) (48-100) N=5		0 (0%) (0-98) N=1		
		N=24	N=19	N=10	N=0	N=4	N=1
COHORT 2 (3-8 YRS)	Day 1	0 (0%) (0-14)	0 (0%) (0-18)	0 (0%) (0-31)		0 (0%) (0-60)	0 (0%) (0-98)
	Day 22	18 (75%) (53-90)	17 (89%) (67-99)	4 (40%) (12-74)		4 (100%) (40-100)	0 (0%) (0-98)
	Day 43						
		N=2	N=1	N=0	N=0	N=4	N=1
COHORT 3 (12-35 MON)	Day 1	0 (0%) (0-84)	0 (0%) (0-98)				
	Day 22	2 (100%) (16-100)	0 (0%) (0-98)				
	Day 43						

Although precise cut-off points have not been defined for MN assay it was noted that at day 22 a very high proportion of tested subjects show an increase of titres of at least 4 times.

A good immune response was also shown when results were tabulated by presence of antibodies detectable at baseline with HI or MN assay. High proportions of subjects show MN titres as high as 1:160.

Clinical Safety

For subjects aged 3 to 17 years (cohorts 1 and 2) local reactions included ecchymosis, erythema, induration, swelling and pain at injection site and systemic reactions headache, arthralgia, chills, fatigue, malaise, myalgia, nausea and sweating.
For subjects aged 6 to 35 months (cohorts 3 and 4) local reactions comprised ecchymosis, erythema, induration, swelling and tenderness and systemic reactions sleepiness, diarrhoea, vomiting, irritability, change in eating habits, shivering and unusual crying.
There was no potentially life threatening event reported.

An overview on local and systemic reaction after the 1st and the 2nd vaccination is provided in the table below.

Table 10: Overview of subjects with at least one reactogenicity sign after the 1st and 2nd vaccination, by vaccine group and age cohort - Safety Set

		Number (%) of Subjects With Solicited Reactions					
		Vaccination 1			Vaccination 2		
		3.75ug_50	7.5ug_100	15ug_0	3.75ug_50	7.5ug_100	15ug_0
9-17 Yrs		N=94	N=95	N/A	N=94	N=94	N/A
	Any	53(56)	64(67)	N/A	43(46)	52(55)	N/A
	Local	48(51)	57(60)	N/A	38(40)	44(47)	N/A
	Systemic	30(32)	36(38)	N/A	27(29)	25(27)	N/A
	Other	4(4)	10(11)	N/A	8(9)	8(9)	N/A
3-8 Yrs		N=89	N=87	N=44	N=88	N=84	N=43
	Any	54(61)	59(68)	19(43)	34(39)	48(57)	15(35)
	Local	39(44)	49(56)	15(34)	30(34)	39(46)	14(33)
	Systemic	31(35)	31(36)	12(27)	16(18)	26(31)	6(14)
	Other	10(11)	10(11)	5(11)	5(6)	13(15)	2(5)
12-35 Mon		N=75	N=72	N=38	N=48	N=42	N=25
	Any	45(60)	43(60)	23(61)	24(50)	25(60)	17(68)
	Local	34(45)	34(47)	14(37)	13(27)	17(40)	11(44)
	Systemic	26(35)	34(47)	19(50)	20(42)	16(38)	11(44)
	Other	12(16)	10(14)	8(21)	9(19)	6(14)	6(24)
6-11 Mon		N=22	N=23	N/A	N=15	N=11	N/A
	Any	13(59)	14(61)	N/A	4(27)	7(64)	N/A
	Local	7(32)	9(39)	N/A	4(27)	2(18)	N/A
	Systemic	9(41)	11(48)	N/A	2(13)	6(55)	N/A
	Other	4(18)	7(30)	N/A	1(7)	4(36)	N/A

Source: Table 14.3.1.1.1.1
Table shows : N (%)

The table below shows the incidence of subjects with local reactions >100 mm diameter, severe pain or severe systemic reactions for cohort 1 (age 9-17 years).

Table 11: Age Cohort 9-17 years – Incidence of subjects with local reactions >100 mm diameter, severe pain or severe systemic reactions

Vaccination		Reaction	Vaccine Group		
			3.75ug_50	7.5ug_100	15ug_0
Day 1			**N=94**	**N=95**	**N/A**
	Local Reaction	Ecchymosis	0	0	N/A
		Erythema	0	0	N/A
		Induration	0	0	N/A
		Swelling	0	0	N/A
		Pain	0	1 (1%)	N/A
	Systemic Reaction	Fever≥40°C	0	0	N/A
		Chills	0	0	N/A
		Myalgia	1 (1%)	0	N/A
		Arthralgia	0	0	N/A
		Nausea	0	1 (1%)	N/A
		Headache	0	0	N/A
		Sweating	0	0	N/A
		Fatigue	1(1%)	0	N/A
		Malaise	0	1 (1%)	N/A
Day 22			**N=94**	**N=94**	**N/A**
	Local Reaction	Ecchymosis	0	0	N/A
		Erythema	0	0	N/A
		Induration	0	0	N/A
		Swelling	0	0	N/A
		Pain	1 (1%)	1 (1%)	N/A
	Systemic Reaction	Fever≥40°C	0	0	N/A
		Chills	0	0	N/A
		Myalgia	0	0	N/A
		Arthralgia	1 (1%)	0	N/A
		Nausea	0	0	N/A
		Headache	2 (2%)	0	N/A
		Sweating	0	0	N/A
		Fatigue	1 (1%)	0	N/A
		Malaise	1 (1%)	0	N/A

Source: Table 14.3.1.1.1.3

Table 12: Age Cohort 3-8 years – Incidence of subjects with local reactions >100 mm diameter, severe pain or severe systemic reactions

Vaccination		Reaction	Vaccine Group		
			3.75ug_50	7.5ug_100	15ug_0
Day 1			N=89	N=87	N=44
	Local Reaction	Ecchymosis	0	0	0
		Erythema	0	0	0
		Induration	0	0	0
		Swelling	0	0	0
		Pain	1(1%)	1 (1%)	1(2%)
	Systemic Reaction	Fever≥40°C	0	0	0
		Chills	0	0	0
		Myalgia	0	0	0
		Arthralgia	0	0	0
		Nausea	1 (1%)	0	0
		Headache	0	0	0
		Sweating	1 (1%)	0	0
		Fatigue	0	0	0
		Malaise	0	0	0
Day 22			N=88	N=84	N=43
	Local Reaction	Ecchymosis	0	0	0
		Erythema	0	0	0
		Induration	0	0	0
		Swelling	0	0	0
		Pain	0	0	1(1%)
	Systemic Reaction	Fever≥40°C	0	0	0
		Chills	0	0	0
		Myalgia	0	0	0
		Arthralgia	0	0	0
		Nausea	1 (1%)	1 (1%)	0
		Headache	0	0	0
		Sweating	0	1 (1%)	0
		Fatigue	0	0	1(2%)
		Malaise	0	0	0

Source: Table 14.3.1.1.1.3

Table 13: Age Cohort 12-35 months – Incidence of subjects with local reactions >100 mm diameter systemic reactions of any severity grade*

Vaccination		Reaction	Vaccine Group		
			3.75ug_50	7.5ug_100	15ug_0
Day 1			N=75	N=72	N=38
	Local Reaction	Ecchymosis	0	0	0
		Erythema	0	0	0
		Induration	0	0	0
		Swelling	0	0	0
		Tenderness	2 (3%)	1 (1%)	0
	Systemic Reaction	Sleepiness *)	15 (20%)	17 (24%)	8 (22%)
		Diarrhea *)	11 (15%)	10 (14%)	7 (19%)
		Vomiting *)	6 (8%)	4 (6%)	3 (8%)
		Irritability *)	15 (20%)	16 (22%)	9 (24%)
		Change in eating habits *)	11 (15%)	11/71 (15%)	5/36 (14%)
		Shivering *)	6/74 (8%)	5/71 (7%)	3/36 (8%)
		Unusual crying*)	16 (21%)	15 (21%)	6 (16%)
		Fever≥40°C	2 (3%)	0	0
Day 22			N=48	N=42	N=25
	Local Reaction	Ecchymosis	0	0	0
		Erythema	0	1 (2%)	0
		Induration	0	0	0
		Swelling	0	0	0
		Tenderness	0	0	0
	Systemic Reaction	Sleepiness *)	10 (21%)	3 (7%)	6 (24%)
		Diarrhea *)	1 (2%)	6 (14%)	2 (8%)
		Vomiting *)	3 (6%)	2 (5%)	2 (8%)
		Irritability *)	11 (23%)	5 (12%)	6 (24%)
		Change in eating habits *)	9 (19%)	3 (7%)	6 (24%)
		Shivering *)	5 (10%)	0	1 (4%)
		Unusual crying*)	5 (10%)	2 (5%)	4 (16%)
		Fever≥40°C	0	0	0

Source: Table 14.3.1.1.1.3

*) No severity grading was required. Assessment whether present or not was required.

Table 14: Age Cohort 6-11 months – Incidence of subjects with local reactions >100 mm diameter systemic reactions of any severity grade*

Vaccination		Reaction	Vaccine Group		
			3.75ug_50	7.5ug_100	15ug_0
Day 1			**N=22**	**N=23**	**N/A**
	Local Reaction	Ecchymosis	0	0	N/A
		Erythema	0	0	N/A
		Induration	0	0	N/A
		Swelling	0	0	N/A
		Tenderness	0	0	N/A
	Systemic Reaction	Sleepiness *)	5 (23%)	8 (35%)	**N/A**
		Diarrhea *)	5 (23%)	4 (17%)	N/A
		Vomiting *)	0	3 (13%)	N/A
		Irritability *)	8 (36%)	4 (17%)	N/A
		Change in eating habits *)	5 (23%)	6 (26%)	N/A
		Shivering *)	1 (5%)	1 (4%)	N/A
		Unusual crying *)	5 (23%)	4 (17%)	N/A
		Fever≥40°C	0	0	N/A
Day 22			**N=14**	**N=11**	**N/A**
	Local Reaction	Ecchymosis	0	0	N/A
		Erythema	0	0	N/A
		Induration	0	0	N/A
		Swelling	0	0	N/A
		Tenderness	0	0	N/A
	Systemic Reaction	Sleepiness *)	1 (7%)	2 (18%)	**N/A**
		Diarrhea *)	1 (7%)	1 (9%)	N/A
		Vomiting *)	1 (7%)	0	N/A
		Irritability *)	1 (7%)	3 (27%)	N/A
		Change in eating habits *)	1 (7%)	0	N/A
		Shivering *)	0	0	N/A
		Unusual crying *)	0	2 (18%)	N/A
		Fever≥40°C	0	0	N/A

Source: Table 14.3.1.1.1.3

*) No severity grading was required. Assessment whether present or not was required.

The use of a reduced dose of the vaccine is associated with a slight reduction of local reactogenicity in subjects of any age. Reactogenicity at the second dose is generally lower compared to the first dose. The reactogenicity for the subgroup recipient of non adjuvanted vaccine is reduced only for local reactions.

In the cohort 3 (12-35 months) most common systemic reactions after both the doses were sleepiness, irritability and unusual crying. There were 2 cases of fever above 40 C in the 3.75 ug group after the first dose.

In the cohort 4 (6-11 months) there was no description of severe local reactions. Most common systemic reactions were irritability, sleepiness, diarrhoea, change in eating habits and unusual crying. There were no cases of fever above 40° C although the number of observations is still low to detect uncommon reactions.

Observations for body temperature and a summary of antipyretic use are provided below.

Table 15: Summary of Systemic Reactions by Vaccination (Cohort 1, 2)

Table 1: Summary of Systemic Reactions by Vaccination (Cohort 1, 2)

			Number (%) of Subjects With Systemic Reactions					
			Inj.: 1			Inj.: 2		
			3.75ug_50	7.5ug_100	15ug_0	3.75ug_50	7.5ug_100	15ug_0
			N=94	N=95	N=0	N=94	N=94	N=0
Age Group: Cohort 1(9-17 Yrs)	Systemic							
	Other							
	Temp. (C)	<38.0 C	92(98)	93(98)		91(97)	92(98)	
		38.0 - 38.9 C	2(2)	2(2)		2(2)	2(2)	
		39.0 - 39.9 C	0	0		1(1)	0	
		≥ 40.0 C	0	0		0	0	
	Analg. Antipyr. Med.Used	Yes	4(4)	10(11)		8(9)	7(7)	

			N=89	N=87	N=44	N=88	N=84	N=43
Age Group: Cohort 2(3-8 Yrs)	Systemic							
	Other							
	Temp. (C)	<38.0 C	82(92)	83(95)	40(91)	84(95)	78(93)	41(95)
		38.0 - 38.9 C	5(6)	3(3)	3(7)	4(5)	4(5)	2(5)
		39.0 - 39.9 C	2(2)	1(1)	1(2)	0	2(2)	0
		≥ 40.0 C	0	0	0	0	0	0
	Analg. Antipyr. Med.Used	Yes	10(11)	8(9)	5(11)	5(6)	11(13)	2(5)

Source: Table 14.3.1.1.1.2

Note: The numbers (N) in the header is the total number of subjects with documented reactions. In instances where data on all the subjects 'N' is not available, both the numerator and denominator are presented.

Table 2: Summary of Systemic Reactions by Vaccination (Cohort 3, 4)

			Number (%) of Subjects With Systemic Reactions					
			Inj.: 1			Inj.: 2		
			3.75ug_50	7.5ug_100	15ug_0	3.75ug_50	7.5ug_100	15ug_0
			N=75	N=72	N=37	N=48	N=42	N=25
Age Group: Cohort 3(12-35 Mon)	Systemic							
	Other							
	Temp. (C)	<38.0 C	68(91)	60(83)	33(89)	41/47(87)	33(79)	21(84)
		38.0 - 38.9 C	3(4)	9(13)	4(11)	3/47(6)	8(19)	4(16)
		39.0 - 39.9 C	2(3)	3(4)	0	3/47(6)	1(2)	0
		≥ 40.0 C	2(3)	0	0	0	0	0
	Analg. Antipyr. Med.Used	Yes	9/73(12)	10/69(14)	6/36(17)	8(17)	6(14)	6(24)

Four subjects reported serious adverse events: 2 subjects who received 7.5µg_100, and 2 subjects with 3.75µg_50. In 3 of the 4 subjects SAE were considered not related to study vaccine and in one subject the SAE (severe pyrexia) was considered probably related to study vaccine.

Unsolicited AEs.

Table 16: Overview on Subjects with Unsolicited AEs - Safety Set

Age Cohort		Vaccine Group		
		3.75ug_50	**7.5ug_100**	**15ug_0**
9-17 years		**N=94**	**N=95**	**N/A**
	Any AE	27 (29)	29 (31)	N/A
	At least possibly related AEs	5 (5)	15 (16)	N/A
	Any Serious AE	2 (2)	0	N/A
	AEs leading to discontinuation	0	0	N/A
3-8 years		**N=85**	**N=85**	**N=43**
	Any AE	33 (39)	27 (32)	15 (35)
	At least possibly related AEs	8 (9)	6 (7)	4 (9)
	Any Serious AE	0	1 (1)	0
	AEs leading to discontinuation	0	0	0
12-35 mo		**N=37**	**N=33**	**N=19**
	Any AE	25 (68)	22 (67)	11 (58)
	At least possibly related AEs	3 (8)	4 (12)	2 (11)
	Any Serious AE	0	1 (3)	0
	AEs leading to discontinuation	0	0	0
6-11 mo		**N=9**	**N=12**	**N/A**
	Any AE	5 (56)	9 (75)	N/A
	At least possibly related AEs	2 (22)	1 (8)	N/A
	Any Serious AE	0	0	N/A
	AEs leading to discontinuation	1 (11)	0	N/A

Update of safety information further to the evaluation of sPSUR 1 and 2

Further to the assessment of sPSUR 1 and 2 covering the periods 5 October 2009 to 02 November 2009 and 03 November to 30 November 2009 respectively the CHMP requested the MAH to update Section 4.8 of the SPC with a Post Marketing Surveillance paragraph specifically for Focetria (H1N1). The table below details adverse events reported after immunisation with Focetria and have been included in the product information.

SOC	Preferred Term	Number of cases (cumulative sPUSR 1 and 2)
Skin and subcutaneous tissue disorders	Pruritus	13
	Urticaria	17
	Non specific rush	15
	Angioedema	5
Gastrointestinal disorders	Nausea	43
	Vomiting	24
	Diarrhoea	24
Nervous system disorders	Headache	102
	Dizziness	32
	Somnolence	15
	Syncope	11
	Neuralgia	2
	Paraesthesia	36
	Convulsions	8
	Neuritis	2
Immune system disorders	Allergic reactions	*see below
	Anaphylaxis	*see below
	Dyspnoea	35
	Bronchospasm	14
	Laryngeal oedema	*see below
	Shock	*see below

* Category Anaphylaxis, as defined via the narrow definition of the SMQ 'Anaphylactic reaction' and the narrow definition of the SMQ 'Angioedema':
5 anaphylactic reaction - 3 anaphylactic shock - 1 circulatory collapse- 17 urticaria- 5 angioedema- 3 eyelid oedema- 4 laryngeal oedema- 1 periorbital oedema- 2 pharyngeal oedema- 2 swelling face- 2 lip swelling- 1 swollen tongue

II. CHANGES TO THE PRODUCT INFORMATION

The proposed changes to sections 4.2, 4.8 and 5.1 of the summary of product characteristics (SPC) were reviewed and generally agreed with. Although study V111_03 is still ongoing, the data on cohort 2 (3-8) is considered quantitatively sufficient to be added to the Product Information. The committee noted that the preliminary H1N1 data in children aged 3-8 years show that there is a further immune response to a second dose of 0.5 ml administered after an interval of three weeks. The posology section has been re-worded to reflect this. In addition further data are available in the 9-17 years cohort. This has been reflected in section 5.1 of the SPC. Immunogenicity data from younger cohorts, and data from the half dose is also reassuring, although numbers are too small to allow any definitive conclusion at this point in time. The respective changes were introduced in the package leaflet (PL). A revision of the wording was submitted taking into account the results of the assessment and this was agreed with by the CHMP.

The proposed changes to SPC section 4.8 regarding the addition of post marketing data for Focetria has been agreed by the CHMP.

Other changes made to the product information include a change to the order of data presentation in section 5.1, to present H1N1 data at the beginning of this section. In addition the MAH updated Annex II regarding the specific obligations. Due to slow enrolment there will be a delay in the availability of data in Cohort 4. In addition the version number of the Detailed Description of the Pharmacovigilance System (DDPS) has been corrected.

III. OVERALL DISCUSSION AND BENEFIT RISK ASSESSMENT

Preliminary data from study V111_03 have previously shown that the use of a single full dose of Focetria in subjects aged 9-17 years may be sufficient. Further data now available from study V111_3 showed that the CHMP criteria were met, and in particular results were considered relevant for an update of the posology related to children aged 3-8 years. In the 3-8 year old cohort, 100% of subjects were seroprotected, with 99% seroconversion or significant increase and GMR of 29. The subgroup analyses by baseline serostatus were reassuring with seronegative subjects also reaching the CHMP criteria. Although the data presented are reassuring regarding the effect of a single full dose of Focetria in subjects aged 3-8 years, preliminary data indicate that there is a further immune response to a second dose: an increase in overall GMT from 281 to 667 was observed and an increase in GMT from 218 to 733 in children who were seronegative at baseline. This has been reflected in the Product Information. Study V111_03 is on-going and further results will provide indications about the effect of the second dose and its potential benefit.

With regards to data in the younger cohorts and the half dose of Focetria it was agreed that the available data are so far too premature to allow for a change of posology. Considering the ongoing immunisation program, and the current recommended posology of administering two full doses of Focetria, the inclusion of results of the first dose is appropriate while considerations about the adoption of half dose are to be postponed to the availability of the complete analyses of data to be submitted in January 2010. Additional statistical analyses by history of flu vaccinations, serostatus at baseline, and age-groups are requested to be included in the final report to be submitted. Variability in immunological results obtained by subjects enrolled across the study sites should also be described.

The preliminary safety data after the first dose in children and adolescents 3-8 years of age suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation. The use of reduced dose of vaccine is associated with a slight reduction of local reactogenicity in subjects of any age. Reactogenicity after the second dose is generally lower compared to the first dose.