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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Celvapan

pandemic influenza vaccine (H1N1) (whole virion, inactivated, prepared in cell culture)

Procedure No.: EMEA/H/C/000982/II/0019/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Scientific discussion

1.1. Introduction

Celvapan is a Vero cell derived, monovalent, whole virion, inactivated H1N1v vaccine. The application for a marketing authorization for Celvapan was supported by a core dossier for pandemic influenza vaccine and the scientific development was based on the guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) and the guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03). The European Commission issued a Marketing Authorisation (MA) under exceptional circumstances for Celvapan (EU/1/08 506/001, containing a non-circulating A/H5N1 strain) on 4 March 2009.

The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 06/10/2009 (EMEA/H/C/982/PU/02). Subsequently the MA was modified as regards the conditions of authorisation from exceptional to full marketing authorisation on 13/08/2010 (EMEA/H/C/982/SW/14). As a result the recommended indication was modified as follows: *Prophylaxis of influenza caused by A(H1N1) 2009 virus (see section 4.4 of the SmPC). Celvapan should be used in accordance with Official Guidance*.

This group of two variations II-19/G aimed at:

1. updating the SmPC sections 4.8 and 4.6 with the safety data obtained from the pandemic observational study 820901 (parts B and C) which was submitted via SOB 30. Supportive data available from the United Kingdom Terratology Information Service (UKTIS) (assessed in PSU051) and from the pandemic vaccination campaign in Jersey were also taken into consideration by the CHMP and were considered consistent with study 820901;
2. the results of the paediatric study 820903 also became available and warranted an update of sections 4.2, 4.8 and 5.1 of the SmPC with new data concerning antibody persistence at 6 and 12 months post-primary vaccination and safety and immunogenicity data post-booster in children and adolescents (stratified by age in four groups and randomised to receive either a full or a half dose of the pandemic H1N1 vaccine).

As a consequence some of the conditions identified in Annex II from the pandemic were fulfilled and this section of the PI was also updated accordingly. In addition the MAH took this opportunity to bring the PI in line with the latest QRD template version 8.1.

1.2. Clinical Efficacy aspects

1.2.1. Methods – analysis of data submitted

Study 820903 Part B and C (FU2 40.1, FU2 40.2)

Study 820903 was an open-label, randomized, multicentre study in healthy infants, children and adolescents aged 6 months to 17 years, which was conducted in Austria and Germany.

The study was designed to determine the preferred dose of the H1N1 pandemic influenza vaccine in a paediatric population, aged 6 months to 17 years, based upon assessment of immunogenicity and safety. Results of safety/reactogenicity and immunogenicity of two doses of 3.75 µg or 7.5 µg HA H1N1 vaccine, obtained for the period up to Day 43 (21 days after the second vaccination/Visit 5),

were presented in the CSR Part A, which was previously assessed (SOB 28 and consequent SO2; variations II-07 and II-13). Part B and C of the study were submitted in the context of FU2 40.1 and FU2 40.2 and cover the following evaluations:

- Antibody persistence measured by Haemagglutination inhibition assay (HI), Microneutralization assay (MN) and Single Radial Haemolysis assay (SRH) for the period up to Day 181 and for the period up to Day 360 following the first vaccination.
- Antibody response 21 days after the booster vaccination measured by HI, MN and SRH assays. Booster vaccination was given at Day 361 using a licensed trivalent seasonal influenza vaccine (Inflexal-V, containing the A/H1N1/California/07/2009 strain, for the season 2010/2011).
- 1-year safety follow-up.

A total of 400 healthy subjects, stratified into 4 age strata (9 to 17 years: Stratum A; 3 to 8 years: Stratum B; 12 to 35 months: Stratum C; 6 to 11 months: Stratum D, with each stratum consisting of approximately 100 subjects), were to be randomized at a ratio of 1:1 to receive two vaccinations of either 3.75 µg or 7.5 µg of H1N1 HA at a 21 day interval. The booster vaccination was to be administered to at least 30 subjects in each of the 4 age strata and only to those who received the 7.5 µg dose for the first and second vaccinations (N=110, as only 20 infants in Stratum D completed two vaccinations at the 7.5 µg dose). Children in Strata A and B received 0.5 ml of the booster vaccine INFLEXAL V, whereas those in Strata C and D received 0.25 ml of INFLEXAL V.

The Part A total vaccinated cohort included 339 subjects (101 in Stratum A, 100 in Stratum B, 100 in Stratum C, 38 in Stratum D) who completed the first and second vaccinations.

During study Part B, 314 subjects with evaluable HI assay results were included in the intent-to-treat (ITT) dataset for Day181. During study Part C, 330 subjects were included for safety follow up until Day 361. A total of 114 subjects received a booster vaccination and were included in the safety and ITT datasets for the booster vaccination.

Detailed disposition of subjects in each of the four age strata and in each dose level as well as the number of subjects receiving booster vaccination at Day 361/Visit 8 is depicted in Tables 10.1-1 and 10.1-2 below.

Table 10.1-1
Subjects included in the safety dataset of study 820903 Parts B and C

	Day 361		Booster vaccination*
	7.5 µg	3.75 µg	
Stratum A	51	50	30
Stratum B	51	49	34
Stratum C	49	51	34
Stratum D	20	15	16

*The booster vaccination was administered to a subset of subjects who had received the 7.5 µg dose vaccine.

Table 10.1-2. Subjects included in the intent-to-treat dataset of study 820903 Parts B and C			
	Day 181		Booster vaccination*
	7.5 µg	3.75 µg	
Stratum A	51	49	30
Stratum B	49	47	34
Stratum C	46	47	34
Stratum D	14	11	16

*The booster vaccination was administered to a subset of subjects who had received the 7.5 µg dose vaccine.

The demographics and baseline characteristics by dose remained largely unchanged throughout the study (when compared with Part A). At Day 361, the male/female distribution was 45.3% vs. 54.7% for the 3.75 µg dose group, and 56.7% vs. 43.3% for the 7.5 µg dose group. Most subjects were white (95.3% and 98.2% in 3.75 µg and 7.5 µg groups, respectively). There was no significant difference in demographic parameters (age/years, weight and height) between the 3.75 µg and 7.5 µg dose groups. Among subjects who received booster vaccination, males slightly outnumbered females (57.9% vs. 42.1%) and 98.2% of the total were white.

1.2.2. Results

Antibody persistence data from study 820903

Antibody persistence was assessed using blood samples at Day 181 (Month 6) and Day 361 (pre-booster, Month 12) using HI and MN assays. In most age groups and both dose groups, the sero-protection rate (SPR) and sero-conversion rate (SCR), geometric mean titres (GMTs) and geometric means (GMs) of fold increase in antibody titres were in general stable between Day 43 and Day 181. In both dose groups at Day 181, all CHMP criteria for immunogenicity, as defined in adults for seasonal influenza vaccines (Note for guidance on harmonisation of requirements for influenza vaccines - CPMP/BWP/214/96), were still met and the differences between age and dose groups were minimal, with slightly lower levels in the youngest age group. As expected, the SPR and SCR, GMTs and GMs of fold increase decreased in all age strata between Day 181 and Day 361 prior to booster vaccine administration. The pre-booster immunogenicity measurements (day 361) were only taken from the group vaccinated with the 7.5 µg HA dose. Tables 1, 2 and 3 display the antibody persistence data for the 7.5µg vaccine group, which corresponds to the formulation currently licensed for Celvapan H1N1.

Table 1. HI Results obtained for Parts B and C of the study 820903 (CI: 95% confidential intervals; FI: fold-increase)

		7.5 µg group		
		D43	D181*	D361**
Stratum A 9 - 17 years	SPR %	100, CI: 93, 100	100, CI: 93, 100	90.0, CI: 73.5, 97.9
	SCR %	98.0, CI: 89.6, 100	94.1, CI: 83.8, 98.8	80.0, CI: 61.4, 92.3
	GMTs	210.0 CI: 169.6, 260.0	212.8 CI: 170.0, 266.4	124.1 CI: 76.9, 200.2
	GM-FI	14.2, CI: 10.9, 18.3	15.2, CI: 11.7, 19.6	8.7, CI: 5.5, 13.7
Stratum B 3 – 8 years	SPR %	100, CI: 93.0, 100	98, CI: 89.1, 99.9	66.7, CI: 48.2, 82.0
	SCR %	96.1, CI: 86.5, 99.5	93.9, CI: 83.1, 98.7	60.6, CI: 42.1, 77.1

	GMTs	196.2 CI: 155.6, 247.3	119.7 CI: 98.5, 145.5	44.0 CI: 29.3, 66.0
	GM-FI	15.6, CI: 11.7, 20.8	9.3, CI: 7.5, 11.7	3.9, CI: 2.6, 5.9
Stratum C 12 – 35 months	SPR %	93.9, CI: 83.1, 98.7	100, CI: 92.3, 100	64.5, CI: 45.4, 80.8
	SCR %	91.8, CI: 80.4, 97.7	97.8, CI: 88.5, 99.9	61.3, CI: 42.2, 78.2
	GMTs	118.9 CI: 89.8, 157.4	115.7 CI: 92.3, 145.1	48.9 CI: 31.4, 76.1
	GM-FI	16.0, CI: 11.6, 22.0	11.4, CI: 8.9, 14.6	4.9, CI: 3.1, 7.7
Stratum D 6 – 11 months	SPR %	84.2, CI: 60.4, 96.6	85.7, CI: 57.2, 98.2	50.0, CI: 21.1, 78.9
	SCR %	78.9, CI: 54.4, 93.9	85.7, CI: 57.2, 98.2	50.0, CI: 21.1, 78.9
	GMTs	99.6 CI: 58.3, 170.0	65.6 CI: 39.5, 109.0	33.6 CI: 17.0, 66.4
	GM-FI	11.1, CI: 6.0, 20.7	7.4, CI: 4.4, 12.7	3.8, CI: 1.9, 7.8

* Day 181 data were from subjects included in the ITT dataset
** Day 361 data were from subjects included in the ITT dataset for the booster vaccination

Table 2. MN Results obtained for Parts B and C of the study 820903 (CI: 95% confidential intervals; FI: fold-increase; SNR: seroneutralization rate)

		7.5 µg group		
		D43	D181*	D361**
Stratum A 9 – 17 years	SNR %	100, CI: 93.0, 100	100, CI: 92.5, 100	88.9, CI: 70.8, 97.6
	SCR %	100, CI: 93.0, 100	100, CI: 92.5, 100	96.3, CI: 81.0, 99.9
	GMTs	851.4 CI: 685.6, 1140.4	520.6 CI: 358.0, 757.2	229.2 CI: 128.2, 409.8
	GM-FI	115.6,CI:87.4, 152.8	66.4, CI: 47.4, 93.1	26.7, CI: 16.6, 43.1
Stratum B 3 – 8 years	SNR %	100, CI: 93.0, 100	100, CI: 92.5, 100	100, CI: 88.8, 100
	SCR %	100, CI: 93.0, 100	100, CI: 92.5, 100	96.8, CI: 83.3, 99.9
	GMTs	880.8 CI: 683.7, 1134.8	379.1 CI: 301.4, 476.9	149.6 CI: 108.4, 206.5
	GM-FI	156.9,CI:119.4,206.2	59.5, CI: 45.1, 78.3	26.5, CI: 18.5, 37.9
Stratum C 12 – 35 months	SNR %	100.0, CI: 92.7, 100	100, CI: 92.5, 100	90.3, CI: 74.2, 98.0
	SCR %	100, CI: 92.7, 100	100, CI: 92.5, 100	93.5, CI: 78.6, 99.2
	GMTs	547.8 CI: 385.0, 779.3	250.9 CI: 189.8, 331.6	117.0 CI: 76.3, 179.3
	GM-FI	108, CI: 75.5, 154.5	40.2, CI: 29.2, 55.4	18.3, CI: 11.2, 29.8
Stratum D 6 – 11 months	SNR %	100, CI: 82.4, 100	100, CI: 75.3, 100	81.8, CI: 48.2, 97.7
	SCR %	100, CI: 82.4, 100	100, CI: 75.3, 100	100, CI: 71.5, 100
	GMTs	303.0 CI: 139.4, 658.3	104.4 CI: 72.6, 150.3	96.6 CI: 39.1, 238.7
	GM-FI			

		60.6, CI: 27.9, 131.7	19.3, CI: 13.8, 27.0	17.6, CI: 7.1, 43.4

* Day 181 data were from subjects included in the ITT dataset
** Day 361 data were from subjects included in the ITT dataset for the booster vaccination

Table 3. SRH Results obtained for Parts B and C of the study 820903 (CI: 95% confidential intervals; FI: fold-increase)

		7.5 µg group		
		D43	D181*	D361**
Stratum A 9 – 17 years	SPR %	88.0, CI: 75.7, 95.5	98.0, CI: 89.4, 99.9	96.6, CI: 82.2, 99.9
	SCR %	84.0, CI: 70.9, 92.8	92.0, CI: 80.8, 97.8	93.1, CI: 77.2, 99.2
	GMTs	52.9 CI: 41.7, 66.9	53.3 CI: 48.1, 59.2	47.9 CI: 41.0, 56.1
	GM-FI	8.9, CI: 6.6, 11.9	7.8, CI: 6.2, 9.9	6.5, CI: 4.7, 9.0
Stratum B 3 – 8 years	SPR %	88.2, CI: 76.1, 95.6	79.6, CI: 65.7, 89.8	54.5, CI: 36.4, 71.9
	SCR %	88.2, CI: 76.1, 95.6	77.6, CI: 63.4, 88.2	57.6, CI: 39.2, 74.5
	GMTs	51.1 CI: 42.4, 61.5	34.5 CI: 29.6, 40.2	24.5 CI: 19.3, 31.1
	GM-FI	8.6, CI: 6.6, 11.3	5.6, CI: 4.5, 7.1	4.5, CI: 3.4, 6.1
Stratum C 12 – 35 months	SPR %	95.9, CI: 86.0, 99.5	68.1, CI: 52.9, 80.9	48.4, CI: 30.2, 66.9
	SCR %	91.8, CI: 80.4, 97.7	63.8, CI: 48.5, 77.3	45.2, CI: 27.3, 64.0
	GMTs	53.9 CI: 46.9, 61.9	27.8 CI: 22.9, 33.8	19.2 CI: 14.0, 26.2
	GM-FI	11.2, CI: 9.3, 13.4	5.7, CI: 4.7, 7.0	4.1, CI: 3.0, 5.5
Stratum D 6 – 11 months	SPR %	78.9, CI: 54.4, 93.9	37.5, CI: 15.2, 64.6	30.8, CI: 9.1, 61.4
	SCR %	84.2, CI: 60.4, 96.6	37.5, CI: 15.2, 64.6	30.8, CI: 9.1, 61.4
	GMTs	37.5 CI: 25.2, 55.8	15.3 CI: 9.8, 23.9	14.5 CI: 8.0, 26.4
	GM-FI	7.6, CI: 4.9, 11.7	2.9, CI: 2.0, 4.4	2.6, CI: 1.5, 4.5

* Day 181 data were from subjects included in the ITT dataset
** Day 361 data were from subjects included in the ITT dataset for the booster vaccination

A repeated mixed model ANCOVA demonstrated that HI titres were significantly affected by age, time, logarithmic titre at baseline and dose/time interaction. Notably, there was no significant difference in adjusted means of HI titres between the 3.75 µg and 7.5 µg dose groups on Day 181.

Post-booster data from study 820903

21-28 days post-booster (Day 382-389), SPR/SNR against the H1N1 strain was 100.0% and SCR was 100.0% compared to baseline whereas slightly lower rates were observed when compared to pre-booster on Day 361 in all age groups as measured by HI and MN. Antibody response measured by SRH assay (especially in GMTs and GM-FI parameters) was lower but generally consistent with the HI and MN results (as shown in table 4).

Table 4. HI, MN and SRH Results obtained for Parts B and C of the study 820903 (CI: 95% confidential intervals; FI: fold-increase)

		Subjects included in ITT dataset for the booster vaccination (**7.5**µg dose level)					
		HI		**MN**		**SRH**	
		Pre-booster*	Post-booster**	Pre-booster*	Post-booster**	Pre-booster*	Post-booster**
Stratum A 9 – 17 years	SPR % or SNR %	90.0, CI: 73.5, 97.9	100, CI: 88.4, 100	88.9, CI: 70.8, 97.6	100, CI: 87.2, 100	86.6, CI: 82.2, 99.9	100, CI: 88.1, 100
	SCR %	80.0, CI: 61.4, 92.3	100, CI: 88.4, 100 (73.3,CI: 54.1, 87.7)	96.3, CI: 81.0, 99.9	100, CI: 87.2, 100 (93.1, CI: 77.2, 99.2)	93.1, CI: 77.2, 99.2	100, CI: 88.1, 100 (40, CI: 22.7, 59.4)
	GMTs	124.1 CI: 76.9, 200.2	752.4 CI: 573.6, 986.9	229.2 CI: 128.2, 409.8	2986.3 CI: 1881.3, 4730.4	47.9 CI: 41.0, 56.1	70.8 CI: 64.9, 77.2
	GM-FI	8.7, CI: 5.5, 13.7	52.6, CI: 37.1, 74.5 (6.1, CI: 4.1, 9.0)	26.7, CI: 16.6, 43.1	3484, CI:1242.7,500 (13.7, CI: 9.4, 20.0)	6.5, CI: 4.7, 9.0	9.6, CI: 7.1, 12.9 (1.5, CI: 1.3, 1.7)
Stratum B 3 – 8 years	SPR % or SNR %	66.7, CI: 48.2, 82.0	100, CI: 89.4, 100	100, CI: 88.8, 100	100, CI: 88.8, 100	54.5, CI: 36.4, 71.9	100, CI: 89.4, 100
	SCR %	60.6, CI: 42.1, 77.1	100, CI: 89.4, 100 (94.1,CI:80.3,99.3)	96.8, CI: 83.3, 99.9	100, CI: 88.8, 100 (100, CI: 89.7, 100)	57.6, CI: 39.2, 74.5	97.0, CI: 84.2, 99.9 (85.3, CI: 68.9, 95)
	GMTs	44.0 CI: 29.3, 66.0	886.3 CI: 681.7, 1152.2	149.6 CI: 108.4, 206.5	4477.2 CI: 2992.4, 6698.6	24.5 CI: 19.3, 31.1	67.7 CI: 61.6, 74.5
	GM-FI	3.9, CI: 2.6, 5.9	78.1, CI: 57.6, 105.9 (18.8, CI:12.7, 27.9)	16.5, CI: 18.5, 37.9	791.8,CI:513.6,1221 (29.8, CI: 20.1, 44.1)	4.5, CI: 3.4, 6.1	12.6, CI: 9.9, 15.6 (2.7, CI: 2.2, 3.4)
Stratum C 12 – 35 months	SPR % or SNR %	64.5, CI: 45.4, 80.8	100, CI: 88.8, 100	90.3, CI: 74.2, 98.0	100, CI: 88.1, 100	48.4, CI: 30.2, 66.9	100, CI: 88.8, 100
	SCR %	61.3, CI: 42.2, 78.2	100, CI: 88.8, 100 (93.5,CI: 78.6, 99.2)	93.5, CI: 78.6, 99.2	100, CI: 88.1, 100 (96.6, CI: 82.2, 99.9)	45.2, CI: 27.3, 64.0	100, CI: 88.8, 100 (87.1, CI:70.2, 96.4)
	GMTs	48.9 CI: 31.4, 76.1	818.5 CI: 613.4, 1092.0	117.0 CI: 76.3, 179.3	4331.2 CI: 2922.8, 6418.3	19.2 CI: 14.0, 26.2	68.3 CI: 61.6, 75.9
	GM-FI	4.9, CI: 3.1, 7.7	21.8, CI: 58.7, 114.1 (16.7, CI:11.1, 25.1)	18.3, CI: 11.2, 29.8	666,CI:426.1,1041 (38.7, CI: 23.9, 62.7)	4.1, CI: 3.0, 5.5	14.5, CI: 12.4, 16.9 (3.6, CI: 2.8, 4.6)
Stratum D 6 – 11 months	SPR % or SNR %	50.0, CI: 21.1, 78.9	100, CI: 73.5, 100	81.8, CI: 48.2, 97.7	100, CI: 66.4, 100	30.8, CI: 9.1, 61.4	100, CI: 71.5, 100
	SCR %	50.0, CI: 21.1, 78.9	100, CI: 73.5, 100 (92.3,CI: 64.0,99.8)	100, CI: 71.5, 100	100, CI: 66.4, 100 (100, CI: 71.5, 100)	30.8, CI: 9.1, 61.4	100, CI: 71.5, 100 (90.9, CI: 58.7,99.8)
	GMTs	33.6 CI: 17.0, 66.4	640.0 CI: 333.9, 1226.6	96.6 CI: 39.1, 238.7	4063.7 CI: 1322.8, 12484.3	14.5 CI: 8.0, 26.4	70.5 CI: 56.7, 87.8
	GM-FI	3.9, CI: 1.9, 7.8	73.9, CI: 39.3, 139.3 (15.2, CI: 6.6, 34.7)	17.6, CI: 7.1, 43.4	752.5,CI:244.1,2320 (29.1, CI: 11.6, 73.1)	2.6, CI: 1.5, 4.5	13.3, CI: 8.0, 22.1 (4.9, CI: 2.7, 8.9)

*pre-booster: Day361, ** post-booster: Day 382-389. Values in () represent SCR or GM-FI data as compared to pre-booster values.

1.2.1. Discussion

The antibody persistence profile for Celvapan H1N1 was shown to be largely stable up to D181 after the first vaccination, as compared with the data at Day 43. The HI and MN results demonstrated the persistence of high titres against the vaccine strain A/H1N1/California/07/2009 up to 360 days after the first vaccination in all age strata and dose groups, with minimal differences between the 3.75 and 7.5 µg HA formulations.

The booster response data presented in this variation have shown that priming with two doses of 7.5 µg HA antigen of H1N1 pandemic influenza vaccine was robust and capable of inducing immunologic memory resulting in a high booster response to the A/H1N1/California/07/2009 strain of the seasonal trivalent influenza vaccine administered approximately one year after the first vaccination.

1.3. Clinical Safety aspects

1.3.1. Methods – analysis of data submitted

Observational safety study 820901

In the framework of SOB030 the MAH provided the final report of the observational study 820901 to assess the safety of two vaccinations of a Vero cell-derived, whole virus H1N1 pandemic influenza vaccine (Celvapan; ref. to SO2 30.6). This study was conducted as part of the risk management plan (RMP). The primary objective of this prospective, multicentre, non-interventional study was to estimate the incidence of any medically-attended adverse events in all vaccinated subjects.

The secondary objectives of this study were:

- To investigate the incidence of injection site and systemic reactions to vaccination in a subset of the cohort;
- To estimate the incidence of serious adverse events (SAEs) and adverse events of special interest (AESI) following an active surveillance of all vaccinated subjects;
- To survey pregnancy outcomes in vaccinated pregnant women and in women who become pregnant after vaccination.

The study was conducted in Austria. Subjects were to be enrolled and vaccinated according to national policy and standard. Contacts were made approximately at 4 to 6 weeks and 6 months after the second vaccination for follow-up on any medically-attended adverse events (AEs), SAEs, AESI, and/or pregnancies. If any clinically relevant event that was not previously recorded was reported during a contact, a follow-up consultation was to be made to collect the relevant medical data. Subjects and/or parent(s)/legal guardian(s) of subjects in the subgroup for evaluation of injection site and systemic reactions were given a diary card for documentation of specifically queried symptoms following each vaccination. The diary cards were to be returned after the 7-day post-vaccination observation period.

- Safety analysis set

A total of 3,216 (100%) subjects enrolled in the study had been vaccinated with H1N1 vaccine at least once; 3,039 (94.5%) subjects had received two vaccinations. A total of 1,948 (60.6%) subjects entered the study at the time of their second vaccination. Most subjects (3,023; 94.0%) had received the H1N1 pandemic influenza vaccine containing 7.5 µg HA antigen for both vaccinations; 11 (0.3%) subjects had received two 3.75 µg doses; 3 (0.1%) subjects had received 3.75 µg followed by 7.5 µg,

and 2 (0.1%) subjects had received 7.5 µg followed by 3.75 µg. Subjects who had received 3.75 µg HA antigen were aged between 2 months and 8 years. A total of 277 (8.6%) subjects were withdrawn prematurely from the study mainly due to being lost to follow-up (N=231; 7.2%); six subjects died during the study. Male and female subjects were enrolled to a similar extent (1599:1617) and subjects' median age in the safety analysis set was 36.0 years (range: 0.2 to 92.0 years), with the largest percentage (35.4%) of subjects aged 18 to 44 years.

- Analysis set for assessment of commonly observed adverse reactions (injection site and systemic) after the first and second vaccination

A total of 648 and 583 subjects were included in the analysis set for assessment of commonly observed ADRs after the first and second vaccination, with a median age of 27.0 and 28.0 years, respectively, and slightly more female than male subjects.

- 4- to 6-week contact analysis set

A total of 3,028 subjects who received the first vaccination with a 7.5 µg vaccine dose had a follow-up contact approximately 4 to 6 weeks thereafter.

- 6-month contact analysis set

A total of 2,939 subjects received the first vaccination and had a follow-up contact approximately 6 months after the first or second vaccination had been performed.

1.3.2. Results

Adverse Events (AEs) - Study 820901

- Deaths

Six deaths occurred during this study, of which four (depression, urothelial cancer, myocardial infarction, pneumonia and sepsis) were considered unrelated to the vaccination, one was considered "unlikely related" (Miliar TB), and one (hepatitis C) was un-assessable according to the MAH and was judged unrelated by the CHMP, as Hepatitis C is not associated with influenza vaccination.

- SAEs

A total of 11 subjects experienced 14 SAEs after the first vaccination and 89 subjects experienced 104 SAEs after the second vaccination (among subjects who received the first and second vaccination, respectively). Two vaccine-related SAEs were reported after the first vaccination (transverse myelitis and febrile convulsion) and four (rash; premature rupture of membranes and caesarean section; febrile convulsion) were reported after the second vaccination. In two subjects, the causality of SAEs after the second vaccination was unknown (details on the nature of the SAEs were not disclosed by the subjects).

- AESIs (adverse events of special interest)

The overall incidence of subjects with medically confirmed non-serious and serious AESIs after the first (n=1; n=3) and second (n=1; n=2) vaccinations, respectively, were very low. Two cases of H1N1 influenza infection were reported (considered AESIs): one was a suspected case 6 days after vaccination in a 13-year old male who received only a single H1N1 vaccination, and the other was a confirmed vaccination failure which was reported > 4 weeks after the second vaccination, administered 4 weeks after the first vaccination in a 35-year old female. Other AESIs after the first vaccination included: a case of epilepsy in a 48 year old male; a case of transverse myelitis, also reported as an SAE; and a case of febrile convulsion in a 9-year old, also reported as an SAE. After the second

vaccination, other AESIs included: febrile convulsions in a 3-year old (also included as a SAE) and in a 12 month-old.

Based on the narratives presented by the MAH, the case of transverse myelitis reflects most likely a para-infectious AE not related to vaccination and both described febrile convulsions (3 and 9 year old children) are most likely related to an infection. The febrile convulsion in the 12 months old child was considered unrelated by the investigator as well as the case of epilepsy 33 days post dose 1 in a 48-year-old-male.

- AEs related to pregnancy

See the paragraph 'Post-marketing data on pregnancy'.

- AEs within 4 weeks after vaccination

The incidence of medically-attended AEs reported within 4 weeks after first and second vaccination was low (2.7% and 3.8%, respectively). Children in the 2- to 23-month age stratum reported highest incidence (6.7% and 13.0%) of medically-attended AEs after the first and second vaccination. The incidence of related medically-attended AEs across all age strata was low and similar (0.4% and 0.5%) after the first and second vaccinations.

Within 4 weeks after the first and second vaccination, 23 and 22 subjects respectively experienced medically-attended fever (pyrexia) across all age strata. Of these, 6 and 4 subjects, respectively, had events of pyrexia that were considered related to vaccination. The incidence of fever was highest (2.6%) in subjects from the 2- to 8-year age stratum after the first vaccination and 3.0% in the 2- to 23-month age stratum after the second vaccination.

- Non-serious systemic reactions from the analysis set

The highest rates of fever among subjects included in the analysis set for commonly observed adverse reactions within 7 days after the first vaccination were in the 2-8 years old age group (9.2%; n/N= 13/141) and the 2-23 month age group (6.8%; 4/59). Very few cases of fever were observed in adults, with those 61 years and older experiencing no fever (0/72). After the second vaccination, fever rates were similar, with 4.1% of 2-8 year olds affected, and 7.5% of 2-23 month olds. No cases of fever within 7 days after the second vaccination were observed in adults over age 18. After the first and second vaccinations, severe fever (39.0 °C – 40.0 °C) was reported in 10 and 2 (1.5% and 0.3%) subjects, moderate in 7 and 1 (1.1% and 0.2%) subjects and mild in 5 and 6 (0.8% and 1.0%) subjects, respectively. Fever > 40.0 °C was reported by 2 and 1 (0.3% and 0.2%) subjects after the first and second vaccination.

Headache, fatigue, muscle pain and joint pain were the most common non-serious systemic reactions after the first and second vaccinations in subjects aged 5 years and older, which were all mild or moderate. In children aged 2 months to 4 years, irritability drowsiness and loss of appetite were the most common non-serious symptoms occurring within 7 days after the first vaccination and drowsiness, loss of appetite and vomiting were most common after the second vaccination.

- Non-serious injection reactions

Overall 18.2% and 13.0% of subjects reported non-serious injection site reactions within 7 days after the first and second vaccination, respectively.

The highest incidence of injection site reactions after first vaccination was reported by subjects in the 9 to 17 years age stratum (26.9%) and the lowest (2.8%) incidence was reported in subjects 61 years and older. Concerning the other age strata, the incidence of injection site reactions was 16.9%,

17.0%, 22.2% and 17.4% in the 2 to 23 months, 2 to 8 years, 18 to 44 years and 45 to 60 years age strata respectively.

The highest incidence of injection site reactions after second vaccination was reported by subjects in the 18 to 44 years age stratum (19.0%) and the lowest (3.1%) incidence was reported in subjects 61 years and older. Concerning the other age strata, the incidence of injection site reactions was 3.8%, 13.8%, 14.3% and 13.4% in 2 to 23 months, 2 to 8 years, 9 to 17 years, and 45 to 60 years age strata respectively.

Injection site pain was the most common specifically queried symptom of non-serious injection site reactions after first and second vaccination and reported by 17.9% and 13.0% of subjects, respectively.

Adverse events - Study 820903

- Unsolicited AEs

Between Day 43 and Day 361, unsolicited AEs were reported at a similar rate in the 3.75µg and 7.5µg dose group: 76.0% and 84.3% in Stratum A, 85.7% and 80.4% in Stratum B, 94.1% and 89.8% in Stratum C and 86.7% and 75.0% in Stratum D. No vaccine-related unsolicited AEs (excluding fever) occurred between Day 43 and Day 361.

For the 3.75 µg dose group, the most frequently reported unsolicited AEs were sinusitis (24%) in Stratum A; tracheitis (26.5%) and acute tonsillitis (24.5%) in Stratum B; otitis media (33.3%) and tracheitis (27.5%) in Stratum C, influenza-like illness (20%), bronchitis (20%), rhinitis (20%) and tracheitis (20%) in Stratum D.

For the 7.5 µg dose group, the most frequently reported unsolicited AEs were sinusitis (21.6%) and acute tonsillitis (17.6%) in Stratum A, acute tonsillitis (27.5%) in Stratum B, otitis media (34.7%), acute tonsillitis (24.5%), bronchitis (22.4%), gastroenteritis (20.4%) and cough (20.4%) in Stratum C, dermatitis diaper (25%), bronchitis (25%) and pharyngitis (20%) in Stratum D.

- Deaths and SAEs

No deaths and no vaccine-related SAEs occurred between Day 43 and Day 361 of this study. A total of 27 unrelated SAEs in 22 subjects were reported.

- Systemic reactions

Within 7 days after the booster vaccination, the majority of subjects experienced no systemic reactions (excluding fever). Rates of non-serious systemic reactions were 6.7% (N=2), 2.9% (N=1), 0.0% and 18.8% (N=3) in Strata A, B, C and D, respectively. No severe systemic reactions occurred. Headache was the most common specifically queried symptom of systemic reactions, occurring in two (6.7%) subjects in Stratum A, followed by fatigue and vomiting in one subject each (2.9%) in Stratum B. No subject in Stratum C experienced symptoms of systemic reactions. Inconsolable or excessive crying and disturbed sleep were the most frequently reported symptoms in Stratum D, each in two subjects (12.5%).

Fever with onset within 7 days after the booster vaccination and considered related to the booster occurred in two subjects each (5.9%) in Strata B and C, and three subjects (18.8%) in Stratum D (none in Stratum A). After the booster vaccination, the vast majority of subjects were determined to have normal body temperatures. Malaise, shivering and irritability were reported at lower rates: Shivering within 7 days after and related to the booster vaccination was reported in one subject in Stratum D. No subject in any strata experienced related malaise within 7 days after booster

vaccination. Only one subject in Stratum D experienced irritability within 7 days after and related to the booster vaccination.

- Injection site reactions

Within 7 days after the booster vaccination, non-serious injection site reaction rates were 13.3% in Stratum A, 8.8% in Stratum B, 11.8% in Stratum C and 6.3% in Stratum D. Most injection site reactions were mild and moderate; one severe case of injection site redness was reported in Stratum A. The most common specifically reported symptoms of local reactions were: injection site pain (5.9-13.3% in Strata A, B, C and D) and injection site induration (5.9-8.8% in Strata B and C). Injection site induration and swelling were not reported for subjects in Stratum A and Stratum D.

Post-marketing data on pregnancy

Pregnancy reports from the pandemic observational study 820901, the pregnancy registry set up by the United Kingdom Teratology Information Service (UKTIS) and national vaccination campaigns were previously submitted and assessed in the PSURs covering the period from October 2009 to October 2011.

Of 33 pregnancies in study 820901, 26 women delivered a child with normal foetal/neonatal status; one female had a child with an unspecified disorder, which was prematurely delivered (30 weeks) by caesarean section (reported as a related SAE). No specification of pregnancy outcome was available for the remaining 6 women. Serious AEs in pregnant women included premature labor (19 days after first vaccination), caesarean section, pulmonary embolism, pregnancy complications (induced labor in one subject 3 weeks prior to due date because foetal heartbeat was not clearly audible – healthy infant) and gastroenteritis, all of which were judged unrelated to vaccination.

The UKTIS conducted a study on Influenza A/H1N1 vaccination during pregnancy. Out of 2307 pregnant women, 10 were vaccinated at least once with Celvapan. Only eight pregnancy outcomes were provided for the Celvapan-vaccinated group, all of which were live births with no congenital abnormalities.

In addition, during the pandemic vaccination campaign in Jersey over 40% of pregnant and post-partum women (total population pregnant or post-partum: 1973 individuals) were vaccinated with Celvapan. No safety signals were reported.

1.3.3. Discussion

Based on the safety data from the paediatric study 820903, booster vaccination was safe and well tolerated, and there was no new safety concern between Day 43 and Day 361 after the priming vaccination.

With regard to the pandemic observational study 820901, safety analysis from a total of 3,216 subjects aged 2 months to 92 years were provided in the final study report. The data confirmed that a two-dose vaccination regimen, with Celvapan H1N1 containing 7.5µg antigen strain A/H1N1/California/07/2009 was well tolerated across all age strata. Low systemic and local reaction rates after both vaccinations were reported and the safety follow-up raised no specific safety concern until 6 months after the second vaccination.

Incidence of fever in the analysis group of commonly observed reactions was low within the 7 days observational window after the first and second vaccination. The rate of fever was highest in subjects aged 2 to 8 years after the first vaccination, and in subjects aged 2 to 23 months after the second vaccination. Fever rates in adults were comparable to those observed in the H1N1 clinical study

820902; instead they were slightly higher in children aged 9 to 17 years and lower in children aged 2 months to 8 years as compared to the paediatric study 820903.

In study 820901 a total of 648 and 583 subjects were included in the analysis set for assessment of commonly observed adverse reactions after the first and second vaccination. As compared to the clinical study in children aged 6 months to 17 years (study 820903), a higher frequency of systemic reactions, i.e. irritability, crying, drowsiness and loss of appetite in children up to 5 years of age, and headache, fatigue and muscle pain in children 6 to 17 years of age, was reported in the commonly observed adverse reactions subset. Similar results were seen for adults aged 18 years and older, with systemic reactions higher in study 820901 in comparison to the clinical study 820902 in adults above 18 years of age. These observations can be partially explained by the inclusion of events with non-assessable causality as "related" events, and also by differences in the recruitment strategy between the observational and the clinical studies. Whereas no specific exclusion criteria except the contraindications to vaccination as specified in the SmPC has been applied for recruitment to the observational study 820901, subjects who were not considered healthy at the time of vaccination were strictly excluded from participation to the clinical study.

Overall, considering the safety data available from observational study 820901 and from the paediatric study 820903, the safety profile of Celvapan remains unchanged. The use of Celvapan H1N1 during pregnancy does not raise any safety concern, although the data available is limited. The product information was updated taking into account these latest results.

1.4. Changes to the Product Information

The MAH proposed the following changes (additions: italic, deletion: strikethrough) to the PI, to which the CHMP agreed:

- **SmPC section 4.2 (Posology)**

Children aged 6 to 35 months
~~Limited data are available in infants and young children aged 6 months to 35 months. If vaccination is considered necessary, the dosing should be in accordance with the recommendations given for children 3to 17 years of age.~~
One dose of 0.5 ml at an elected date.
A second dose of vaccine should be given after an interval of at least three weeks.

- **SmPC section 4.6 (Pregnancy and Lactation)**

*Fertility, p*regnancy and lactation

~~There are currently no data available on the use of Celvapan in pregnancy.~~ *The safety of Celvapan in pregnancy and lactation has been assessed in a limited number of pregnant women.*

Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity.

Animal *reproductive and developmental toxicity* studies with H5N1 strain vaccines (A/Vietnam/1203/2004 and A/Indonesia/05/2005) do not indicate *direct or indirect harmful effects with respect to female fertility, pregnancy, embryonal/foetal development, parturition or post-natal development* ~~reproductive toxicity~~ (see section 5.3).

The use of Celvapan may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Celvapan may be used in lactating women.

- **SmPC section 4.8 (Undesirable effects)**

Post-marketing surveillance

Pandemic Observational Study with Celvapan (H1N1)v
~~Preliminary results from the pandemic observational study with Celvapan (H1N1)v confirmed the safety profile as observed in the clinical studies.~~
In an observational safety study including 3216 subjects aged 6 months to 60 years and older, the nature of adverse events was consistent with those observed in other clinical studies in adults and children. The following adverse reactions were reported at a higher frequency category than in the other clinical studies:

Adults aged 18 years and older:
Very common: Injection site pain, injection site redness, muscle pain
Uncommon: influenza like illness

Children and adolescents aged 5 to 17 years:
Very common: fatigue, headache
Uncommon: cough

Children aged 6 months to 5 years:
Very common: Injection site redness, drowsiness, irritability, loss of appetite, crying

~~Preliminary safety data from 425 children (above 5 years of age), adolescents and adults showed that within 7 days after the first vaccination 37. 9% of subjects reported systemic reactions and 25.4% reported injection site reactions.~~

~~In 91 children aged 6 months to 5 years systemic reactions were reported after the first vaccination in 35.2% and injection site reactions occurred in 23.1% of subjects.~~
~~After the second dose adverse reactions occurred at a lower frequency.~~

~~Very common reactions reported in adults:~~
~~Injection site reactions, fatigue, headache, muscle pain, joint pain, gastrointestinal symptoms, increased sweating.~~

~~Very common reactions reported in children above 5 years of age and adolescents:~~
~~Injection site reactions, fatigue, headache, muscle pain, gastrointestinal symptoms~~

~~Very common reactions reported in children aged 6 months to 5 years:~~
~~Injection site reactions, drowsiness, irritability, loss of appetite, diarrhea~~

- **SmPC section 5.1 (Pharmacodynamic properties)**

Safety and immunogenicity data obtained three weeks after administration of two doses of Celvapan (H1N1)v to healthy children aged 6 months to 17 years were included in this section. For details of the changes please refer to the annexed PI in track change.

During the procedure, the CHMP requested further amendments to the SmPC section 5.1 for better readability and inclusion of the booster response from the paediatric study 820903.

- **Additional changes to the SmPC**

The MAH took this opportunity to update in section 4.8 the number of subjects enrolled in clinical trials with a version of Celvapan containing a H5N1 vaccine strain from "approximately 3500" to "approximately 3700" as the safety dataset now includes additional data that have become available from a Phase I/II clinical study (clinical study protocol 810802) conducted in 230 subjects aged 18 to 60 years. Furthermore in section 5.1 a sentence that safety and immunogenicity data is available in special risk groups with the A/H5N1/Vietnam/1203/2004 strain vaccine has been added as a result of a

Phase III clinical study (clinical study protocol 810705) that included approximately 300 immunocompromised and approximately 300 chronically ill subjects.

Safety data from studies 810802 and 810705 were submitted in context of the initial MAA for the prepandemic H5N1 vaccine Vepacel. The data are already assessed and discussed by the CHMP. The currently approved product information of Vepacel reflects these study results accordingly. Therefore the MAH's proposal to update sections 4.8 and 5.1 with these minor details was agreed by the CHMP.

- **Additional changes to the PI**

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP.

In addition, minor linguistic amendments were made in the SmPC and in the Labelling.

- **Changes to the Annex II**

The CHMP agreed with the MAH proposal to update the list of obligations in Annex II as reported in section 4 of this assessment report, based on their fulfilled status. The completed obligations are the following:

1. **SOB 30** (pharmacovigilance, *The MAH will conduct a prospective cohort safety study in at least 9,000 patients in different age groups, including immunocompromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed)*: study 820901 was submitted on 03/12/2009. Variations II-12, II-13 and II-19/G originated from this observational study.
2. **FUM 37** (quality, *The final stability study reports for the PMVH, MVB and final container should be submitted as soon as they become available*): the final container data (FCP) have been submitted via variation IB-18 received on 10/03/2011.
3. **FUM 40** (clinical, *The MAH commits to provide the final Reports for the following study performed in children: Study 820903 ((H1N1)v clinical trial) Part B (Day 181) + Part C (up to Day 381*): the interim results for this study were submitted on 01/04/2010 and with the consequent measures as the data became available (FUMs 40.1, 40.2, 40.3). Variations II-15 and II-19/G have originated from this paediatric study.
4. **S-PSURs** (Pharmacovigilance, *The MAH commit to submit on a monthly basis a report including: i) a frequency table of all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively; ii) a frequency table of all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively; iii) a line listing of Adverse events of special interest (as defined in the CHMP Recommendations [EMEA/359381/2009]) reported from countries of the European Economic Area. The MAH commits to submit 6-monthly PSURs for the medicinal product authorised by this decision until further review by CHMP.*): the MAH submitted six simplified Periodic Safety Update Reports (S-PSURs) (from PSU11 to PSU16) since the launch of the vaccine. PSU11 was received on 30-11-2009 and PSU16 covered the period from 09 Mar 2010 through 05 Apr 2010. There was no additional distribution of the vaccine within the EU and outside the EU since 05 Apr 2010. Thus, the safety profile of Celvapan did not change since assessment of the sixth PSUR. The variation II-13 was submitted to update section 4.8 of the SmPC. The first full PSUR (PSU43) covered the

period 06.10.09 - 30.04.10. No new relevant safety information emerged after the cut-off date of the sixth simplified PSUR.

2. Overall conclusion and impact on the benefit/risk balance

The MAH provided the final results on antibody persistence, booster and safety follow-up from the clinical study 820903 performed in children and adolescents.

The antibody persistence profile following two-dose vaccination with Celvapan H1N1 was shown to be largely stable up to D181 after the first dose, as compared with the data at Day 43 after the first dose.

Booster response data has shown that priming with two doses of vaccine was robust and capable of inducing immunologic memory resulting in a high booster response to the A/H1N1/California/07/2009 strain of the seasonal trivalent influenza vaccine administered approximately one year after the first vaccination. Booster vaccination was safe and well tolerated, and there was no new safety concern between Day 43 and Day 361 after the priming vaccination.

The final safety data from a total of 3,216 subjects aged 2 months to 91 years enrolled in the observational pandemic study 820901 confirmed that a two-dose vaccination regimen with Celvapan containing 7.5µg HA was well tolerated across all age strata. Low systemic and local reaction rates after both vaccinations were reported and the safety follow-up raised no specific safety concern until 6 months after the second vaccination. In addition the use of Celvapan H1N1 during pregnancy did not raise any safety concern, although the data available from post-marketing are limited.

The product information was appropriately amended to reflect these results.

In conclusion the immunogenicity and safety results discussed for this group of variations do not impact on the product benefit/risk balance, which remains positive.

3. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variation(s) accepted		Type
C.I.3.b	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II
C.I.3.b	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II

Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC to reflect the results on immunogenicity and safety from the pandemic observational study 820901 (SOB 30) and the paediatric study 820903 (FUM 40). The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include minor amendments in the SmPC and Labelling.

Furthermore, the PI is being brought in line with the latest QRD template version 8.1.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

The CHMP is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex II:

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

(…)

Obligation to complete post-authorisation measures

The ~~Marketing Authorisation Holder~~ MAH shall complete, within the stated timeframe, the following measures: ~~programme of studies within the specified time frame, the results of which shall form the basis of the continuous reassessment of the benefit/risk profile.~~

Description	Due date
~~Pharmacovigilance FUM 30: The MAH will conduct a prospective cohort safety study in at least 9,000 patients in different age groups, including immune-compromised subjects, in accordance with the protocol submitted with the Risk Management Plan. Observed-to-Expected analyses will be performed.~~	~~Final report to be submitted: 31 Oct 2011~~
~~Pharmacovigilance FUM 31:~~ The MAH commits to provide the results of a study in a pregnancy registry.	Results to be provided in the PSURs
The final stability study reports for the PMVH and MVB ~~and final container~~ should be submitted as soon as they become available.	PMVH: 31/10/2012 MVB: 31/12/2012 ~~FCP: 31/05/2011~~
~~Clinical FUM 40: The MAH commits to provide the final Reports for the following Study performed in children: Study 820903 ((H1N1)v clinical trial) Part B (Day 181) + Part C (up to Day 381)~~	~~31/07/2011~~
~~Pharmacovigilance: The MAH commit to submit on a monthly basis a report including: - a frequency table of all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively - a frequency table of all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively. - a line listing of Adverse events of special interest (as defined in the CHMP Recommendations [EMEA/359381/2009]) reported from countries of the European Economic Area. The MAH commits to submit 6-monthly PSURs for the medicinal product authorised by this decision until further review by CHMP.~~	~~Data lock point for first regular PSUR: 30 April 2010 for submission 30 June 2010~~

4. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC to reflect the results on immunogenicity and safety from the pandemic observational study 820901 and the paediatric study 820903. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include minor amendments in the SmPC and Labelling. Furthermore, the PI is being brought in line with the latest QRD template version 8.1. Some of the obligations (Conditions to the Marketing Authorisation) have been deleted from the Annex II as fulfilled.

Summary

The final results on antibody persistence, booster and safety follow-up from the clinical study 820903 performed in children and adolescents were provided. The antibody persistence profile following two-dose vaccination with Celvapan H1N1 was shown to be largely stable up to D181 after the first dose, as compared with the data at Day 43 after the first dose. Booster response data has shown that priming with two doses of vaccine was robust and capable of inducing immunologic memory resulting in a high booster response to the A/H1N1/California/07/2009 strain of the seasonal trivalent influenza vaccine administered approximately one year after the first vaccination. Booster vaccination was safe and well tolerated, and there was no new safety concern between Day 43 and Day 361 after the priming vaccination.

The final safety data from a total of 3,216 subjects aged 2 months to 92 years enrolled in the observational pandemic study 820901 confirmed that a two-dose vaccination regimen with Celvapan containing 7.5µg HA was well tolerated across all age strata. Low systemic and local reaction rates after both vaccinations were reported and the safety follow-up raised no specific safety concern until 6 months after the second vaccination. In addition the use of Celvapan H1N1 during pregnancy did not raise any safety concern, although the data available from post-marketing are limited.

The PI was updated to reflect these new data and the obligations which have been fulfilled were deleted from Annex II.