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/0015**

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 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 on 28 October 2009 for the study V111_03 in children and adolescents. 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 applied for a variation to reflect the results of this study in the PI and to include a correction to the warning on subcutaneous use.

## 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).

***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

[1] HA = haemagglutinin

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.

| 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) | 64 | 66 | N/A |
| | | 43 (HI) | 9 | 10 | N/A |
| | | 22 (MN) | 61 | 58 | N/A |
| | | 43 (MN) | 7 | 5 | N/A |
| | L&S | Post 1st | 93 | 93 | N/A |
| | | Post 2nd | 79 | 82 | N/A |
| | AE* | | 86 | 86 | N/A |
| 3-8 years | Enrolled | | **88** | **88** | **44** |
| | IMM | 22 (HI) | 27 | 25 | 13 |
| | | 43 (HI) | -- | -- | -- |
| | | 22 (MN) | 24 | 23 | 11 |
| | | 43 (MN) | -- | -- | -- |
| | L&S | Post 1st | 88 | 84 | 43 |
| | | Post 2nd | 43 | 38 | 19 |
| | AE* | | 62 | 62 | 31 |
| 12-35 months | Enrolled | | **51** | **45** | **24** |
| | IMM | 22 (HI) | 2 | 1 | 0 |
| | | 43 (HI) | -- | -- | -- |
| | | 22 (MN) | 2 | 1 | -- |
| | | 43 (MN) | -- | -- | -- |
| | L&S | Post 1st | 48 | 43 | 24 |
| | | Post 2nd | 9 | 9 | 5 |
| | AE* | | 16 | 16 | 10 |
| 6-11 months | Enrolled | | **15** | **11** | **N/A** |
| | IMM | 22 (HI) | -- | -- | N/A |
| | | 43 (HI) | -- | -- | N/A |
| | | 22 (MN) | -- | -- | N/A |
| | | 43 (MN) | -- | -- | N/A |
| | L&S | Post 1st | 15 | 11 | N/A |
| | | Post 2nd | 2 | 2 | N/A |
| | AE* | | 3 | 2 | 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 (28 October 2009)

The data provided were used for the interim assessment of the effect of vaccination at day 22. Data were considered insufficient in the younger cohorts, while data for cohort 1 (children and adolescents aged 9-17 years of age) was considered sufficient. For cohort 1 some data at day 43 are also reported, however this was not considered for this assessment as they are presently very limited. Results for cohorts other than 1 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)**

| **Age Cohort** | **Day** | **Vaccine Group** | | |
|---|---|---|---|---|
| | | **3.75ug_50** | **7.5ug_100** | **15ug_0** |
| 9-17 years<br>N(%) and 2-tailed 95% CI | 1 | 7/64 (11%)<br>(5-21%) | 9/66 (14%)<br>(6-24%) | N/A |
| | 22 | 61/64 (95%)<br>(87-99%) | **63/66 (95%)**<br>**(87-99%)** | N/A |
| | 43 | 9/9 (100%)<br>(66-100%) | 10/10 (100%)<br>(69-100%) | N/A |
| 3-8 years<br>N(%) and 2-tailed 95% CI | 1 | 0/27 (0%)<br>(0-12%) | 2/25 (8%)<br>(1-26%) | 1/13 (8%)<br>(0-9%) |
| | 22 | 26/27 (96%)<br>(81-100%) | 25/25 (100%)<br>(86-100%) | 9/13 (69%)<br>(39-91%) |

**Seroconversion or significant increase**

| **Age Cohort**<br>n/N (%) and 2-tailed 95% CI | **Day** | **Vaccine Group** | | |
|---|---|---|---|---|
| | | **3.75ug_50** | **7.5ug_100** | **15ug_0** |
| 9-17 years | 22 | 56/64 (88%)<br>(77-94%) | **61/66 (92%)**<br>**(83-97%)** | N/A |
| | 43 | 7/9 (78%)<br>(40-97%) | 10/10 (100%)<br>(69-100%) | N/A |
| 3-8 years | 22 | 26/27 (96%)<br>(81-100%) | 25/25 (100%)<br>(86-100%) | 8/13 (62%)<br>(32-86%) |

**Geometric mean titers and geometric mean ratio**

| **Age Cohort** | **Day** | **Vaccine Group** | | |
|---|---|---|---|---|
| | | **3.75ug_50** | **7.5ug_100** | **15ug_0** |
| 9-17 years:<br>GMT and 2-tailed 95% CI | | | | |
| | 1 | 17<br>(12-24)<br>N=64 | 16<br>(12-23)<br>N=66 | N/A |
| | 22 | 549<br>(351-858)<br>N=64 | 691<br>(456-1049)<br>N=66 | N/A |
| | 22 to 1 | 32<br>(19-54)<br>N=64 | **43**<br>**(26-69)**<br>**N=66** | N/A |
| | 43 | 795<br>(368-1719)<br>N=9 | 2193<br>(1104-4357)<br>N=10 | N/A |
| | 43 to 1 | 56<br>(15-214)<br>N=9 | 326<br>(99-1072)<br>N=10 | N/A |
| 3-8 years<br>GMT and 2-tailed 95% CI | | **N=27** | **N=25** | **N=13** |
| | 1 | 10<br>(7.43-15) | 11<br>(8.2-16) | 8.9<br>(5.8-13) |
| | 22 | 214<br>(120-380) | 334<br>(190-585) | 105<br>(52-213) |
| | 22 to 1 | 20<br>(11-38) | 29<br>(16-53) | 12<br>(5.6-25) |

Results for seroprotection and GMR (HI) according to seropositivity at baseline (< 1:10 or ≥ 1:10, respectively) are shown below for cohort 1.

## Seroprotection (HI)

Percentage of Subjects with HI Titer >= 1:40 by Baseline Positivity (<1:10 vs >=1:10) by Age Cohort - FAS

HI_H1N1_CALIFORNIA09
Age Group : COHORT 1(9-17 YRS) Seropositive at Baseline (>= 1:10)? : NO

| | | Vaccine Group | | |
|---|---|---|---|---|
| | | 3.75ug_50 | 7.5ug_100 | 15ug_0 |
| Day 1 | | | | |
| | Number | 0 | 0 | |
| | Percentage | 0% | 0% | |
| | 95% Conf Int | 0%-10% | 0%-10% | |
| | N | 34 | 34 | 0 |
| Day 22 | | | | |
| | Number | 32 | 31 | |
| | Percentage | 94% | 91% | |
| | 95% Conf Int | 80%-99% | 76%-98% | |
| | N | 34 | 34 | 0 |
| Day 43 | | | | |
| | Number | 5 | 6 | |
| | Percentage | 100% | 100% | |
| | 95% Conf Int | 48%-100% | 54%-100% | |
| | N | 5 | 6 | 0 |

Percentage of Subjects with HI Titer >= 1:40 by Baseline Positivity (<1:10 vs >=1:10) by Age Cohort - FAS

HI_H1N1_CALIFORNIA09
Age Group : COHORT 1(9-17 YRS) Seropositive at Baseline (>= 1:10)? : YES

| | | Vaccine Group | | |
|---|---|---|---|---|
| | | 3.75ug_50 | 7.5ug_100 | 15ug_0 |
| Day 1 | | | | |
| | Number | 7 | 9 | |
| | Percentage | 23% | 28% | |
| | 95% Conf Int | 10%-42% | 14%-47% | |
| | N | 30 | 32 | 0 |
| Day 22 | | | | |
| | Number | 29 | 32 | |
| | Percentage | 97% | 100% | |
| | 95% Conf Int | 83%-100% | 89%-100% | |
| | N | 30 | 32 | 0 |
| Day 43 | | | | |
| | Number | 4 | 4 | |
| | Percentage | 100% | 100% | |
| | 95% Conf Int | 40%-100% | 40%-100% | |
| | N | 4 | 4 | 0 |

**GMR (HI)**

Geometric Mean HI Titers by Baseline Positivity (<1:10 vs >=1:10) by Age Cohort - FAS

HI_H1N1_CALIFORNIA09
Age Group : COHORT 1(9-17 YRS) Seropositive at Baseline (>= 1:10)? : YES

| | Vaccine Group | | |
|---|---|---|---|
| | 3.75ug_50 | 7.5ug_100 | 15ug_0 |
| Day 1 | | | |
| GMT | 36 | 36 | |
| 95% Conf Int | 23-57 | 23-54 | |
| Median | 20 | 20 | |
| Min, Max | 10,1280 | 10,640 | |
| N | 30 | 32 | 0 |
| Day 22 | | | |
| GMT | 608 | 874 | |
| 95% Conf Int | 360-1029 | 536-1424 | |
| Median | 387 | 640 | |
| Min, Max | 20,5120 | 80,5120 | |
| N | 30 | 32 | 0 |
| Day 43 | | | |
| GMT | 1174 | 2347 | |
| 95% Conf Int | 277-4970 | 554-9939 | |
| Median | 1733 | 2560 | |
| Min, Max | 160,5120 | 905,5120 | |
| N | 4 | 4 | 0 |
| Day 22/Day 1 | | | |
| GMR | 17 | 24 | |
| 95% Conf Int | 9.47-30 | 14-42 | |
| Median | 14 | 16 | |
| Min, Max | 1,128 | 2.81,256 | |
| N | 30 | 32 | 0 |

Geometric Mean HI Titers by Baseline Positivity (<1:10 vs >=1:10) by Age Cohort - FAS

HI_H1N1_CALIFORNIA09
Age Group : COHORT 1(9-17 YRS) Seropositive at Baseline (>= 1:10)? : NO

| | Vaccine Group | | |
|---|---|---|---|
| | 3.75ug_50 | 7.5ug_100 | 15ug_0 |
| Day 1 | | | |
| GMT | 5.13 | 5.13 | |
| 95% Conf Int | 5.02-5.25 | 5.02-5.25 | |
| Median | 5 | 5 | |
| Min, Max | 5,7 | 5,7 | |
| N | 34 | 34 | 0 |
| Day 22 | | | |
| GMT | 390 | 405 | |
| 95% Conf Int | 218-699 | 229-717 | |
| Median | 320 | 547 | |
| Min, Max | 5,2560 | 5,5120 | |
| N | 34 | 34 | 0 |
| Day 43 | | | |
| GMT | 606 | 2129 | |
| 95% Conf Int | 320-1149 | 1228-3693 | |
| Median | 453 | 1920 | |
| Min, Max | 320,1280 | 1280,5120 | |
| N | 5 | 6 | 0 |
| Day 22/Day 1 | | | |
| GMR | 76 | 79 | |
| 95% Conf Int | 42-136 | 45-140 | |
| Median | 64 | 91 | |
| Min, Max | 1,512 | 1,1024 | |
| N | 34 | 34 | 0 |

The CHMP criteria were met with both formulations of the adjuvated vaccines. At day 22 GMRs are higher in subjects seronegative at baseline. Subjects seropositive at baseline show higher GMRs following the administration of the full dose of Focetria. However the clinical meaning of these observations is currently unclear.

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

**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 |
| | | N=33 | N=31 | N=0 | N=27 | N=27 | N=0 |
| COHORT 1 (9-17 YRS) | 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 | |

**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 | | |

**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 | | |

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.

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.

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

| Age Cohort | | Vaccine Group | | |
|---|---|---|---|---|
| | | **3.75ug_50** | **7.5ug_100** | **15ug_0** |
| 9-17 years | **Post 1st vaccination** | **N=93** | **N=93** | N/A |
| | Any | 51(55%) | 62(67%) | N/A |
| | Local | 45(48%) | 54(58%) | N/A |
| | Systemic | 27(29%) | 34(37%) | N/A |
| | Other | 4(4%) | 10(11%) | N/A |
| | **Post 2nd vaccination** | **N=79** | **N=82** | N/A |
| | Any | 32(41%) | 38(46%) | N/A |
| | Local | 27(34%) | 34(41%) | N/A |
| | Systemic | 17(22%) | 16(20%) | N/A |
| | Other | 6(8%) | 5(6%) | N/A |
| 3-8 years | **Post 1st vaccination** | **N=88** | **N=84** | **N=43** |
| | Any | 49(56%) | 48(57%) | 18(42%) |
| | Local | 33(38%) | 40(48%) | 14(33%) |
| | Systemic | 27(31%) | 26(31%) | 11(26%) |
| | Other | 9(10%) | 7(8%) | 4(9%) |
| | **Post 2nd vaccination** | **N=43** | **N=38** | **N=19** |
| | Any | 12(28%) | 16(42%) | 5(26%) |
| | Local | 11(26%) | 13(34%) | 5(26%) |
| | Systemic | 4(9%) | 6(16%) | 1(5%) |
| | Other | 1(2%) | 0 | 1(5%) |
| 12-35 months | **Post 1st vaccination** | **N=48** | **N=43** | **N=24** |
| | Any | 16(33%) | 20(47%) | 12(50%) |
| | Local | 15(31%) | 16(37%) | 9(38%) |
| | Systemic | 6(13%) | 15(35%) | 9(38%) |
| | Other | 4(8%) | 6(14%) | 4(17%) |
| | **Post 2nd vaccination** | **N=9** | **N=9** | **N=5** |
| | Any | 4(44%) | 3(33%) | 2(40%) |
| | Local | 2(22%) | 2(22%) | 2(40%) |
| | Systemic | 2(22%) | 2(22%) | 0 |
| | Other | 2(22%) | 0 | 0 |
| 6-11 months | **Post 1st vaccination** | **N=15** | **N=11** | N/A |
| | Any | 9(60%) | 4(36%) | N/A |
| | Local | 6(40%) | 3(27%) | N/A |
| | Systemic | 5(33%) | 2(18%) | N/A |
| | Other | 3(20%) | 3(27%) | N/A |
| | **Post 2nd vaccination** | **N=2** | **N=2** | N/A |
| | Any | 1(50%) | 1(50%) | N/A |
| | Local | 1(50%) | 1(50%) | N/A |
| | Systemic | 0 | 0 | N/A |
| | Other | 0 | 0 | N/A |

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).

| Vaccination | | Reaction | Vaccine Group | | |
|---|---|---|---|---|---|
| | | | 3.75ug_50 | 7.5ug_100 | 15ug_0 |
| Day 1 | | | **N=93** | **N=93** | **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 | 0 | 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 | 0 | 0 | N/A |
| | | Malaise | 0 | 1 (1%) | N/A |
| Day 22 | | | **N=79** | **N=82** | **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 | 0 | N/A |
| | Systemic Reaction | Fever≥40°C | 0 | 0 | N/A |
| | | Chills | 0 | 0 | N/A |
| | | Myalgia | 0 | 0 | N/A |
| | | Arthralgia | 0 | 0 | N/A |
| | | Nausea | 0 | 0 | N/A |
| | | Headache | 1 (1%) | 0 | N/A |
| | | Sweating | 0 | 0 | N/A |
| | | Fatigue | 1 (1%) | 0 | N/A |
| | | Malaise | 1 (1%) | 0 | N/A |

The preliminary data available showed that local reactions are frequently reported. After the first dose (where more observations are available) the rates ranged from 31% to 58%. Data also suggested that local reactions are slightly higher in the older children and in the groups receiving the full dose, although the figures do not allow a conclusion to be made. The use of reduced dose of vaccine seems to be associated with a slight reduction of local reactogenicity in subjects above 3 years of age. In younger subjects the difference is not observed. Reactogenicity at the second dose seemed lower compared to the first one, however data are too scarse, especially in the younger cohorts to allow conclusions in the reported events, such as fever. Body temperature will be reported with the threshold of ≥38-≥40 in the final report.

There was 1 subject in the group 3.75ug_50 (cohort 1) with a serious adverse event (mild appendicitis) reported at study day 21 and not considered related to study vaccine. The second vaccination was delayed for this subject.

The overview of subjects with unsolicited AEs is presented below.

| Age Cohort | | Vaccine Group | | |
|---|---|---|---|---|
| | | **3.75ug_50** | **7.5ug_100** | **15ug_0** |
| 9-17 years | | **N=86** | **N=86** | **N/A** |
| | Any AE | 17 | 23 | N/A |
| | At least possibly related AEs | 5 | 14 | N/A |
| | Any Serious AE | 1 | 0 | N/A |
| | AEs leading to discontinuation | 0 | 0 | N/A |
| 3-8 years | | **N=62** | **N=62** | **N=31** |
| | Any AE | 18 | 13 | 10 |
| | At least possibly related AEs | 3 | 1 | 0 |
| | Any Serious AE | 0 | 0 | 0 |
| | AEs leading to discontinuation | 0 | 0 | 0 |
| 12-35 mo | | **N=16** | **N=16** | **N=10** |
| | Any AE | 5 | 8 | 5 |
| | At least possibly related AEs | 1 | 2 | 1 |
| | Any Serious AE | 0 | 0 | 0 |
| | AEs leading to discontinuation | 0 | 0 | 0 |
| 6-11 mo | | **N=3** | **N=2** | **N/A** |
| | Any AE | 2 | 1 | N/A |
| | At least possibly related AEs | 1 | 0 | N/A |
| | Any Serious AE | 0 | 0 | N/A |
| | AEs leading to discontinuation | 1 | 0 | N/A |

**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. The committee noted that H1N1 data in adults after administration of one dose of Focetria, and also in children and adolescents aged 9-17 years suggest that a single dose may be sufficient. Immunogenicity data from younger cohorts is also reassuring and reaching CHMP criteria, although numbers are too small to allow any definitive conclusion at this point in time. This is in line with the evidence seen in adults. The posology section was therefore slightly reworded. 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 correction regarding subcutaneous (SC) use in section 4.4 of the SPC, labelling and PL was noted. No clinical data have been generated with the seasonal adjuvanted (Fluad) or pandemic adjuvanted (Focetria) vaccines with respect to the SC route of administration.
Adjuvanted vaccines are known to have a higher local reactogenicity than the unadjuvanted conventional vaccines and when Fluad was initially licensed in Italy in 1997 there was no contraindication for a SC injection. Such precaution was introduced during the mutual recognitition procedure in 2000 to reduce the theoretical risk of local reaction like e.g. pain or enduration which could be intensified if the injection is performed less deeply in the muscle.

Overall 27 reports of Fluad given SC were received between 1998 and 2009, an average of 1 to 5 reports per year:
1) 13 of these cases reported local adverse events, in most of them the size was not specified. In three of these 13 reports, the size of the local reaction was above 10 cm in diameter.
2) Two other cases showed no adverse events but were only reported because of the incorrect administration route (i.e. SC instead of the recommended IM).
3) 3 reports were a report of fever and other systemic reactions which in MAH view has nothing to do with the SC route.
4) 9 reports showed features like cardiac decompensation, Henoch-Schoenlein-Purpura and others which may have not been linked with the SC route of administration.
Based on the exposure of several million subjects these reports were not considered a concern.

**Overall discussion and benefit risk assessment**

Preliminary results from study V111_03 showed that the CHMP criteria were met, and in particular results were considered relevant for children and adolescents aged 9-17 years. In this cohort, 95% of subjects were seroprotected, with 92% seroconversion or significant increase and GMR of 43. The subgroup analyses by baseline serostatus were reassuring with seronegative subjects also reaching the CHMP criteria. Therefore the data presented are reassuring in the fact that the use of a single full dose of Focetria in subjects aged 9-17 years may be sufficient. This is in line with the results seen in adults. Study V111_03 is on-going and further results will provide indications about the effect of the second dose and its potential benefit.

The preliminary safety data after the first dose in children and adolescents 9-17 years of age suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation. Regarding reactogenicity, it is noted that local reactions are frequently reported. The use of reduced dose of vaccine seems to be associated with a slight reduction of local reactogenicity in subjects above 3 years of age. In younger subjects the difference is not present. Reactogenicity after the second dose seemed lower compared to the first one, but the numbers are too small to allow definitive conclusions. However, immunogenicity results of a second dose have not yet been completed and submitted. These data are awaited.

Data in the younger cohorts and with the half dose were still considered very scarse to propose a change in the posology, especially taking into account the results of the detailed subgroup analysis performed in adults.

Based on the evidence submitted by the MAH regarding the amendment of the information on the SC administration, the revision of the wording of the product information to allow an alternative route of administration to be considered in subjects with a blood disorder or under a therapy for which IM injection is contraindicated was agreed with.