



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Infanrix hexa

diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and Haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000296/P46/123

Note

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



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1. Introduction

In 2012, the MAH submitted the results of a double-blind, randomised, multicentre study (DTPA-HBV-IPV-124) to assess safety and immunogenicity of 2 new formulations of the MAH's DTPa-HBV-IPV/Hib vaccine compared to the licensed Infanrix -hexa vaccine when co-administered with Prevenar 13 to healthy infants as a **primary vaccination** course at 2, 3 and 4 months of age.

The study failed to meet its primary inferential non-inferiority criteria due to lower anti-PRN antibody concentration with both new formulations: the upper limits of the 97.5% CI on the GMC ratio for anti-PRN was 1.54 (Control group divided by Form A group) and 1.84 (Control group divided by Form B group), and exceeded the pre-defined non-inferiority margin of 1.5. A trend to higher reactogenicity was observed for solicited symptoms and grade 3 solicited symptoms, in particular with regard to pain and fever ($p < 0.001$): the observed incidence of solicited adverse events tended to be higher in the investigational groups than in the Control group. Overall solicited incidence of fever $> 38^\circ\text{C}$ per subject was higher in Form A (33.8%) and Form B (30.8) compared to the control group (18.1%).

Based on the clinical study results, the Company has decided to stop the clinical evaluation of the candidate formulations evaluated in this clinical study 113948 (DTPA-HBV-IPV-124 PRI). In addition, given the modified benefit/risk ratio observed in the clinical study for the candidate formulations the Company has decided to stop the project. Consequently the preclinical evaluation to try to identify the root cause—of these observed differences has been stopped.

The current report concerns the study 114843 (DTPA-HBV-IPV-125 BST: 124), a phase II, double-blind, multicentre study to evaluate the safety and immunogenicity of a booster dose of new formulations of GlaxoSmithKline (GSK) Biological's combined DTPa-HBV-IPV/Hib vaccine in healthy toddlers in the second year of life, previously primed with three doses of the same vaccine in the previous cited study 113948 (DTPA-HBV-IPV-124 PRI).

1.1. Steps taken for the assessment

Submission date:	19/08/2016
Start of procedure:	12/09/2016
CHMP Rapporteur's preliminary assessment report circulated on:	17/10/2016
CHMP Rapporteur's updated assessment report circulated on:	28/10/2016
CHMP opinion:	10/11/2016

2. Assessment of the post-authorisation measure PAM 123 Abridged Clinical Study Report for Study 114843 (DTPA-HBV- IPV-125 BST: 124).

Study initiation date: 14-October-2011 / Study completion date: 10-October-2012

Data lock point (Date of database freeze):14-April-2016 / Date of report: Final: 29-June-2016

The **design** of this booster study was similar to the one of the primary study DTPa-HBV-IPV-124 (GSK Study N° 113948).

This was a double-blind, randomised, multicentre study with three parallel groups, conducted in the Dominican Republic and Finland. Two blood samples were drawn from all subjects: 3.5 mL of blood was collected before the first vaccine dose and 5 mL of blood was collected one month after the third vaccine dose. Subjects were allocated to one of the two sub-cohorts depending on the country of recruitment. Sub-cohort 1 included all subjects in Finland (pneumococcal assays were performed only for this sub-cohort of subjects) and sub-cohort 2 included all subjects from the Dominican Republic.

The three study groups were as follows:

- Form A Group: received three doses of GSK Biologicals' investigational DATAvaccine and Pfizer's 13-valent pneumococcal vaccine (Prevenar13) at 2, 3 and 4 months of age.
- Form B Group: received three doses of GSK Biologicals' investigational DBTBvaccine and Pfizer's 13-valent pneumococcal vaccine (Prevenar13) at 2, 3 and 4 months of age.
- Control Group: received three doses of GSK Biologicals' licensed **DTPa-HBV-IPV/Hib vaccine (Infanrix hexa)** and Pfizer's 13-valent pneumococcal vaccine (Prevenar13) at 2, 3 and 4 months of age.

Primary objectives:

To demonstrate that the immunogenicity of at least one investigational combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus and Haemophilus influenzae type b vaccine (DTPa-HBV-IPV/Hib) formulation is non-inferior to the licensed formulation in terms of seroprotection rates to diphtheria, tetanus, hepatitis B, poliovirus types 1, 2 and 3 and PRP antigens and in terms of antibody geometric mean concentrations (GMCs) for pertussis antigens one month after the booster dose.

Criteria for non-inferiority:

For each investigational formulation:

– Non-inferiority in terms of immune response to diphtheria, tetanus, hepatitis B, poliovirus types 1, 2 and 3, and PRP antigens was demonstrated if the upper limits of the 97.5% confidence interval (CI) on the group difference [control minus investigational] in the percentage of seroprotected subjects for each antigen was $\leq 10\%$, and,

– Non-inferiority in terms of immune response to pertussis antigens was demonstrated if, for each of the three antigens, the upper limits of the 97.5% CI on the GMC ratio [control divided by investigational] was ≤ 1.5 .

Immunogenicity results

The inferential analysis linked to the primary objective was not performed. Note that the primary study DTPa-HBV-IPV-124 (113948) failed to demonstrate its primary objective with respect to PRN. Hence, in

view of the sequential nature of analysis, non-inferiority for PRP could not be concluded for both investigational formulations. As indicated in the statistical method section, the inferential analysis linked to the primary objective was not performed following protocol amendment 2.

Secondary objectives, (descriptive analysis):

One month post-booster vaccination (ATP cohort for immunogenicity),

- Note that for the PRN antigens, the booster with the same formulation as primary vaccination showed trend for lower anti-PRN antibodies for both Form A and Form B groups. Such trend was also visible in the control group with Infanrix hexa as a booster where Infanrix hexa after Infanrix hexa primary vaccination showed higher GMT for all pertussis antigens.
- **For subjects administered with Form A, Form B or Infanrix hexa vaccine (before protocol amendment 2):** One month post booster vaccination, 100% of the subjects had antibodies above the cut-off against diphtheria, tetanus and PRP. Between 98.7% to 100% subjects had antibodies above the cut-off against hepatitis B. Between 97.3% to 100% of the subjects had antibodies above the cut-off against the three poliovirus types. Seropositive antibody levels against PT, FHA and PRN were observed in 100% subjects in the three groups. The **Geometric mean concentrations (GMC) against PT, FHA and PRN** in Form A group was 76.1, 393.7 and 213, Form B group was 74.3, 372.4 and 180.0 and in the control group was **96.0, 423.0 and 372.9**, respectively.
- **For subjects administered with Infanrix hexa (all subjects after amendment 2):** One month post booster vaccination, 100% of the subjects had antibodies above the cut-off against diphtheria and tetanus. Between 99.2% to 100% of the subjects had antibodies above the cut-off against PRP. Between 98.3% to 99.1% subjects had antibodies above the cut-off against hepatitis B. Between 99.0% to 100% of the subjects had antibodies above the cut-off against the three poliovirus types. The Geometric mean concentration (**GMC) against PT, FHA and PRN** for Form A group was 92.4, 467.3 and 253.2, Form B group was 93.6, 446.2 and 181.0 and in the control group was **132.6, 582.9 and 401.1**, respectively.

Safety objectives:

- Injection site pain was the most frequently reported solicited local symptom in the three groups for subjects administered with Form A, Form B or Infanrix hexa vaccine (before the protocol amendment 2) following 65.9%, 76.1% and **63.6%** subjects in the Form A, Form B and Control groups respectively; after the protocol amendment 2 the incidence was 58.0%, 50.8% and **51.6%** subjects in the Form A, Form B and Control groups, vaccinated with Infanrix hexa respectively.
- For all subjects administered with Form A or Form B vaccine or Infanrix hexa, Irritability (any and grade 3) was the most frequently reported solicited general symptom in the three groups. Overall solicited incidence of fever $>38^{\circ}$ C per subject was higher in Form A (49.4%) and Form B (46.6%) compared to the control group (**37.4%**) in subjects administered with Form A or Form B vaccine or Infanrix hexa vaccine. The incidence of fever $>38^{\circ}$ C appeared similar in all groups when Infanrix hexa was given as a booster (44.3%, 38.5%, **41.9%**).
- At least one unsolicited AE was reported for 49.4%, 44.3%, and **50.5%** subjects in the Form A, Form B and Control groups in subjects administered with Form A or Form B vaccine and Infanrix hexa. At least one unsolicited AE was reported for 29.0%, 20.8%, and **25.0%** subjects in the Form A, Form B and Control groups in subjects administered with Infanrix hexa (after protocol amendment 2). SAEs were reported for 2 subjects administered with Infanrix

hexa in the Form B group. Pneumonia and dehydration were reported for one subject, for the other subject the reported SAE was pneumonia. None of the SAEs were considered to be potentially related to vaccination by the investigator. No fatal SAE was reported during the entire study period.

3. Rapporteur's overall conclusion

The MAH sent a stand-alone submission of the final study report for this study, in accordance with Article 46 of Regulation (EC) No 1901/2006. This study is not part of a PIP. The Company concluded that currently no changes in the benefit/risk of Infanrix hexa or to the Product Information of Infanrix hexa are needed and the benefit/risk of Infanrix hexa remains the same.

The Rapporteur endorses the discussion and conclusion of the Applicant concerning immunogenicity and safety of the post-booster results of Infanrix hexa in this standalone submission of the paediatric study DTPA-HBV-IPV-125 BST:124.

PAM fulfilled (all commitments fulfilled) - No further action required

PAM not fulfilled (not all commitments fulfilled) and further action required: