EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 April 2010
EMA/CHMP/625773/2010
Evaluation of Medicines for Human Use

CHMP variation assessment report

Invented name/Name: Focetria
International non-proprietary name/Common name: pandemic influenza vaccine (surface antigen, inactivated, adjuvanted) a/california/7/2009 (H1N1)v like strain (x-181)

Type II Variation: EMEA/H/C/710/II/19

Indication summary (as last approved):	prophylaxis of influenza (pandemic situation)
Marketing Authorisation Holder:	Novartis Vaccines and Diagnostics S.r.l.

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

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of sections 4.2, 4.8 and 5.1 of the summary of product characteristics regarding administration of Focetria to children of 12 to 35 months of age based on results of study V111_3 in children. Furthermore, posology recommendation in children is updated in light of the availability of the overall data set of study V111_3. The Package Leaflet has been updated accordingly.
Rapporteur:	Daniela Melchiorri
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	
Product Information affected:	SPC and Package Leaflet (Attachment 1 - changes highlighted)

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2. Steps taken for the assessment

Submission date:	8 January 2010
Start of procedure:	8 January 2010
Rapporteur's assessment report circulated on:	13 January 2010
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 January 2010
MAH's responses submitted to the CHMP on:	29 January 2010
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	1 February 2010
Rapporteur's assessment report on Multivariate Analysis of Immunogenicity Data circulated on:	2 February 2010
Rapporteur's assessment report on the MAH responses circulated on:	4 February 2010
Rapporteur's updated assessment report circulated on:	5 February 2010
Rapporteur's final assessment report circulated on:	15 February 2010
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 February 2010
MAH's responses submitted to the CHMP on:	27 March 2010
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 April 2010
Rapporteur's updated assessment report circulated on:	30 April 2010
CHMP opinion:	22 April 2010

3. Scientific discussion

3.1. Introduction

Within this variation sections 4.2, 4.8 and 5.1 of the summary of product characteristics are updated regarding administration of Focetria to children based on results of study V111_03 in children.

The study has been designed to assess the preferable vaccine formulation, antigen and adjuvant dose, and schedule in the age group 6 months 17 years. The study assesses the effect of two doses of Focetria administered with an interval of three weeks. In the protocol the effect of a booster dose after 12 months apart has also been included.

Data from the full Cohort 1 (children and adolescents 9-17 years of age) has been submitted and assessed within variation II 15. One full dose has been recommended in this age group. The full data set is now available from Cohorts 2, (3-8 years), cohort 3 (12-35 months) and cohort 4 (6-11 months) and the outcome of the assessment of this data is addressed in this report.

Study design
Study V111_03 is a 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 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)

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 number of subjects available for the analysis of immunogenicity and safety are shown in the tables below.

6-11 months
In total 161 subjects aged 6 to 11 months were enrolled (Table1).

[1] HA = haemagglutinin

Table 1: Summary of study Terminations up to Day 43 enrolled population 6-11 months.

	3.75_ halfMF59	7.5_ fullMF59
Enrolled (N)	81	80
Completed study until day 43 (%)	79 (98%)	75 (94%)
Premature withdrawals[a]	2 (2%)	5 (6%)
Withdrew consent (%)	1 (1%)	4 (5%)
Adverse event	1 (1%)	0
Protocol deviation/violation	0	1 (1%)

Source: Table 14.1.1.2, [a]primary reason

In total 207 subjects aged 12 to 35 months were enrolled (Table 2).

Table 2: Summary of Study Terminations up to Day 43-Enrolled Population: 12 to 35 Months

Vaccine administered	**3.75_ halfMF59**	**7.5_ fullMF59**	**15_ noMF59**
Enrolled (N)	83	82	42
Completed study until day 43 (%)	81 (98%)	79 (96%)	41 (98%)
Premature withdrawals a	2 (2%)	3 (4%)	1 (2%)
Withdrew consent (%)	2 (2%)	2 (2%)	0
Lost to follow-up	0	0	1 (2%)
Protocol deviation/violation	0	1 (1%)	0

3-8 years old

In total 220 subjects aged 3 to 8 years were enrolled (Table 3).

Table 3: Summary of Study Terminations up to Day 43-Enrolled Population

	3 to 8 years		
Vaccine administered	3.75_halfMF59	7.5_fullMF59	15_noMF59
Enrolled (N)	88 (100%)	88 (100%)	44 (100%)
Completed study until day 43 (%)	85 (97%)	85 (97%)	43 (98%)
Premature withdrawals [a]	2 (2%)	3 (3%)	1 (2%)
Withdrew consent (%)	1 (1%)	2 (2%)	1 (2%)
Lost to follow-up	0	1 (1%)	0
Protocol deviation/violation	1 (1%)	0	0
Missing primary reason	1 (1%)	0	0

Clinical aspects

Immunogenicity Evaluation: Data Sets Analyzed

The per protocol set (PPS) was used to assess the immunogenicity end points. The HI analysis and MN analysis on the PPS included from 71% to 79% subjects in 6 to 11 months age group, from 80% to 86% subjects in 12 to 35 months age group and 78% to 89% of those enrolled in the 3 to 8 years age stratum.

The protocol deviations have lead to analyze a reduced number of subjects in both groups (3.75_halfMF59 and 7.5_fullMF59) with a slightly higher proportion of protocol deviations for the highest vaccine dose (up to 29% of the enrolled subjects).

Baseline Characteristics

6-11 months

In the enrolled population, most subjects were Hispanics (68% to 71%), followed by Caucasians (23% to 26%), and the gender distribution was similar between both the vaccine groups (Table 4). Other demographic and baseline characteristics were balanced among the vaccine groups and were within the expected ranges for the enrolled population.

Table 4 Demography and Other Baseline Characteristics – Enrolled Population (6 to 11 Months)

	3.75_halfMF59 N=81	7.5_fullMF59 N=80	TOTAL N=161
Age (Months):	8.7 ± 1.4	8.3 ± 1.5	8.5 ± 1.5
Gender:			
Male	40 (49%)	38 (48%)	78 (48%)
Female	41 (51%)	42 (53%)	83 (52%)
Ethnic Origin:			
Asian	2 (2%)	0	2 (1%)
Black	2 (2%)	0	2 (1%)
Caucasian	19 (23%)	21 (26%)	40 (25%)
Hispanic	55 (68%)	57 (71%)	112 (70%)
Other	3 (4%)	2 (3%)	5 (3%)
Weight (kg):	8.95 ± 1.21	8.83 ± 1.18	8.89 ± 1.19
Height (cm):	71.8 ± 3.7	70.8 ± 3.8	71.3 ± 3.8
Body Mass Index:	17.38 ± 1.92	17.62 ± 2.01	17.50 ± 1.96
Previous Influenza Vaccination:			
No	81 (100%)	79 (99%)	160 (99%)
Yes	0	1 (1%)	1 (<1%)
Met Entry Criteria Yes	81 (100%)	78 (98%)	159 (99%)

Source: Table 14.1.1.3; Categorical parameters: N (%), non-categorical parameters: Mean±Std

12-35 months

In the enrolled population, most subjects were Hispanics (49% to 51%), followed by Caucasians (35% to 38%), and the gender distribution was similar across the vaccine groups (Table5). Other demographic and baseline characteristics were balanced among the vaccine groups and were within the expected ranges for the enrolled population.

Table 5 Demography and Other Baseline Characteristics – Enrolled Population (12 to 35 Months)

	3.75ug_50 N=83	7.5ug_100 N=82	15ug_0 N=42	TOTAL N=207
Age (Yrs):	1.5±0.5 (N=71)	1.5±0.5 (N=70)	1.6±0.5 (N=36)	1.5±0.5 (N=177)
Age (Months):	24.1±7.4	23.5±6.4	24.5±6.5	23.9±6.8
Gender:				
Male	44 (53%)	47 (57%)	19 (45%)	110 (53%)
Female	39 (47%)	35 (43%)	23 (55%)	97 (47%)
Ethnic Origin:				
Asian	4 (5%)	4 (5%)	2 (5%)	10 (5%)
Black	1 (1%)	2 (2%)	1 (2%)	4 (2%)
Caucasian	29 (35%)	30 (37%)	16 (38%)	75 (36%)
Hispanic	42 (51%)	40 (49%)	21 (50%)	103 (50%)
Other	7 (8%)	6 (7%)	2 (5%)	15 (7%)
Weight (kg):	12.37±2.22	12.45±1.94	12.70±2.13	12.47±2.09
Height (cm):	86.5±7.2	87.1±5.7	88.0±6.6	87.0±6.5
Body Mass Index:	16.50±2.07	16.39±1.69	16.40±2.24	16.43±1.96
Previous Influenza Vaccination:				
No	50 (60%)	52 (63%)	23 (55%)	125 (60%)
Yes	33 (40%)	30 (37%)	19 (45%)	82 (40%)
Met Entry Criteria:	83 (100%)	82 (100%)	42 (100%)	207 (100%)

Source: Table 14.1.1.3; Categorical parameters: N (%), non-categorical parameters: Mean±Std

3-8 years

In the enrolled population 22% to 23% were Hispanics. Gender distribution was similar across the vaccine groups (Table 6). Other demographic and baseline characteristics were balanced among the vaccine groups and were within the expected ranges for the enrolled population.

Table 6: Demography and other Baseline Characteristics – Enrolled population (3-8 years)

Age Cohort: Cohort 2 (3-8 Yrs)	N=88	N=88	N=44
Age (Yrs):	5.3 ± 1.7	5.5 ± 1.7	5.1±1.6
Gender:			
Male	46 (52%)	50 (57%)	16 (36%)
Female	42 (48%)	38 (43%)	28 (64%)
Ethnic Origin:			
Asian	0	1 (1%)	1 (2%)
Black	3 (3%)	0	1 (2%)
Caucasian	63 (72%)	61 (69%)	30 (68%)
Hispanic	19 (22%)	20 (23%)	10 (23%)
Other	3 (3%)	6 (7%)	2 (5%)
Weight (kg):	22.02 ± 6.49	22.21 ± 6.39	21.47 ± 6.52
Height (cm):	115.2 ± 13.0	117.1 ± 12.1	114.7 ± 11.9

Immunogenicity results

The seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibody to H1N1 in children aged 3-8 years by HI assay after administration of 7.5 µg of Focetria were as follows in Table 7:

	Children (3-8 years)			
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=70	Seronegative at baseline N=48	Total N=70	Seronegative at baseline N=48
Seroprotection rate (95% CI)	100% (95-100)	100% (93-100)	100% (95-100)	100% (93-100)
GMR (95% CI)	37 (25-55)	50 (32-76)	81 (52-125)	146 (100-212)
Seroconversion or Significant Increase (95% CI)	99% (92-100)	100% (93-100)	99% (92-100)	100% (93-100)

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 319 to 702 (N=70) and an increase in GMT from 247 to 726 in children who were seronegative at baseline (N=48).

The seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibody to H1N1 in children aged 12-35 months by HI assay after administration of 7.5 µg of Focetria were as follows in Table 8:

Children 12-35 months				
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=66	Seronegative at baseline N=45	Total N=66	Seronegative at baseline N=45
Seroprotection rate (95% CI)	100% (95-100)	100% (92-100)	100% (95-100)	100% (92-100)
GMR (95% CI)	33 (21-51)	48 (29-79)	93 (54-159)	145 (88-238)
Seroconversion or Significant Increase (95% CI)	100% (95-100)	100% (92-100)	100% (95-100)	100% (92-100)

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 307 to 873 (N=66) and an increase in GMT from 243 to 733 in children who were seronegative at baseline (N=45).

The seroprotection rate, seroconversion rate and the seroconversion factor for anti-HA antibody to H1N1 in infants aged 6-11 months by HI assay after administration of 7.5 µg of Focetria were as follows in Table 9:

Infants 6-11 months				
Anti-HA antibody	21 days after 1st dose(day 22)		21 days after 2nd dose (day 43)	
	Total N=57	Seronegative at baseline	Total N=57	Seronegative at baseline

		N=37		N=37
Seroprotection rate (95% CI)	100% (94-100)	100% (91-100)	100% (94-100)	100% (91-100)
GMR (95% CI)	21 (14-30)	32 (18-55)	128 (74-221)	274 (196-383)
Seroconversion or Significant Increase (95% CI)	96% (88-100)	100% (91-100)	98% (91-100)	100% (91-100)

Data on responses to a second dose administered after an interval of three weeks showed an increase in overall GMT from 274 to 1700 (N=57) and an increase in GMT from 162 to 1399 in children who were seronegative at baseline (N=37).

Conclusion Immunogenicity data

In children aged 3-8 years all CHMP criteria were met after a single dose of the adjuvanted vaccine. It is the CHMP opinion that overall data on immunogenicity support the use of a single dose of the adjuvanted vaccine in the age-stratum 3-8 years, in line with the current posology recommended for influenza seasonal vaccines.

In the 6 to 35 months age stratum immunogenicity results for one full dose of the adjuvanted vaccine met all three CHMP criteria as early as 3 weeks after the first vaccination, achieving the HI seroprotection threshold of 1:40. However a further dose has been shown to augment the immune response and this has been reflected in the summary of product characteristics.

Safety
Summary of the safety results is presented hereafter per Cohort

Extent of Exposure
All of the enrolled subjects in 6 to 11, 12-35 months stratum and 3-8 years age stratum were included in the safety analyses. This represents 80 infants 6-11 months old, 82 toddlers 12-35 months old and 87 children 3-8 years old.

Safety 6-11 months

Overview of Solicited Reactions

Table 10 below shows the number of subjects reporting solicited local and systemic reactions during the 7 day period after each vaccination for 6-11 month age stratum.

Table 10 Numbers (%) of Subjects Reporting Solicited Local and Systemic Reactions During the 7-Day Period after Each Vaccination: Safety Set (6-11 Months)

	First Vaccination		Second Vaccination	
	3.75_ halfMF59 N=81	7.5_ fullMF59 N=80	3.75_ halfMF59 N=78	7.5_ fullMF59 N=75
Any	62(77%)	63(79%)	46(59%)	49(65%)
Local	32(40%)	35(44%)	26(33%)	22(29%)
Systemic	51(63%)	55(69%)	39(50%)	41(55%)
Other	25(31%)	23(29%)	14(18%)	21(28%)

Source: Table 14.3.1.1.1.1

Overview of Unsolicited Reactions
Table 11 below shows the number of subjects with AE's after first vaccination and second vaccination up to day 43 for 6-11 month age stratum.

Table 11 Number (%) of Subjects with AEs after First Vaccination and Second Vaccination up to Day 43: Safety Set (6-11 Months)

	First Vaccination		Second Vaccination	
	3.75_ halfMF59 N=81	7.5_ fullMF59 N=80	3.75_ halfMF59 N=78	7.5_ fullMF59 N=75
Any AEs	34 (42%)	32 (40%)	26 (33%)	25 (33%)
At least possibly related AEs	6 (7%)	10 (13%)	5 (6%)	5 (7%)
Serious AEs	0	0	1 (1%)	1 (1%)
At least possibly related SAEs	0	0	0	0
AEs leading to discontinuation	1 (1%)	0	0	0

Source: Table 14.3.1.1.11, Table 14.3.1.1.14, Table 14.3.1.1.6, Table 14.3.1.1.7, Table 14.3.1.1.8

Safety 12-35 months
Overview of Solicited Reactions

Table 12 below shows the number of subjects reporting solicited local and systemic reactions during he 7 day period after each vaccination for 12-35 month age stratum.

	First Vaccination			Second Vaccination		
	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59
	N=83	N=82	N=42	N=81	N=81	N=41
Any	61 (73%)	57 (70%)	29 (69%)	48 (59%)	57 (70%)	29 (71%)
Local	41 (49%)	41 (50%)	16 (38%)	30 (37%)	39 (48%)	18 (44%)
Systemic	43 (52%)	45 (55%)	25 (60%)	37 (46%)	36 (44%)	23 (56%)
Other	17 (20%)	17 (21%)	10 (24%)	19 (23%)	18 (22%)	6 (15%)

Overview of Unsolicited Reactions
Table 13 below shows the Number (%) of Subjects with AEs after First Vaccination and Second Vaccination up to Day 43 (12-35 Months) - Safety Set

	First Vaccination			Second Vaccination		
	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59	3.75_ halfMF59	7.5_ fullMF59	15_ noMF59
	N=83	N=82	N=42	N=81	N=81	N=41
Any AEs	30 (36%)	26 (32%)	13 (31%)	29 (36%)	28 (35%)	14 (34%)
At least possibly related AEs	6 (7%)	4 (5%)	1 (2%)	4 (5%)	4 (5%)	1 (2%)
Serious AEs	0	1 (1%)	0	0	2 (2%)	0
At least possibly related SAEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	1 (1%)	0

3-8 years safety
Overview of Solicited Reactions

Table 14 below shows the Numbers (%) of Subjects Reporting Solicited Local and Systemic Reactions during the 7-Day Period after Each Vaccination: Safety Set (3-8 Years).

	First Vaccination			Second Vaccination		
	3.75_halfMF59	7.5_fullMF59	15_noMF59	3.75_halfMF59	7.5_fullMF59	15_noMF59
	N=89	N=87	N=44	N=88	N=85	N=43
Any	53 (60%)	58 (67%)	18 (41%)	34 (39%)	52 (61%)	15 (35%)
Local	39 (44%)	49 (56%)	15 (34%)	30 (34%)	42 (49%)	15 (35%)
Systemic	30 (34%)	30 (34%)	11 (25%)	14 (16%)	26 (31%)	5 (12%)
Other	10 (11%)	11 (13%)	5 (11%)	5 (6%)	13 (15%)	2 (5%)

Overview of Unsolicited Reactions
Table 15 below shows the Number (%) of Subjects with AEs after First and Second Vaccination up to Day 43 (3-8 Years) - Safety Set.

	First Vaccination			Second Vaccination		
	3.75_halfMF59	7.5_fullMF59	15_noMF59	3.75_halfMF59	7.5_fullMF59	15_noMF59
	N=89	N=87	N=44	N=88	N=85	N=43
Any AEs	24 (27%)	21 (24%)	13 (30%)	19 (22%)	17 (20%)	9 (21%)
At least possibly related AEs	8 (9%)	5 (6%)	3 (7%)	0	4 (5%)	2 (5%)
Serious AEs	0	0	0	0	1 (1%)	0
At least possibly related SAEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0

Conclusion safety

Overall the safety data after first and second dose of Focetria H1N1 (both half and full dose) in children and adolescents 6 months -8 years of age suggested a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation. The use of half dose of vaccine was associated with a slight reduction of local reactogenicity in subjects of any age. Reactogenicity after the second dose was generally lower compared to the first dose.

The full sets data provided for children 6 months to 8 years old confirmed that vaccine, at any dose of antigen and adjuvant, up to date day 22 was generally safe. No death and no related severe AE were reported.

Overall Discussion and conclusion

Taking into account the availability of data in all age cohorts, considerations have been made regarding the posology in children and adolescents. All CHMP criteria have been met already at Day 22 for both studied vaccine formulations, achieving the HI seroprotection threshold of 1:40. Multivariate analysis shows that after controlling for all factors that may affect immunogenicity (serostatus at baseline, ethnicity etc.), GMT values are satisfactory already at Day 22 after the administration of the full dose of the adjuvanted vaccine. In children 6–35 months a further dose has been shown to augment the immune response, this has been reflected in the SPC.

The non-inferiority of the half dose compared to the full dose of the adjuvanted vaccine has not been fully established at this stage and further analysis would be needed in order to accept the half dose posology.

With regards to safety the full sets of data provided for children 6 months to 8 years old confirmed that vaccine, at any dose of antigen and adjuvant, up to date day 22 was generally safe.

Overall the benefit risk of one full dose of Focetria in children 6 months to 8 years is considered positive. Of note this posology is in line with the previously agreed posology for 9-17 years of one dose as agreed in variation II 15.

4. Conclusion

On 30 April 2010 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.