19 February 2015
EMA/121454/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

Adjupanrix

Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

Prepandrix

Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

Procedure No: EMA/H/C/001206/P46/032 and EMA/H/C/000822/P46/054

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

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Administrative information

Invented name of the medicinal product:	Adjupanrix Prepandrix
INN (or common name) of the active substance(s):	Adjupanrix: Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) Prepandrix: Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)
MAH:	GSK Biologicals
Currently approved Indication(s)	*Adjupanrix: Prophylaxis of influenza in an officially declared pandemic situation. Pandemic influenza vaccine should be used in accordance with official guidance (section 4.2 and 5.1)* *Prepandrix: Active immunisation against H5N1 subtype of Influenza A virus. This indication is based on immunogenicity data from healthy subjects from the age of 18 years onwards following administration of two doses of vaccine prepared with H5N1 subtype strains (see section 5.1). Prepandrix should be used in accordance with official guidance.*
Pharmaco-therapeutic group (ATC Code):	J07BB02
Pharmaceutical form(s) and strength(s):	vaccines
Rapporteur:	Dr Ian Hudson

Introduction

On 4th April, the MAH submitted the D203 report and annex report (Day 364) for paediatric study FLU D-PAN H5N1-032 for Adjupanrix (mock-up pandemic license) and Prepandrix (pre-pandemic license), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. Monodose Hepatitis A vaccine Havrix was used as an active control in this study.

The applicant states that the above mentioned study is part of a clinical development program and acknowledges that this study was performed with another strain (A/Indonesia/05/2005 (H5N1) like PR8-IBDC-RG2 influenza strains) than the strain included in Adjupanrix (A/VietNam/1194/2004 (H5N1) like strain used (NIBRG-14)). Nevertheless the data were deemed useful from the perspective of licenses for both Adjupanrix and Prepandrix.

A short clinical expert statement has been provided.

The applicant stated that, in accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require taking further regulatory action on the marketing authorisation for the above mentioned product.

Scientific discussion

Information on the development program

The MAH stated that FLU D-PAN H5N1-032 is a part of a clinical development program. A line listing of the concerned study was annexed.

Information on the pharmaceutical formulation used in the studies

As in initial MAA

Clinical aspects

1. Introduction

The MAH submitted interim report for: FLU D-PAN H5N1-032.

2. Clinical study

The study FLU D-PAN H5N1-032 was a phase III, randomized, open, active-controlled study to evaluate the safety and immunogenicity of a prime-boost schedule of the H5N1 candidate vaccine adjuvanted with AS03B administered to children aged 3 to 17 years old. The priming and boosting H5N1 antigens were D-Pan H5N1 A/Indonesia/5/2005 and A/turkey/Turkey/01/2005, respectively, adjuvanted with $AS03_B$. The D-Pan formulation administered in the study corresponded to the half of an adult dose, i.e. H5N1 vaccine formulation containing 1.9 µg of HA antigen and $AS03_B$.

The study was conducted in a single centre in Philippines.

Methods

- Objective(s)

Co-primary immunogenicity objective:

- To assess the superiority of the HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following H5N1 vaccination on Day 182 (1.9 µg A/turkey/Turkey/01/2005 [H5N1] HA antigen adjuvanted with AS03B) in subjects previously primed with two doses of heterologous

A/Indonesia/5/2005 (H5N1) vaccine (Group H5N1_H5N1) versus non primed subjects (Group Havrix_H5N1).

Criterion to be used for the co-primary objective:

- If the lower limit of the two-sided 95% confidence interval (CI) for the HI geometric mean titer (GMT) ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) is greater than 1.0, then the superiority of priming vaccination was shown and an anamnestic immune response demonstrated.

Co-primary safety objective:

- To evaluate the safety of the pediatric H5N1 vaccine when administered as a two-dose primary vaccination to subjects 3 to 17 years of age in terms of occurrence of medically attended adverse events (MAEs) from Day 0 to Day 182 **[**and to Day 364**]**.

Secondary safety objective:

- To evaluate, after each vaccination, safety and reactogenicity in terms of 7-day solicited local and general symptoms, unsolicited adverse events (AEs) for 21 days after each dose and Day 0 to Day 84 overall, and potential immune-mediated diseases (pIMDs) and serious adverse events (SAEs) during the entire study.

- Study design

This is a phase III, randomized, open, active-controlled, single-center study to evaluate the safety and immunogenicity of a prime-boost schedule of the H5N1 candidate vaccine adjuvanted with AS03B administered to children 3 to 17 years of age. Subjects were assigned to four treatment groups in a ratio of 3:3:2:2 at the first visit, stratified by age (3-9 years and 10-17 years).

Blood samples were to be collected:
- On Days 0, 42, 182, 192 and on Day 364 for Group H5N1_H5N1 and Group Havrix_H5N1;
- On Days 0, 42, 182 and on Day 364 for Group H5N1_Havrix;
- On Days 0, 42, and 182 for Group Havrix_Havrix.

Treatment Group (n)	Day 0	Day 21	Day 182	Day 364**
H5N1_H5N1 (156)	A/Indonesia + AS03	A/Indonesia + AS03	A/turkey/Turkey + AS03	*Havrix* or *Havrix Junior**
H5N1_Havrix (156)	A/Indonesia + AS03	A/Indonesia + AS03	*Havrix* or *Havrix Junior**	*Havrix* or *Havrix Junior**
Havrix_H5N1 (104)	*Havrix* or *Havrix Junior**	-	A/turkey/Turkey + AS03	*Havrix* or *Havrix Junior**
Havrix_Havrix (104)	*Havrix* or *Havrix Junior**	-	*Havrix* or *Havrix Junior**	-

A/Indonesia + AS03 = 1.9 µg A/Indonesia/5/2005 (H5N1) HA antigen adjuvanted with AS03B
A/turkey/Turkey + AS03 = 1.9 µg A/turkey/Turkey/01/2005 (H5N1) HA antigen adjuvanted with AS03B
* *Havrix* (for subjects >15 years old) and *Havrix Junior* (for subjects ≤15 years old)
** Subjects in Group H5N1_H5N1 are to receive the second dose of *Havrix* or *Havrix Junior* outside the study setting

- Study population / Vaccination schedule

Healthy male or female children 3 to 17 years of age inclusive at the time of the first study vaccination for whom the investigator believed that their parent(s)/legally acceptable representative(s) would comply with the requirements of the protocol. Female subjects of childbearing potential had to use adequate contraception for 30 days prior to vaccination and agreed to continue such precautions for two months after completion of the vaccination series.

The total duration of the study for each vaccine was 12 months.

Treatment Group	Day 0	Day 21	Day 182	Day 364*
H5N1_H5N1	A/Indonesia + AS03	A/Indonesia + AS03	A/turkey/Turkey + AS03	*Havrix or Havrix Junior*
H5N1_Havrix	A/Indonesia + AS03	A/Indonesia + AS03	*Havrix or Havrix Junior*	*Havrix or Havrix Junior*
Havrix_H5N1	*Havrix or Havrix Junior*	-	A/turkey/Turkey + AS03	*Havrix or Havrix Junior*
Havrix_Havrix	*Havrix or Havrix Junior*	-	*Havrix or Havrix Junior*	-
A/Indonesia + AS03 = 1.9 µg A/Indonesia/5/2005 (H5N1) HA antigen adjuvanted with $AS03_B$ A/turkey/Turkey + AS03 = 1.9 µg A/turkey/Turkey/01/2005 (H5N1) HA antigen adjuvanted with $AS03_B$ * Subjects in Group H5N1_H5N1 are to receive the second dose of *Havrix* or *Havrix Junior* outside the study setting				

- Statistical Methods

Primary confirmatory analysis:

The primary analysis of immunogenicity was performed on the ATP cohort for analysis of immunogenicity. Since the percentage of subjects excluded from this ATP cohort was greater than 5% in any treatment group, a second analysis based on the Total Vaccinated cohort (TVc) was performed. The GMT ratio was obtained using an ANCOVA model on the logarithm-transformed titers. The ANCOVA model included the treatment group as fixed effect and the pre-vaccination (Day 182) log-transformed titer as regressor. The GMT ratio and its 95% CI were derived as exponential-transformation of the corresponding group contrast in the model. If the lower limit of the two-sided 95% CI for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was greater than 1.0, then the superiority of priming vaccination was shown and an anamnestic immune response demonstrated.

Secondary confirmatory analysis:

No confirmatory analyses were performed on secondary objectives.

Results

- Study population (total vaccinated cohort)

Overall, 520 subjects received study treatment including 312 subjects who received 2 doses of D-Pan H5N1 1.9 mg HA+AS03B (A/Indonesia strain) and 208 subjects who received one dose of Havrix (or Havrix Junior) up to Day 42. On Day 182, 260 subjects received the booster dose of D-Pan H5N1 1.9 mg HA+ AS03b (A/Turkey strain), while 260 subjects received the booster dose of Havrix (or Havrix Junior). More than 98% of subjects in every group completed the study until the day 364 study contact.

Number of subjects	H5_H5	H5_Hav	Hav_H5	Hav_Hav
Planned, N	156	156	104	104
Randomized, N (Total Vaccinated Cohort)	156	156	104	104
Completed, n (%)	156 (100)	155 (99.4)	104 (100)	103 (99.0)
Females: Males	81:75	81:75	52:52	52:52
Mean Age, years (SD)	9.7 (4.26)	9.4 (3.88)	9.3 (3.87)	9.6 (4.23)
Asian – South East Asian heritage, n (%)	156 (100)	156 (100)	104 (100)	104 (100)
H5_H5 = H5N1_H5N1:two doses (D0, D21) of H5N1 Indo and one booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), one dose (D364) of *Havrix* H5_Hav = H5N1_Havrix: two doses (D0, D21) of H5N1 Indo (1.9 µg HA + $AS03_B$) and two doses (D182, D364) of *Havrix* Hav_H5 = Havrix_H5N1: one dose (D0) of *Havrix* and one dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), one dose (D364) of *Havrix* Hav_Hav = Havrix_Havrix: two doses (D0, D182) of *Havrix*				

- Immunogenicity results

The co-primary immunogenicity objective was met and thus an anamnestic immune response was demonstrated, as the lower limit of the 95% CI for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was greater than 1 (the value of the lower 95% CI was 7.30).

Seropositivity rates and GMTs of HI antibodies against A/turkey/Turkey/01/2005 strain on Day 192 (Month 6 ATP cohort for immunogenicity)

				≥ 10 1/DIL				GMT				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Flu A/Turk/01/05 (H5N1).HA Ab	H5_H5	PIII(D192)	127	127	100	97.1	100	737.6	646.8	841.1	113.0	3620.0
	Hav_H5	PII(D192)	84	76	90.5	82.1	95.8	24.7	19.7	31.0	<10.0	320.0

H5_H5 = H5N1_H5N1: 2 doses (D0,D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Hav_H5 = Havrix_H5N1: 1 dose (D0) of Havrix and 1 dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PII(D192) = Visit Day 192
PIII(D192) = Visit Day 192

Adjusted GMT ratios of HI antibodies post vaccination between Group H5N1_H5N1 and Group Havrix_H5N1 for A/turkey/Turkey/01/2005 strain on Day 192 (Month 6 ATP cohort for immunogenicity)

				Adjusted GMT ratio (H5_H5 / Hav_H5)		
H5_H5		Hav_H5			95% CI	
N	**Adjusted GMT**	**N**	**Adjusted GMT**	**Value**	**LL**	**UL**
127	510.4	84	43.1	11.84	7.30	19.20

H5_H5 = H5N1_H5N1: 2 doses (D0,D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Hav_H5 = Havrix_H5N1: 1 dose (D0) of Havrix and 1 dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer (baseline = Day 182)
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer (baseline = Day 182) - pooled variance ; LL = lower limit, UL = upper limit

Seropositivity rates and GMTs of HI antibodies against A/Indonesia/05/2005 strain on Day 192 (Month 6 ATP cohort for immunogenicity)

				≥ 10 1/DIL				GMT				
						95% CI			95% CI			
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**	**Min**	**Max**
Flu A/Ind/05/05 (H5N1).HA Ab	H5_H5	PIII(D192)	127	127	100	97.1	100	674.1	595.0	763.8	113.0	3620.0
	Hav_H5	PII(D192)	84	37	44.0	33.2	55.3	7.6	6.7	8.5	<10.0	40.0

H5_H5 = H5N1_H5N1: 2 doses (D0,D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9µg HA + $AS03_B$), 1 dose (D364) of Havrix

Hav_H5 = Havrix_H5N1: 1 dose (D0) of Havrix and 1 dose (D182) of H5N1 Turkey (1.9µg HA + $AS03_B$), 1 dose (D364) of Havrix

GMT = geometric mean antibody titre calculated on all subjects

N = number of subjects with available results

n/% = number/percentage of subjects with titre equal to or above specified value

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

MIN/MAX = Minimum/Maximum

PIII(D192) = Visit Day 192

PII(D192) = Visit Day 192

- Safety results

The percentage of subjects with MAEs up to Day 182 was 36.9% in the pooled H5N1 groups versus 30.8% in the pooled control groups. Results suggest an increase in fever following the second and particularly the third dose of H5N1 vaccine for children <6 years of age. No other safety concerns were identified.

Serious adverse events:

Up to Day 203, seven non fatal SAEs were reported for five subjects. All events were resolved and none were assessed by the investigator to be causally related to vaccination.

Withdrawals due to adverse events/serious adverse events:

There were no SAEs leading to premature discontinuation.

Pregnancies

In addition to one subject (group H5N1_Havrix) who reported pregnancy up to Day 203, five other subjects reported pregnancy during this study period until Day 364. Two of the subjects were in the group H5N1_Havrix, while three subjects were in the H5N1_H5N1 group. All subjects were exposed to the vaccine before conception. Three subjects out of the five gave birth to male live infants, whereas pregnancy was still ongoing on Day 364 for the remaining two.

Rapporteur's overall conclusion and recommendation

The D203 report of the study D-Pan H5N1-032 allows the following conclusions to be made:

- The co-primary immunogenicity objective was met and an anamnestic immune response was demonstrated;
- The percentage of subjects with MAEs up to Day 182 was 36.9% in the pooled H5N1 groups versus 30.8% in the pooled control groups;
- Results suggest an increase in fever following the second and particularly the third dose of H5N1 vaccine for children <6 years of age;
- No other safety concerns were identified.

The Annex report (Day 364) did not reveal new safety issues.

In the absence of any significant new data on vaccine effectiveness or new safety concerns, there is no need for an update of the product information.

In accordance with Article 16(2) of Regulation (EC) No 726/2004, the data submitted do not influence the benefit-risk balance for the above mentioned product and therefore do not require further regulatory action on the marketing authorisation for the above mentioned product.

☒ **Fulfilled**

No further action required

Additional clarifications requested

Not applicable