24 September 2014
EMA/544203/2014
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/1206/P46/033 and EMA/H/C/0822/P46/055

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

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# Introduction

On 30th April, the MAH submitted the D364 Annex Report for paediatric study FLU D-PAN H5N1-013 for Adjupanrix (mock-up pandemic license) and Prepandrix (pre-pandemic license), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The applicant states that the above mentioned study is part of a clinical development program and acknowledges that this study is relevant 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 H5N1-013 is a part of a clinical development program and is included in the current Paediatric Investigation Plan (PIP) of both products (EMEA-000160-PIP01-07-M02).

## *Information on the pharmaceutical formulation used in the studies*

As in initial MAA

## *Clinical aspects*

### *1. Introduction*

The MAH submitted an annex report for: FLU D-PAN H5N1-013

### 2. Clinical study

The study FLU D-PAN H5N1-013 was a phase II, non-randomized, open-label to evaluate the safety and immunogenicity of the adjuvanted (pre-) pandemic H5N1 influenza candidate vaccine following a heterologous prime-boost schedule (six months apart) in children aged 6 to 35 months. The study was conducted in 4 centres in Australia and 2 in Singapore.

**Methods**

- Objective(s) pertaining to annex report

*Secondary:*

- To assess the HI response against A/Indonesia/05/2005 (H5N1 virus) and A/turkey/Turkey/01/2005

(H5N1 virus) strains in terms of seropositivity rates, geometric mean titers (GMTs), seroconversion rates (SCRs), seroprotection rates (SPRs) and mean geometric increases (MGIs) on Day 364.

- To further describe the humoral immune responses in terms of the three age strata used for enrolment in this study.

To describe, in all subjects, the H5N1 neutralizing antibody responses against A/Indonesia/05/2005 (H5N1 virus) and A/turkey/Turkey/01/2005 (H5N1 virus) strains on Day 0, Day 42*, Day 182, Day 192 and Day 364.

**Only for the A/Indonesia/05/2005 (H5N1 virus) strain*

- To evaluate medically-attended AEs (MAEs), potential immune-mediated diseases (pIMDs), and serious adverse events (SAEs) during the entire study.

*Tertiary:*

- To describe anti-NA antibody response in a subset of subjects in order to further characterize the immune response.

- Study design

This is a phase II, non-randomized, open, study to evaluate the safety and immunogenicity of a heterologous prime-boost schedule of the H5N1 candidate vaccine adjuvanted with AS03B administered to children 6 to 35 months of age. To note, the age stratification ratio of 2:1:1 for children 6-11 months, 12-23 months and 24-35 months of age, respectively was not maintained due to recruitment difficulties in the younger age range (6-11 months).

| Treatment Group (n) | Day 0 | Day 21 | Day 182 |
|---|---|---|---|
| H5N1 (120) | A/Indonesia + AS03 | A/Indonesia + AS03 | A/turkey/Turkey + AS03 |

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

Blood samples were collected on Day 0, Day 42, Day 182, Day 192 and Day 364.

- Study population / Vaccination schedule

Healthy male or female children 6-35 months 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.

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

- Statistical Methods

The analysis of immunogenicity was performed on the ATP cohort for analysis of immunogenicity. As the percentage of vaccinated subjects with serological results excluded from the ATP cohort was more than 5%, a second analysis based on the Total Vaccinated cohort (TVc) was performed to complement the ATP analysis.

- For the humoral immune response in terms of H5N1 HI antibodies against A/Indonesia/05/2005 (H5N1 virus) and A/turkey/Turkey/01/2005 (H5N1 virus) strains, GMTs, seropositivity rates, SCRs, SPRs, MGIs, Booster SCRs and BFs were calculated with 95% confidence intervals (CIs) at specified blood sampling time points, overall and by age stratum.

- For the humoral immune response in terms of serum neutralizing antibodies against A/Indonesia/05/2005 (H5N1 virus) and A/turkey/Turkey/01/2005 (H5N1 virus) strains, GMTs,

seropositivity rates, VRRs and Booster VRRs were calculated with their 95% CIs at specified blood sampling time points, overall and by age stratum.

- For the humoral immune response in terms of serum neuraminidase inhibition (NI) antibodies against A/Indonesia/05/2005 (H5N1 virus) strains (in a subset of subjects), GMTs and seropositivity rates were calculated with their 95% CIs at specified blood sampling time points, overall and by age stratum.

Results

- Study population (total vaccinated cohort)

| **Number of subjects** | **6<12 M** | **12<24 M** | **24<36 M** | **All** |
|---|---|---|---|---|
| Planned, N | 60 | 30 | 30 | 120 |
| Randomized, N (Total Vaccinated cohort) | 46 | 34 | 33 | 113 |
| Completed to PHC - D203, n (%) | 45 (97.8) | 31 (91.2) | 33 (100) | 109 (96.5) |
| Completed to visit 6 - D364, n (%) | 43 (93.5) | 31 (91.2) | 33 (100) | 107 (94.7) |
| **Demographics** | **6<12 M** | **12<24 M** | **24<36 M** | **All** |
| N (Total Vaccinated cohort) | 46 | 34 | 33 | 113 |
| Females:Males | 25:21 | 19:15 | 19:14 | 63:50 |
| Mean Age, months (SD) | 8.3 (1.56) | 16.1 (3.44) | 29.6 (3.38) | 16.9 (9.29) |
| Asian - south east asian heritage, n (%) | 34 (73.9) | 25 (73.5) | 22 (66.7) | 81 (71.7) |

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All = 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$)
N = total number of subjects, PHC = Physician contact, D = day, n/% = number/percentage of subjects,
SD = standard deviation

- Immunogenicity results

The immunogenicity analysis was performed on the ATP cohort (primary analysis) and on the total vaccinated cohort.

- The adjuvanted (pre-) pandemic H5N1 influenza candidate vaccine induced a humoral immune response in terms of H5N1 HI antibodies and neutralizing antibodies against A/Indonesia/5/2005 and A/turkey/Turkey/01/2005 (H5N1virus) strains that persisted to Day 364.

- All three CHMP criteria were met at Day 364.

- Antibody persistence in terms of GMT against A/Indonesia/5/2005 and A/turkey/Turkey/01/2005 (H5N1 virus) strains for HI tended to be higher for subjects 6 < 12 months of age.

- All subjects from the subset were seropositive or had anti-NA antibodies against A/Indonesia/5/2005 (H5N1 virus) strain at Day 364.

**Booster seroconversion rate (SCR) for HI antibodies against A/turkey/Turkey/01/2005 H5N1 virus strain at Day 364 by age stratum (Month 12 ATP cohort for immunogenicity).**

| | | | Booster SCR | | | |
|---|---|---|---|---|---|---|
| | | | | | 95% CI | |
| Strain | Group | N | n | % | LL | UL |
| Flu A/Turk/01/05 (H5N1).HA Ab | 6<12 M | 41 | 41 | 100 | 91.4 | 100 |
| | 12<24 M | 26 | 26 | 100 | 86.8 | 100 |
| | 24<36 M | 32 | 28 | 87.5 | 71.0 | 96.5 |
| | All | 99 | 95 | 96.0 | 90.0 | 98.9 |

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All = 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$)
Booster seroconversion defined as:
For seronegative subjects at Day 182, antibody titer ≥ 40 1/DIL after vaccination
For seropositive subjects at Day 182, antibody titer after vaccination ≥ 4 fold the pre-booster vaccination (Day 182) antibody titer
N = Number of subjects with pre- and post-vaccination results available
n/% = Number/percentage of seroconverted subjects
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit

**Seroprotection rates (SPR) for HI antibodies against A/Indonesia/05/2005 H5N1 and A/turkey/Turkey/01/2005 H5N1 virus strains at Day 0 and Day 364 by age stratum (Month 12 ATP cohort for immunogenicity).**

| | | | | SPR | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | |
| Strain | Group | Timing | N | n | % | LL | UL |
| Flu A/Ind/05/05 (H5N1).HA Ab | 6<12 M | PRE | 41 | 0 | 0.0 | 0.0 | 8.6 |
| | | PIII(D364) | 41 | 41 | 100 | 91.4 | 100 |
| | 12<24 M | PRE | 27 | 0 | 0.0 | 0.0 | 12.8 |
| | | PIII(D364) | 27 | 27 | 100 | 87.2 | 100 |
| | 24<36 M | PRE | 32 | 0 | 0.0 | 0.0 | 10.9 |
| | | PIII(D364) | 32 | 32 | 100 | 89.1 | 100 |
| | All | PRE | 100 | 0 | 0.0 | 0.0 | 3.6 |
| | | PIII(D364) | 100 | 100 | 100 | 96.4 | 100 |
| Flu A/Turk/01/05 (H5N1).HA Ab | 6<12 M | PRE | 41 | 0 | 0.0 | 0.0 | 8.6 |
| | | PIII(D364) | 41 | 41 | 100 | 91.4 | 100 |
| | 12<24 M | PRE | 27 | 0 | 0.0 | 0.0 | 12.8 |
| | | PIII(D364) | 27 | 27 | 100 | 87.2 | 100 |
| | 24<36 M | PRE | 32 | 1 | 3.1 | 0.1 | 16.2 |
| | | PIII(D364) | 32 | 32 | 100 | 89.1 | 100 |
| | All | PRE | 100 | 1 | 1.0 | 0.0 | 5.4 |
| | | PIII(D364) | 100 | 100 | 100 | 96.4 | 100 |

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All = 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$)
N = Number of subjects with available results
n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL)
95% CI = 95% confidence interval, LL = Lower Limit, UL = Upper Limit
SPR=seroprotection rate
PRE=Visit Day 0
PIII(D364)=Visit Day 364

**Seropositivity rates and GMTs of neutralizing antibodies against A/Indonesia/05/2005 H5N1 and A/turkey/Turkey/01/2005 H5N1 virus strains at Day 0 and Day 364 by age stratum (Month 12 ATP cohort for immunogenicity).**

| | | | | ≥ 28 1/DIL | | | | GMT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | | | |
| Strain | Group | Timing | N | n | % | LL | UL | value | LL | UL | Min | Max |
| Flu A/Ind/05/05 (H5N1) Ab | 6<12 M | PRE | 36 | 0 | 0.0 | 0.0 | 9.7 | 14.0 | 14.0 | 14.0 | <28.0 | <28.0 |
| | | PIII(D364) | 37 | 37 | 100 | 90.5 | 100 | 6420.9 | 4851.0 | 8498.9 | 905.0 | 18100.0 |
| | 12<24 M | PRE | 25 | 0 | 0.0 | 0.0 | 13.7 | 14.0 | 14.0 | 14.0 | <28.0 | <28.0 |
| | | PIII(D364) | 27 | 27 | 100 | 87.2 | 100 | 4730.9 | 3237.5 | 6913.0 | 570.0 | 18100.0 |
| | 24<36 M | PRE | 26 | 2 | 7.7 | 0.9 | 25.1 | 15.2 | 13.4 | 17.1 | <28.0 | 57.0 |
| | | PIII(D364) | 31 | 31 | 100 | 88.8 | 100 | 2422.9 | 1674.9 | 3504.9 | 280.0 | 18100.0 |
| | All | PRE | 87 | 2 | 2.3 | 0.3 | 8.1 | 14.3 | 13.8 | 14.9 | <28.0 | 57.0 |
| | | PIII(D364) | 95 | 95 | 100 | 96.2 | 100 | 4283.3 | 3485.8 | 5263.2 | 280.0 | 18100.0 |
| Flu A/Turk/01/05 (H5N1) Ab | 6<12 M | PRE | 36 | 0 | 0.0 | 0.0 | 9.7 | 14.0 | 14.0 | 14.0 | <28.0 | <28.0 |
| | | PIII(D364) | 37 | 37 | 100 | 90.5 | 100 | 4149.7 | 3028.8 | 5685.4 | 570.0 | 18100.0 |
| | 12<24 M | PRE | 25 | 0 | 0.0 | 0.0 | 13.7 | 14.0 | 14.0 | 14.0 | <28.0 | <28.0 |
| | | PIII(D364) | 27 | 27 | 100 | 87.2 | 100 | 3030.8 | 2036.2 | 4511.4 | 226.0 | 18100.0 |
| | 24<36 M | PRE | 26 | 1 | 3.8 | 0.1 | 19.6 | 14.4 | 13.6 | 15.2 | <28.0 | 28.0 |
| | | PIII(D364) | 31 | 31 | 100 | 88.8 | 100 | 1317.8 | 898.4 | 1933.0 | 113.0 | 18100.0 |
| | All | PRE | 87 | 1 | 1.1 | 0.0 | 6.2 | 14.1 | 13.9 | 14.3 | <28.0 | 28.0 |
| | | PIII(D364) | 95 | 95 | 100 | 96.2 | 100 | 2610.2 | 2085.3 | 3267.2 | 113.0 | 18100.0 |

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All = 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + AS03B)
DIL= Dilution
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE=Visit Day 0
PIII(D364)=Visit Day 364

**Seropositivity rates and GMTs of serum anti-neuraminidase antibodies against A/Indonesia/05/2005 H5N1 virus strain at Day 0 and Day 364 by age stratum (Month 12 ATP cohort for immunogenicity, subset of subjects).**

| | | | | ≥ 20 1/DIL | | | | GMT | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | | 95% CI | | | |
| Strain | Group | Timing | N | n | % | LL | UL | value | LL | UL | Min | Max |
| Flu A/Ind/05/05 (H5N1).NA Ab | 6<12 M | PRE | 21 | 0 | 0.0 | 0.0 | 16.1 | 10.0 | 10.0 | 10.0 | <20.0 | <20.0 |
| | | PIII(D364) | 20 | 20 | 100 | 83.2 | 100 | 502.3 | 341.3 | 739.4 | 57.0 | 1810.0 |
| | 12<24 M | PRE | 13 | 0 | 0.0 | 0.0 | 24.7 | 10.0 | 10.0 | 10.0 | <20.0 | <20.0 |
| | | PIII(D364) | 13 | 13 | 100 | 75.3 | 100 | 452.5 | 276.9 | 739.6 | 80.0 | 1280.0 |
| | 24<36 M | PRE | 15 | 1 | 6.7 | 0.2 | 31.9 | 10.5 | 9.5 | 11.6 | <20.0 | 20.0 |
| | | PIII(D364) | 16 | 16 | 100 | 79.4 | 100 | 287.1 | 205.3 | 401.5 | 80.0 | 905.0 |
| | All | PRE | 49 | 1 | 2.0 | 0.1 | 10.9 | 10.1 | 9.9 | 10.4 | <20.0 | 20.0 |
| | | PIII(D364) | 49 | 49 | 100 | 92.7 | 100 | 407.1 | 324.6 | 510.5 | 57.0 | 1810.0 |

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All = 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$)
DIL= Dilution
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
MIN/MAX = Minimum/Maximum
PRE=Visit Day 0
PIII(D364)=Visit Day 364

Safety results

The analysis of safety was performed on the total vaccinated cohort.

- Up to the Day 364 visit, MAEs were reported for 63.0% of subjects 6 < 12 months of age, for 55.9% of subjects 12 < 24 months of age and for 60.2% of subjects 24 < 36 months of age. The most frequently reported events were upper respiratory tract infections (23.0%), cough (17.7%), rhinorrhea (10.6%), pyrexia (7.1%) and nasopharyngitis (7.1%).

*Serious adverse events:*

From Day 0 up to the Day 364 visit, SAEs were reported for five (10.9%) subjects 6 < 12 months of age and for four (11.8%) subjects 12 < 24 months of age. None of the SAEs reported was considered causally related to the study vaccine in the opinion of the investigator. There were no fatal SAEs.

*Withdrawals due to adverse events/serious adverse events:*

- No (S)AEs leading to premature discontinuation of study vaccine were reported in this study from

Day 0 up to the Day 364 visit.

# Rapporteur’s overall conclusion and recommendation

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

These results suggest that a lower antigen content (1.9 µg HA) combined with ASO3B can induce an efficient homologous & heterologous immune response in terms of HI antibodies in children aged 6 to 35 months . It is reassuring that all CHMP criteria were met consistently in all age strata in relation to both homologous and heterologous strains. In the absence of significant new data on vaccine effectiveness or new safety concerns following vaccination, there is no need for 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