14 November 2014
EMA/708632/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

VEPACEL

International non-proprietary name: prepandemic influenza vaccine

Procedure No: EMEA-H-C-2089-P46-008

Note

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

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1. Introduction

Baxter hereby submits to the EMA the final report for clinical study 810706 – A Phase I/II Study to Assess the Safety and Immunogenicity of a Vero Cell-Derived Whole Virus H5N1 Influenza Vaccine in Healthy Infants, Children and Adolescents Aged 6 Months to 17 Years in accordance with article 46 of Regulation (EC) No 1904/2006.

A short critical expert overview has also been provided.

Study 810706 is a stand-alone study.

Study 810706 is part of a clinical development program. Variation application applying for pediatric indication for Vepacel is planned to be submitted by April/May 2013.

2. Synopsis of the study

Name of Sponsor/Company

Baxter Innovations GmbH

Name of Investigational Product (IP) H5N1 influenza vaccine

Name(s) of Active Ingredient(s) Vero cell-derived, formaldehyde- and UV-inactivated, sucrose gradient- purified Influenza virus subtype A/H5N1/a/

Subjects falling outside the 24-59 month age range were also excluded from the analysis.

Study Period: First subject in 2009 Dec 21.

Last subject out: 2012 May 24

Duration: 2 years and 5 months

Study Objectives

The objectives of this study are:

- To assess the safety and tolerability of a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the primary immune response to a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the immunogenicity of two different doses of a non-adjuvanted H5N1 influenza vaccine in healthy infants and children aged 6 months to 8 years;
- To assess persistence of H5N1 influenza antibodies 360 days after the first vaccination with a nonadjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years;
- To assess the immune response to a heterologous booster vaccination with a non-adjuvanted H5N1 influenza vaccine in healthy infants, children and adolescents aged 6 months to 17 years.

Primary endpoints

Safety:

- Frequency and severity of systemic reactions until 7 days after the first vaccination.
- Immunogenicity:
- Rate of subjects with antibody response to the vaccine strain associated with protection 21 days after the second vaccination defined as titer measured by Microneutralization (MN) test ≥ 1:20.

Secondary endpoints

The secondary objectives were:

Safety:

- Frequency and severity of systemic reactions until 21 days after the first, second and booster vaccination;
- Frequency and severity of injection site reactions until 21 days after the first, second and booster vaccination;
- Rate of subjects with fever, malaise or shivering (in children and adolescents aged 3 to 17 years) and fever and irritability (in infants and young children aged 6 to 35 months) with onset within 7 days after the first, second and booster vaccination;
- Frequency and severity of adverse events (AES) observed during the entire study period.

Immunogenicity

- Rate of subjects with antibody response associated with protection 21 days after the first and second vaccination defined as Hemagglutination Inhibition Antibody (HIA) titer ≥ 1:40 or Single Radial Hemolysis (SRH) area ≥ 25 mm2;
- Rate of subjects with antibody response associated with protection 21 days after the first vaccination defined as titer measured by MN test ≥ 1:20;
- Antibody response 21 days after the first and second vaccination as measured by MN, HI and SRH assay;
- Fold increase of antibody response 21 days after the first and second vaccination as compared to baseline as measured by MN, HI and SRH assay;
- Rate of subjects with seroconversion (defined as a minimum four fold titer increase as compared to baseline [for MN and HI assay] or as either a ≥ 25 mm2 hemolysis area after the vaccination in case of a negative pre-vaccination sample [≤ 4 mm2] or a ≥ 50% increase in hemolysis area if the prevaccination sample is > 4 mm2 [for SRH assay]) 21 days after the first and second vaccination as measured by MN, HI and SRH assay;
- Rate of subjects with antibody response associated with protection 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;
- Antibody response 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;

- Fold increase of antibody response 21 days after the booster vaccination as compared to before the booster vaccination as measured by MN, HI and SRH assay;
- Rate of subjects with seroconversion 21 days after the booster vaccination as measured by MN, HI and SRH assay.

Study Design

Phase I/II clinical study

Control Type uncontrolled

Study Indication Type Pediatric vaccination

Intervention, model Prospectively stratified by age (aged 9-17 years-Stratum A; aged 3-8 years-Stratum B; aged 6-35 months- Stratum C). Part-randomised to 2 doses (Strata B and C only).

Blinding/masking partially blinded for children aged 3-8 years (Stratum B) and infants and young children aged 6-35 months (Stratum C) only. For this reason, unblinding is not applicable for this study.

This was a partially blinded Phase I/II clinical study.

A total of at least 670 male and female infants, children and adolescents were to be included in the study. All subjects were to receive two intramuscular injections of either the 3,75 µg or 7,5 µg H5N1 HA antigen dose of the H5N1 influenza vaccine (whole virion, Vero cell-derived, inactivated, strain A/Vietnam/1203/2004) in a non-adjuvanted formulation on Day 0 and Day 21.

On Day 360, a subset of subjects were to receive a heterologous booster vaccination (strain A/Indonesia/05/2005) The booster vaccination was to be administered at the same time used for primary vaccination.

Subjects were stratified by age as follows:

Stratum A:

Approximately 300 children and adolescents aged 9 to 17 years. Subjects in Stratum A were to be vaccinated with the 7.5 µg H5N1

HA antigen dose. A subset of at least 75 subjects were to receive a booster vaccination.

Stratum B:

Approximately 300 children aged 3 to 8 years. Subjects in Stratum B were to be randomised 1:1 to receive either 7.5 µg or 3.75 µg H5N1 HA antigen dose. A subset of at least 150 subjects (75 in each sode group) were to receive vaccination.

Stratum C:

Approximately 70 infants and young children aged 6 to 35 months. Subjects in Stratum C were to be randomized 1:1 to receive either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. All subjects were to receive a booster vaccination.

Subjects were recruited into five study cohorts:

Cohort 1: Cohort 1 consisted of the first aproximately 30 subjects from StratumA. Safety data obtained at day 7 after the first vaccination were to be reviewed by a Data Monitoring (DMC) and a

recommendation obtained (i) to administer the second vaccination to Cohort 1 and (ii) to proceed to Cohort 2.

The DMC evaluated the following parameters:

- Aes
- Results of physical examinations

Cohort 2: Cohort 2 consisted of the remaining approximately 270 subjects from Stratum A. When Safety data through Day 7 after the first vaccination for approximately 120 subjects in this cohort were available, these were reviewed by a DMC (as described for Cohort 1) and a recommendation obtained to proceed to Cohort 3. The DMC review also included all safety data after the first and second vaccination for subjects in Cohort 1 available at that point in time.

Cohort 3: Cohort 3 consisted of the first approximately 30 subjects from Stratum B randomized 1:1 to either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. Safety data through Day 7 after the first vaccination were reviewed by a DMC (as described above for Cohort 1) and a recommendation obtained to proceed to Cohort 4. The DMC review also included all safety data after the first and second vaccination for subjects in Stratum A available at that point in time.

Cohort 4: Cohort 4 consisted of the remaining approximately 270 subjects from Stratum B and the first approximately 30 subjects from Stratum C, both randomized 1:1 to either the 7.5 µg or 3.75 µg H5N1 HA antigen dose. When safety data through Day 7 after the first vaccination for the approximately 30 subjects in Stratum C were available, these were reviewed by a DMC (as described above for Cohort 1) and a recommendation obtained to proceed to Cohort 5. The DMC review also included all safety data after the first and second vaccination for subjects in Stratum A and Stratum B available at that point in time.

Cohort 5: Cohort 5 consisted of the remaining approximately 40 subjects from Stratum C randomized 1:1 to either the 7.5 µg or 3.75µg H5N1 HA antigen dose.

The study was planned to be conducted in two parts:

Part A: Part A was to start with the screening visit of subjects in Strata A and B and to be concluded when the last subject in Strata A and B had completed the last visit. A separate clinical study report was to be prepared for Part A of the study.

Part B: Part B was to start with the screening visit in Stratum C and to be concluded when the last subject enrolled in Stratum C had completed the last visit. A separate clinical study report was to be prepared for Part B of the study.

Criteria for evaluation

Immunogenicity

Primary Immunogenicity Outcome:

- Rate of subjects with antibody response to the vaccine strain associated with protection 21 days after the second vaccination defined as titer measured by Microneutralization (MN) test ≥ 1:20.

Secondary Immunogenicity Outcome(s):

- Rate of subjects with antibody response associated with protection 21 days after the first and second vaccination defined as Hemagglutination Inhibition Antibody (HIA) titer ≥ 1:40 or Single Radial Hemolysis (SRH) area ≥ 25 mm2;
- Rate of subjects with antibody response associated with protection 21 days after the first vaccination defined as titer measured by MN test ≥ 1:20;
- Antibody response 21 days after the first and second vaccination as measured by MN, HI and SRH assay;
- Fold increase of antibody response 21 days after the first and second vaccination as compared to baseline as measured by MN, HI and SRH assay;
- Rate of subjects with seroconversion (defined as a minimum four fold titer increase as compared to baseline [for MN and HI assay] or as either a ≥ 25 mm2 hemolysis area after the vaccination in case of a negative pre-vaccination sample [≤ 4 mm2] or a ≥ 50% increase in hemolysis area if the prevaccination sample is > 4 mm2 [for SRH assay]) 21 days after the first and second vaccination as measured by MN, HI and SRH assay;
- Rate of subjects with antibody response associated with protection 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;
- Antibody response 360 days after the first vaccination and 21 days after the booster vaccination as measured by MN, HI and SRH assay;
- Fold increase of antibody response 21 days after the booster vaccination as compared to before the booster vaccination as measured by MN, HI and SRH assay;
- Rate of subjects with seroconversion 21 days after the booster vaccination as measured by MN, HI and SRH assay.

Safety:

Primary Safety Outcome:

- Frequency and severity of systemic reactions until 7 days after the first vaccination.

Secondary Safety Outcome(s):

- Frequency and severity of systemic reactions until 21 days after the first, second and booster vaccination;
- Frequency and severity of injection site reactions until 21 days after the first, second and booster vaccination;
- Rate of subjects with fever, malaise or shivering (in children and adolescents aged 3 to 17 years) and fever and irritability (in infants and young children aged 6 to 35 months) with onset within 7 days after the first, second and booster vaccination; Frequency and severity of AEs observed during the entire study period.

Investigational Product(s) H5N1 Influenza Vaccine (Whole virion, Vero cell-derived, Inactivated) containing either 7,5µg per 0.5 mL or 3.75 µg per 0.25 ml of H5N1 HA Antigen strain A/Vietnam/1203/2004 in a non-adjuvanted formulation.

Dosage form: multi dose vials (i.e. 10 doses of 0.5 mL).

Dose frequency: 2 doses 21 days apart

Mode of Administration: injection into the deltoid muscle in the upper arm for children aged 3 years of age or older, or the anterolateral muscle of the thigh of children under the age of 1 year. For children between the age of 1 and 3 years the investigator may use his/her discretion as to whether the vaccine should be given in the thigh or the arm.

Batch number(s): VNV1J001A, VNV1K005A and VNV1K006A

Duration of treatment: 201 days or 381 days if booster vaccination received.

Subject Selection

Planned

Planned At least 670 male and female adolescents, children and infants (300 in Strata A [9 to 17 years] and B [3 to 8 years] and 70 in Stratum C [6 to 35 months]) who meet all inclusion criteria and none of the exclusion criteria listed below were invited to participate in the study.

Analyzed

Safety dataset - 675 subjects (300 Stratum A, 303 Stratum B and 72 Stratum C) Intend-to-treat (ITT) dataset- 656 subjects (296 Stratum A, 291 Stratum B and 69 Stratum C) Per-protocol (PP) dataset - 591subjects (270 Stratum A, 259 Stratum B and 62 Stratum C)

Diagnosis and Main Criteria for Inclusion

Inclusion Criteria:

Male and female subjects will be eligible for participation in this study if:

- They are 9 to 17vi years of age on the day of screening (for Stratum A only);
- They are 3 to 8vii years of age on the day of screening (for Stratum B only);
- They are 6 to 35viii months of age on the day of screening (for Stratum C only);
- They were born at full term of pregnancy (≥ 37 weeks) with a birth weight ≥ 2 kg (for Stratum C only);
- They and/or their parents/legal guardians understand the nature and procedures of the study and agree to its provisions.

Statistical Methods

Sample Size Calculation:

As recommended in Guideline EMEA/CHMP/VWP/263499/2006 x, the study was to enroll approximately 300 children and adolescents (9 to 17 years of age, Stratum A) and 300 children (3 to 8 years of age, Stratum B). Additionally, approximately 70 infants and young children (6 to 35 months of age, Stratum C) were to be enrolled in this study.

Assuming an approximate dropout rate of 10%, it was expected that 270 subjects in Strata A and B (and 63 subjects in Stratum C) would have evaluable immunogenicity results after two vaccinations. With a sample size of 270 subjects, the two-sided 95% confidence interval (CI) of the proportion of subjects with antibody response associated with protection in Stratum A and B, expressed in percentages, does not extend more than 5.6% (13.8% with 63 subjects in Stratum C) from the sample proportion assuming that the estimated proportion is 70%.

The sample size of 300 subjects in Strata A and B provides a 95.1% chance (50.5% chance with 70 subjects in Stratum C) to detect at least one AE that occurs at a frequency of 1:100.

Statistical Analysis:

Analysis of Primary Endpoint:

Safety:

The rates of subjects with at least one systemic reaction within 7 days after the first vaccination and their two-sided 95% CIs were calculated separately for each age stratum.

The analysis was performed on the safety analysis dataset.

Immunogenicity:

The rates of subjects with antibody response to the vaccine strain associated with protection 21 days after the second vaccination defined as titer measured by MN test ≥ 1:20 and their two -sided 95% CIs were calculated separately for each age stratum.

In addition, a separate immunogenicity analysis within each age stratum may be performed on subjects who have versus those who have not received an H1N1 pandemic influenza vaccine between 7 days after the first and 21 days after the second vaccination.

The analysis was performed on the intent-to-treat (ITT) and per-protocol (PP) dataset.

Analysis of Secondary Endpoints:

Safety:

Point estimates and two-sided 95% CIs were calculated for all secondary safety endpoints separately for each age stratum.

Probability of occurrence of queried symptoms and their two-sided 95% CIs were calculated separately for each age stratum.

Symptoms of local and systemic AEs observed during the entire study period are presented in summary tables. Summary tables indicate the number of subjects who experienced local and systemic

events related to the vaccination separately for the first, second and booster vaccination sorted by age stratum.

In addition, tables were prepared to list each AE, the number of subjects in each age stratum who experienced an event at least once, and the rate of subjects with AE(s). AEs were grouped by system organ class. Each event was then divided into defined severity grades (mild, moderate, severe). The tables also divided the AEs into those considered at least possibly related to the vaccine and those considered not related.

All AEs for each subject, including the same event on several occasions were listed, giving both MedDRA preferred term and the original term used by the investigator, system organ class, duration, severity grade, seriousness, relation to vaccination, date of onset and timing of onset in relation to vaccination. If a serious adverse event (SAE) occurred, outcome, treatment, and relevant medical history were also included. The listings were sorted by age stratum.

In addition, a separate safety analysis within each age stratum may be performed on subjects who have versus those who have not received an H1N1 pandemic influenza vaccine between 7 days after the first and 21 days after the second vaccination.

The analysis was performed on the safety analysis dataset.

Immunogenicity:

Point estimates and two-sided 95% CIs were calculated for all secondary immunogenicity endpoints. The analysis was carried out separately for each age stratum.

For the log-transformed MN antibody titers in Stratum B and C, a longitudinal analysis was performed within a repeated mixed model ANCOVA framework, accounting for the fixed effect of vaccine doses, study Days (21 or 42), interaction of vaccine doses and study days, baseline titer as a covariate and for the random subject effect. Least-square vaccine group means and 95% CIs were computed and then back transformed by exponentiation into geometric means.

In addition, a separate immunogenicity analysis within each age stratum may be performed on subjects who have versus those who have not received an H1N1 pandemic influenza vaccine between 7 days after the first and 21 days after the second vaccination.

The analysis was performed on the ITT dataset.

Extent of exposure

The H5N1 influenza vaccine was administered i.m. in a 2-dose primary vaccination scheme at a 21-day interval, followed by a heterologous booster 360 days after the first vaccination. Healthy infants, children and adolescents aged 6 months to 17 years (N = 675) were administered the first vaccination with the H5N1 vaccine containing the strain A/Vietnam/1203/2004 at a dose of 7.5 µg (N = 300: Stratum A, N = 153: Stratum B, and N = 36: Stratum C) or 3.75 µg (N = 150: Stratum B, and N = 36: Stratum C), and 657 received a second vaccination at the same HA dose 21 days after the first (7.5 µg: N = 296: Stratum A, N = 148: Stratum B, and N = 34: Stratum C; 3.75 µg: N = 143: Stratum B, and N = 36: Stratum C). The booster vaccination, containing the strain A/Indonesia/05/2005, was administered to 402 subjects 360 days after the first vaccination (7.5 µg: N = 191: Stratum A, N = 77: Stratum B, and N = 28: Stratum C; 3.75 µg: N = 73: Stratum B, and N = 33: Stratum C).

Immunogenicity results

The immune response to a non-adjuvanted Vero cell-derived H5N1 vaccine containing 7.5 μg or 3.75 μg HA antigen of the clade 1 A/Vietnam/1203/2004 strain, given at a 2-dose schedule 21 days apart was assessed in 3 different age groups comprised of subjects from 6 months to 17 years of age (Stratum A: 9-17 years, 7.5 μg dose; Stratum B: 3-8 years, 7.5 μg or 3.75 μg dose; Stratum C: 6-35 months, 7.5 μg or 3.75 μg dose. In addition, the immune response to a 12 month booster vaccination with a heterologous non-adjuvanted Vero cell-derived H5N1 vaccine (A/Indonesia/05/2005) containing the same dose as used for the 2-dose primary vaccination was assessed (also in the 3 pediatric age groups).

It has been demonstrated that the MN assay is more sensitive and/or specific than the HI assay for detection of functional/protective antibodies against avian influenza strains. Thus, due to the reports that the HI assay may not be an appropriate method for evaluation of human immune responses to avian hemagglutinin and particularly in children; immunogenicity evaluation was focused on the MN assay, supported by antibody response determined by SRH (as recommended by EMA).

The SRH assay generally supported MN results in this study; antibody levels according to the HI assay were much lower and highly inconsistent with those determined by MN and SRH.

The H5N1 vaccine containing the strain A/Vietnam/1203/2004 induced a substantial antibody response after two vaccinations in subjects from 6 months to 17 years old. Rates of subjects with MN antibody levels associated with protection (MN titer ≥1:20) were highest among the oldest subjects at 21 days after two vaccinations, with 85.4% in Stratum A, compared to 72.9% in Stratum B, and 68.8% in Stratum C (for those receiving the 7.5μg antigen dose). In the younger age strata, where both the 7.5 μg HA and the 3.75μg HA doses were administered, a trend of somewhat higher protection levels was observed among subjects receiving the 7.5μg HA antigen dose. Among those receiving the 3.75μg dose, 57.1% of subjects in Stratum B, and 54.3% of those in Stratum C showed MN antibody levels associated with seroprotection (MN titer ≥1:20) after two vaccinations.

Results of this study also demonstrated that a booster vaccination with a cross clade influenza H5N1 booster strain (A/Indonesia/05/2005) 12 months after a 2-dose primary vaccination induces a strong antibody response against the strains used for the booster and primary vaccinations.Among subjects receiving the 7.5μg HA antigen dose, 93.1% of subjects in Stratum A 97.2% in Stratum B and 100.0% in Stratum C showed MN antibody titers associated with protection (MN titer ≥1:20) against the A/Indonesia strain at 21 days after the booster vaccination; among those receiving the 3.75μg dose, these rates were 91.4% (Stratum B) and 100.0% (Stratum C). When tested against the A/Vietnam strain at 21 days among those receiving the 7.5μg HA antigen dose, 94.1% of subjects in Stratum A, 94.7% in Stratum B and 100.0% in Stratum C, showed MN antibody titers associated with protection (MN titer ≥1:20) at 21 days after the booster vaccination; among subjects receiving the 3.75μg dose, 91.7% and 92.8% of those in Strata B and C, respectively, reached these MN antibody levels.

Safety Results

A 2-dose vaccination regimen with the inactivated H5N1 influenza vaccine (whole virion, Vero cellderived) containing either 7.5 μg or 3.75 μg HA antigen of strain A/Vietnam/1203/2004, and a heterologous booster vaccination containing either 3.75 μg or 7.5 μg HA antigen of strain A/Indonesia/05/2005, administered approximately one year later, was safe and well tolerated in healthy infants, children and adolescents aged 6 months to 17 years. No deaths, vaccine-related SAEs or unusual or medically significant AEs were reported. Adverse reactions were predominantly mild to moderate in severity.

The majority of subjects experienced no systemic or injection site reactions after vaccination. In addition, no apparent dose effect was observed in the younger age groups aged 6 months to 8 years (Strata B and C) in which both a 7.5 µg and 3.75 µg vaccine dose were assessed.

Within 7 days after the first vaccination, systemic reaction rates (excluding fever) in the 7.5 µg and 3.75 µg dose groups respectively were: 30.0% in Stratum A , 15.7% and 20.7% in Stratum B, and 33.3% and 30.6% in Stratum C. Symptoms lasted a few days and all subjects recovered. Only few systemic reactions were reported in the period from 7 to 21 days after the first vaccination as shown by the slight increase in systemic reaction rates observed within 21 days after first vaccination: 30.3% in Stratum A, 16.3% and 21.3% in Stratum B, and 36.1% and 30.6% in Stratum C, in the 7.5 µg and 3.75 µg dose groups, respectively.

The majority of reactions were mild to moderate in severity.

Within 21 days after the second, systemic reaction rates (excluding fever) were 18.6% of subjects in Stratum A, 9.4% and 12.0% in Stratum B, and 29.4% and 27.8% in Stratum C in the 7.5 µg and 3.75 µg dose groups respectively Severe systemic reactions occurring after the first and second vaccinations were; fatigue and nausea (1 subject), arthralgia and myalgia (1 subject), vomiting, myalgia and headache (1 subject), nasopharyngitis (1 subject) and myalgia (1 subject), fatigue (1 subject) in Stratum A and cough (1 subject) in Stratum C. The most commonly-reported specifically queried symptoms after the first and second vaccinations were headache , malaise, fatigue and muscle pain in Strata A and B, and irritability, nconsolable or excessive crying, disturbed sleep, loss of appetite and drowsiness in Stratum C.

Systemic reaction rates (excluding fever) within 21 days of the booster vaccination with the

A/Indonesia/05/2005 strain were: 21.5% in Stratum A, 10.3% and 13.9% in Stratum B, and 17.9% and 6.1% in Stratum C in the 7.5 µg and 3.75 µg dose groups respectively. The majority of reactions were mild to moderate in severity. Severe systemic reactions occurring after the booster vaccination were headache (1 subject) and fatigue (1 subject) in Stratum A.The most commonly-reported specifically queried symptoms after the booster vaccination were headache, malaise, fatigue and muscle pain in Strata A and B, and irritability, loss of appetite and drowsiness in Stratum C.

3. Conclusions and further requests

The data submitted do not influence the benefit/risk balance for Vepacel (Prepandemic Influenza Vaccine) and therefore do not require to take urgent regulatory action on the marketing authorisation for Vepacel (PrePandemic Influenza Vaccine).

The data indicate that the H5N1 influenza vaccine was shown to be safe and well tolerated in a pediatric population aged 6 months to 17 years.

The immunogenicity is somewhat lower in younger individuals. Whether these data can support an extension of the use of Vepacel to children aged 6 to 17 years has to be evaluated in a separate Type II variation. The FUM is considered fulfilled. The MAH intends to submit a type II variation for a paediatric indication in April/May 2013.