European Medicines Agency

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TYPE II VARIATION ASSESSMENT REPORT
(Safety variation)

EMEA/H/C/000982/II/0006

Celvapan
pandemic influenza vaccine (H1N1) (whole virion, vero cell derived, inactivated)
A/California/07/2009 (H1N1)v

Indication (brief): prophylaxis of pandemic influenza in an officially declared pandemic situation

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

=Introduction
Celvapan is a pandemic H1N1v vaccine. The strain change of the mock-up vaccine from H5N1 to H1N1v was approved on 06/10/2009 (EMEA/H/C/982/PU/02). As committed by the marketing authorisation holder (MAH), preliminary safety data from the ongoing clinical trials in children and adults (including the elderly) evaluating different H1N1v vaccine formulations was submitted. Following assesment of this data, the MAH was requested to update the product information to reflect the current safety information available. The variation was submitted on 19 October 2009.

Clinical

Assessment

Study 820902 adults (including the elderly)

Design and demographics of clinical study 820902

Study **820902** is a phase I/II prospective, randomised, open label, multicentre study designed to assess immunogenicity and safety of an investigational H1N1 pandemic influenza vaccine in healthy subjects aged 18 years of age and older.

Primary Objective
The primary objective of the study is to measure the immune response, as determined by HI (haemagglutination inhibition) assay.

Secondary Objectives
- To assess the immune response as determined by microneutralisation (MN) assay
- To identify the optimal dose level of an investigational H1N1 pandemic influenza vaccine
- To investigate the safety characteristics

Subjects were recruited in equal numbers to two age strata of 18 to 59 years of age (Stratum A) and 60 years of age and older (Stratum B). Within each stratum, subjects were randomised 1:1 to receive two intramuscular injections of the whole virion, Vero cell-derived influenza vaccine at the same dose level of either 3.75 µg or 7.5 µg of H1N1v (A/California/07/2009) HA antigen (Cohort 1) on Day 1 and Day 22. Cohort 1 consists of approximately 400 subjects (200 adults, 200 elderly).

Dose Level	Cohort	Adults 18-59 Years	Elderly ≥ 60 Years
7.5 µg	1	100	100
3.75 µg	1	100	100

Enrolment started in August 2009 and 411 adult and elderly subjects were included in cohort 1.
Subjects of cohort 1 were vaccinated with 7.5 µg or 3.75 µg HA of the pandemic vaccine. Currently only a snapshot of the safety data base is available.

Snapshot of the safety data base 21 days after the first vaccination
The safety data provided differentiate between the two administered dose groups 3.75 µg and 7.5 µg, but do not distinguish between the two age groups of adults and elderly subjects.
The preliminary analysis of the safety data base throughout a 21 days observation period after the first vaccination demonstrates a favourable safety profile (Table 1).

Table 1: Summary of adverse experiences reported after the first vaccination in adults and elderly

	Adults and elderly

Dose [µg]	3.5 N=195 n (%)	7.5 N=192 n (%)
any systemic symptom	28 (14.4)	34 (17.7)
fever	1 (0.5)	3 (1.6)
fever + any systemic symptom	0	1 (0.5)
shivering	1 (0.5)	1 (0.5)
sweating	10 (5.1)	15 (7.8)
headache	10 (5.1)	15 (7.8)
malaise	5 (2.6)	4 (2.1)
fatique	15 (7.7)	18 (9.4)
muscle pain	4 (2.1)	8 (4.2)
joint pain	3 (1.5)	5 (2.6)
local reactions	16 (8.2)	13 (6.8)

Local reactions occurred at a low rate, i. e. 8.2 % and 6.8 % in subjects vaccinated with the 3.75 µg and 7.5 µg doses, respectively.
Local reactions were considered by subjects mostly mild and only for one case it was recorded as severe reaction. This event started on the day of the first vaccination and lasted for one day.

The frequency of systemic reactions either combined or individually was low, i.e. 14.4 % and 17.7 % in subjects vaccinated with the 3.75 µg and the 7.5 µg dose. Only 4 fever cases were observed within 387 subjects with onset days 3, 4, 5 and 8 days after the vaccination. The three cases of fever occurring in subjects who received the 7.5 µg dose were of moderate severity (between 38.5° and 38.9°C) whereas the fever case in one subject vaccinated with the 3.75 µg dose was of mild severity (between 38.0°C and 38.4°C). The fever resolved within 1-2 days.
Systemic reactions (fatigue, sweating, headache, muscle pain and joint pain) were observed by 62 out of 387 subjects and were generally described as mild.

Two serious adverse events (SAEs) considered unrelated occurred within 21 days after vaccination:

- pulmonary embolism (10 days after vaccination) and
- one case of dialysis of the retina of the right eye; the patient was hospitalised for surgery.

Some events, which might be summarised as allergic reactions were observed, such as burning eyes, warm sensation at vaccination site, exanthema and allergic rhinitis.

Study 820903 (6 months to 17 years)

This study is an ongoing open-label phase I/II study to assess the immunogenicity and safety of 2 different dose levels of H1N1 pandemic influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years.

Study subjects will be stratified into 4 age strata with each stratum consisting of approximately 100 subjects (Total N = 400).

Planned number of subjects:

Dose /Age Stratum	7.5 µg	3.75 µg
Stratum A: 9 - 17 years	50	50
Stratum B: 3 – 8 years	50	50
Stratum C: 12 – 35 months	50	50
Stratum D: 6 – 11 months	50	50

Snapshot of the safety data base 7 days after the first vaccination

The analysis was conducted on the available data from all subjects (N=146) available on 22 September 2009. Enrolement started on 07 September 2009.

In Cohort 1 of the study, a total of 101 children and adolescents aged 9 – 17 years were vaccinated in Stratum A, 24 children aged 3 -8 years in Stratum B and 21 infants and young children aged 6 - 35 months in Strata C and D. In all 3 age strata, children were randomly assigned in a 1:1 ratio to either the 3.75 µg or the 7.5 µg dose of the vaccine.

Current number of enrolled subjects:

Dose /Age Stratum	**7.5 µg**	**3.75 µg**
Stratum A: 9 - 17 years	49	52
Stratum B: 3 – 8 years	11	13
Strata C+D: 6 – 35 months	11	10

Results

Summary of adverse experiences reported after the first vaccination in children and adolescents

Age Stratum	9-17 years		3-8 years	
Dose [µg]	3.5 N=49 n (%)	7.5 N=52 n (%)	3.5 N=11 n (%)	7.5 N=13 n (%)
any systemic symptom	6 (12.2)	7 (13.5)	0	3 (23.1)
fever	1 (2.0)	0	2 (18.2)	1 (7.7)
fever + any systemic symptom	0	0	0	1 (7.7)
shivering	0	1 (1.9)	0	0
nausea	1 (2.0)	3 (5.8)	0	1 (7.7)
vomiting	0	1 (1.9)	0	0
sweating	0	0	0	0
headache	3 (6.1)	4 (7.7)	0	0
malaise	0	1 (1.9)	0	1 (7.7)
fatique	0	0	0	1 (7.7)
muscle pain	3 (6.1)	1 (1.9)	0	0
joint pain	1 (2.0)	0	0	0
local reactions	8 (16.3)	8 (15.4)	0	1 (7.7)

Sweating was not reported at all in both age groups. The single fever case in the age group of the 9-17 years old occurred in a 12-year old subject and was not associated with any other systemic symptom. Fever occurred in the age group of 3-8 years three times and was reported once in the 7.5 µg group associated with additional systemic symptoms (mild malaise). Only one child who received the higher dose, experienced local reactions in this age group.

Summary of adverse experiences reported after the first vaccination in children 6-35 months

Age Stratum	6-35 months	
Dose [µg]	3.5 N=11 n (%)	7.5 N=10 n (%)
any systemic symptom	6 (54.5)	3 (30.0)
fever	2 (18.2)	0
fever + any systemic symptom	1 (9.1)	0
shivering	0	0
nausea	0	0
vomiting	1 (9.1)	1 (10.0)
sweating	0	0
irritability	0	0
inconsolable or excessive crying	1 (9.1)	0
disturbed sleep	5 (45.5)	2 (20.0)
loss of appetite	0	0
drowsiness	0	0
local reactions	2 (18.2)	1 (10.0)

Inconsolable or excessive crying occurred in one child in the 3.75 µg dose group only, whereas shivering, nausea, sweating, irritability, loss of appetite and drowsiness were not reported at all in this age group. In one of these subjects, fever was associated with additional systemic reactions (mild disturbed sleep).

The few reported fever cases did not show temperatures above 38.9°C in all dose and age groups. Mostly the fever persisted for less than 24 hours. Two fever cases in children aged 6-35 months lasted 3 days (one in each dose group). The day of onset of the fever cases varied in all strata between day 0 and day 4.

No SAE occurred within the first 7 days after the vaccinations.

CHANGES TO THE PRODUCT INFORMATION

The MAH was requested to update the product information to include the following statement:

SPC (summary of product chracteristics):
Clinical Trials with Celvapan (H1N1)
Limited preliminary safety data after the first dose from clinical trials in adults aged over 18 years (N=387) and children aged from 9 to 17 years (N=101), 3 to 8 years (N=24) and 6 to 35 months (N=21) investigating two different dose levels (3.75µg or 7.5µg) of Celvapan (H1N1)v suggest a comparable safety profile with that reported for the H5N1 mock-up vaccine formulation.

PL (package leaflet):
From ongoing clinical trials, where a first dose of Celvapan (H1N1) was given to a limited number of adults, elderly and children similar adverse events were observed in the first days after vaccination to those previously seen with Celvapan (H5N1) vaccine.

Annex II was amended to reflect the fulfilment of the appropriate specific obligations, reflecting submission of the requested data.

The MAH submitted updated annexes including the above mentioned change and this was considered acceptable by the CHMP.

OVERALL DISCUSSION AND BENEFIT-RISK ASSESSMENT

The CHMP noted that the preliminary data reported for the ongoing studies in children and adults (including the elderly) are only a snapshot the safety data, which were not audited and cleaned. Notwithstanding this fact, the data suggest a comparable safety profile to that reported for the mock-up vaccine and this should be reflected in the product information.

Adults (including the elderly)
The data demonstrate a comparable safety profile to that observed for seasonal flu vaccines and in previous clinical trials with the H5N1 mock-up vaccine.
The analysis stratified into the respective age strata of the adults and elderly revealed that in general regardless of the vaccine formulation administered slightly more adverse reactions were reported for adults compared with elderly subjects. Only headache occurred more frequently in adults (~ 12%) than the elderly (5.2%).
The information on the preliminary day 21 safety data reported was included in the product information.

Children
The majority of subjects who experienced symptoms reported symptoms of mild severity in all age groups regardless of the dose used. Very few symptoms of moderate severity were reported and local or systemic adverse reactions of severe severity were not reported.
Although data on a very low number subjects, especially in the lower age groups, is available, overall the safety database involving 146 subjects might suggest a favourable safety profile with regard to systemic reactions. This limited and preliminary information was included in the product information.