15 November 2012
EMA/359929/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report under Article 46

Infanrix hexa

International non-proprietary name: 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/P46/106

Note

Variation 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:	Infanrix Hexa
INN (or common name) of the active substance(s):	Diphtheria toxoid, adsorbed/ Tetanus toxoid, adsorbed/ Pertussis toxoid, adsorbed/ Filamentous haemagglutinin, adsorbed/ Pertactin, adsorbed/ Recombinant Hepatitis B surface Antigen (S protein), adsorbed/ Inactivated type 1 Poliovirus/ Inactivated type 2 Poliovirus/ Inactivated type 3 Poliovirus/ Conjugate of Haemophilus influenzae type b capsular polysaccharide and Tetanus toxoid, adsorbed
MAH:	GSK Biologicals (GlaxoSmithKline Biologicals) S.A.-N.V.(Belgium)
Currently approved Indication(s)	Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b.
Pharmaco-therapeutic group (ATC Code):	J07CA09 - Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B
Pharmaceutical form(s) and strength(s):	Powder and suspension for suspension for injection in a pre-filled syringe After reconstitution, 1 dose (0.5 ml) contains: Diphtheria toxoid not less than 30 International Units (IU) Tetanus toxoid not less than 40 International Units (IU) *Bordetella pertussis* antigens Pertussis toxoid ** 25 micrograms Filamentous Haemagglutinin ** 25 micrograms Pertactin ** 8 micrograms Hepatitis B surface antigen ** 10 micrograms Poliovirus (inactivated) type 1 (Mahoney strain) ** 40 D-antigen unit type 2 (MEF-1 strain) ** 8 D-antigen unit type 3 (Saukett strain) ** 32 D-antigen unit *Haemophilus influenzae* type b polysaccharide (10 micrograms) (polyribosylribitol phosphate) conjugated to tetanus toxoid as carrier protein approximately 25 micrograms.

1. Executive Summary

No SmPC and PL changes are proposed.

2. Recommendation

The MAH submitted the results of a study 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 administered to healthy infants as a primary vaccination course at 2, 3 and 4 months of age. Non-inferiority was not demonstrated for all vaccine components according to the criteria set for non-inferiority.

No changes in the SmPC are warranted.

3. INTRODUCTION

On 12/07/2012, the MAH submitted a completed paediatric study for Infanrix Hexa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has been provided.

The MAH stated that the submitted paediatric study does no influence the benefit risk for Infanrix Hexa and that there is no consequential regulatory action.

4. SCIENTIFIC DISCUSSION

Information on the pharmaceutical formulation used in the study(ies)

See study design section.

Clinical aspects

4.1. Introduction

The MAH submitted a final report for Study nr: 113948 (DTPA-HBV-IPV-124 PRI): A phase I/II, double-blind, randomized, multicentre study to evaluate the safety and immunogenicity of new formulations of GlaxoSmithKline Biologicals' DTPa-HBVIPV/Hib vaccine when co-administered with Prevenar 13 to healthy infants as a primary vaccination course at 2, 3 and 4 months of age.

4.2. Clinical study

A phase I/II, double-blind, randomized, multicentre study to evaluate the safety and immunogenicity of new formulations of GlaxoSmithKline Biologicals' DTPa-HBVIPV/ Hib vaccine (GSK217744) when co-administered with Prevenar 13 to healthy infants as a primary vaccination course at 2, 3 and 4 months of age (Study nr: 113948 (DTPA-HBV-IPV-124 PRI)). The MAH declared that this study is a stand alone study.

Description

Methods

- Objective(s)

Primary objective:

To demonstrate that the immunogenicity of at least one DTPa-HBV-IPV/Hib formulation is non-inferior to the licensed formulation in terms of seroprotection rates to diphtheria, tetanus, hepatitis B and PRP antigens and in terms of antibody geometric mean concentrations (GMCs) for pertussis antigens one month after the third dose of the primary vaccination.

Criteria for non-inferiority:

- Non-inferiority in terms of immune response to diphtheria, tetanus, hepatitis B and PRP antigens was demonstrated if the upper limit of the 97.5% confidence interval (CI) on the group difference [Control minus investigational] in the percentage of seroprotected subjects for each antigen was ≤ 10% and,
- Non-inferiority in terms of immune response to pertussis antigens was demonstrated if, for each of the three antigens, the upper limit of the 97.5% CI on the GMC ratio [Control divided by investigational] was ≤ 1.5.

Secondary objective:

- To assess the immunological response to the study vaccines in terms of seroprotection status, seropositivity status and antibody concentrations or titres, one month after the third dose of the primary vaccination.
- To assess the immunological status towards diphtheria, tetanus pertussis and polio antigens in terms of seroprotection status, seropositivity status and antibody concentrations, before the first dose of the primary vaccination.
- To assess the immunological response to pertussis antigens in terms of vaccine response, one month after the third dose of the primary vaccination.
- To assess the safety and reactogenicity of the study vaccines in terms of solicited and unsolicited, local and general symptoms and serious adverse events.

- Study design

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 DATAPa-HBVIPV/HibGD vaccine 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 DBTBPa-HBVIPV/HibGD vaccine 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.

- Study population /Sample size

Study Population: Healthy male or female subjects between and including, 60 and 90 days of age at the time of the first vaccination. The subject should not have had previous or intercurrent diphtheria, tetanus, pertussis, polio, hepatitis B, Hib and/or pneumococcal vaccination or disease, with the exception of hepatitis B vaccination at birth. Written informed consent was obtained from the parents/legally acceptable representative(s) [LAR(s)] of the subject before entry into the study.

- Treatments

See Table below for treatments.

The vaccines used, D_AT_APa-HBV-IPV/Hib and D_BT_BPa-HBV-IPV/Hib contained D and T antigens produced at GSK facility in Gödöllö, Hungary and differed in the process by which the detoxified diphtheria and tetanus antigens were adsorbed onto aluminium hydroxide. The PRP antigen was conjugated to T antigen produced in Gödöllö, while the other antigens were identical.			
Vaccines	**Formulations (per dose volume of 0.5 ml)**	**Lot Nos.**	**Schedules and administration**
GSK Biologicals' combined D_AT_APa-HBV-IPV/Hib vaccine	Diphtheria toxoid ≥ 30IU (25Lf), Tetanus toxoid ≥ 40IU (10Lf), PT 25µg, FHA 25µg, PRN 8µg, HBsAg (recombinant) 10 µg, Poliovirus type 1: 40 D Ag units, Poliovirus type 2: 8 D Ag units, Poliovirus type 3: 32 D Ag units, PRP: 10µg, conjugated to tetanus toxoid 20-40µg, Aluminium as salts: 0.82mg.	D_AT_APa-HBV-IPV lot no.: DC21A030A, Hib lot no: DHIBA031A	2-3-4 months of age, intramuscular injection in the right thigh.
GSK Biologicals' combined D_BT_BPa-HBV-IPV/Hib vaccine		D_BT_BPa-HBV-IPV lot no.: DC21A031A, Hib lot no: DHIBA031A	2-3-4 months of age, intramuscular injection in the right thigh.
Reference vaccine /Comparator, dose and mode of administration, lot no.:			
Vaccine	**Formulation (per dose volume of 0.5 ml)**	**Lot Nos.**	**Schedule and administration**
GSK Biologicals' combined DTPa-HBV-IPV/Hib-vaccine (*Infanrix hexa*)	The composition of the antigens is the same as that detailed for the above D_AT_APa-HBV-IPV/Hib and D_BT_BPa-HBV-IPV/Hib formulations.	DTPa-HBV-IPV lot no.: DC21A029A Hib lot no.: DHIBA030A	2-3-4 months of age, intramuscular injection in the right thigh.
Vaccine	**Formulation (per dose volume of 0.5 ml)**	**Lot Nos.**	**Schedule and administration**
Pfizer's 13-valent pneumococcal vaccine (*Prevenar13*)	Mixture of 13 pneumococcal CRM_{197} conjugates serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19 A, 19F, 23F. Each dose contains 2.2 µg of saccharide of serotypes 4, 9V, 14, 18C, 19F and 23F, and 4.4 µg of serotype 6B, 0.125 mg of aluminium.	Lot no.: DEXTA390AZ DEXTA412AZ	2-3-4 months of age, intramuscular injection in the left thigh

- Outcomes/endpoints

Primary Outcome/Efficacy Variable:

Immunogenicity with respect to the components of the study vaccines.

- Anti-diphtheria, anti-tetanus, anti-HBs and anti-PRP seroprotection status one month after the third dose of primary vaccination.
- Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations one month after the third dose of primary vaccination.

Secondary Outcome/Efficacy Variables:

Immunogenicity with respect to the components of the study vaccines.

- Anti-diphtheria, anti-tetanus, anti-HBs, anti-poliovirus type 1, anti-poliovirus type 2, antipoliovirus type 3, anti-PRP, anti-PT, anti-FHA, anti-PRN, anti-pneumococcal serotypes* 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F antibody concentrations or titres, and seroprotection and/or seropositivity status one month after the third dose of primary vaccination.

  *Note: Only performed for subjects in Finland (Sub-cohort 1).

Vaccine response to PT, FHA and PRN one month after the third dose of primary vaccination.

Anti-diphtheria, anti-tetanus, anti-PT, anti-FHA, anti-PRN, anti-poliovirus type 1, antipoliovirus type 2 and anti-poliovirus type 3 antibody concentrations or titres and seroprotection and/or seropositivity status before the first dose of primary vaccination.

Solicited local and general adverse events.

- Occurrence of solicited local symptoms during the 8-day (Day 0–7) follow-up period after each vaccination.
- Occurrence of solicited general symptoms during the 8-day (Day 0–7) follow-up period after each vaccination.

Unsolicited adverse events.

- Occurrence of unsolicited AEs during the 31-day (Day 0–30) follow-up period after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

Serious adverse events.

- Occurrence of serious adverse events from Dose 1 up to study end

- Statistical Methods

Analyses were performed as specified in the protocol and in the Statistical Analysis Plan (SAP).

Results

- Recruitment/ Number analysed

See Tables 2 and 3.

Table 2 Number of subjects at each visit and list of withdrawn subjects (Total vaccinated cohort)

Group	VISIT	N	Withdrawn Subject numbers	Reason for withdrawal
FormA	VISIT 1 (D0)	240		
			no. 507	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
			no. 1929	DEATH
	VISIT 2 (M1)	238		
	VISIT 3 (M2)	238		
	VISIT 4 (M3)	238		
FormB	VISIT 1 (D0)	242		
			no. 257	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
			no. 403	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
			no. 1928	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
	VISIT 2 (M1)	239		
	VISIT 3 (M2)	239		
	VISIT 4 (M3)	239		
Control	VISIT 1 (D0)	239		
			no. 1895	CONSENT WITHDRAWAL, NOT DUE TO AN ADVERSE EVENT
	VISIT 2 (M1)	238		
	VISIT 3 (M2)	238		
	VISIT 4 (M3)	238		

FormA = DTPa-HBV-IPV/Hib Form A + Prevenar 13 at 2, 3 and 4 months of age
FormB = DTPa-HBV-IPV/Hib Form B + Prevenar 13 at 2, 3 and 4 months of age
Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age
N = Number of subjects who completed the visit
Withdrawn = Subject who did not return after the visit
Subject 1929 from FormA group died from asphyxia, interstitial lung disease, considered not related to vaccination, 17 days after Dose 1

Table 3 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal (Total vaccinated cohort)

	FormA	FormB	Control	Total
Number of subjects vaccinated	**240**	**242**	**239**	**721**
Number of subjects completed	**238**	**239**	**238**	**715**
Number of subjects withdrawn	**2**	**3**	**1**	**6**
Reasons for withdrawal :				
Serious Adverse Event	0	0	0	0
Non-Serious Adverse Event	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an adverse event)	1	3	1	5
Migrated/moved from study area	0	0	0	0
Lost to follow-up (subjects with incomplete vaccination course)	0	0	0	0
Lost to follow-up (subjects with complete vaccination course)	0	0	0	0
Sponsor study termination	0	0	0	0
Other: Death	1	0	0	1

FormA = DTPa-HBV-IPV/Hib Form A + Prevenar 13 at 2, 3 and 4 months of age
FormB = DTPa-HBV-IPV/Hib Form B + Prevenar 13 at 2, 3 and 4 months of age
Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Other: Subject 1929 from FormA group died from asphyxia, interstitial lung disease, considered not related to vaccination, 17 days after Dose 1

- Efficacy results

Immunogenicity:

The immunogenicity analysis was performed on the ATP cohort and Total vaccination cohort.

Primary objectives: non-inferiority in terms of immune response to diphtheria, tetanus, hepatitis B, pertussis and PRP:

Analysis was performed one month post-primary vaccination, for each investigational group:

- The upper limits of the standardized asymptotic 97.5% CI on the difference between the groups (Control minus each investigational group) in terms of diphtheria, tetanus, hepatitis B and PRP seroprotection rates were all below 10%.
- The upper limits of the 97.5% CI on the anti-PT and anti-FHA GMC ratio (Control divided by each investigational group) were all below 1.5, but, the upper limit of the 97.5% CI on the anti-PRN GMC ratio (Control divided by each investigational group) exceeded 1.5.
- Thus, the non-inferiority of the investigational DATAPa-HBV-IPV/HibGD and DBTBPa-HBVIPV/HibGD vaccines co-administered with *Prevenar 13* to the licensed *Infanrix hexa* vaccine coadministered with *Prevenar 13* was not demonstrated.

Secondary objectives (descriptive analysis):

One month post-primary vaccination (ATP cohort for immunogenicity)

- Seroprotective concentrations of antibodies against diphtheria and tetanus were observed in 100% of subjects in the three groups.
- At least 97.5% subjects in all groups had seroprotective levels of anti-HBs antibody concentrations.
- Seropositive antibody levels against PT, FHA and PRN were observed in 100% subjects in the three groups. Across groups, vaccine response to PT, FHA and PRN was mounted by at least 97.1%, 96.9% and 91% of subjects, respectively.
- The percentage of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/ml was 92.1% in Form A group, 87.9% in Form B group and 88.5% in the Control Group.
- Seroprotective titres of antibodies against poliovirus types 1 and 3 were observed in at least 97.4% and 97.9% of subjects, respectively. Seroprotective titres against poliovirus type 2 ranged from 90.5% to 94.8% across the three groups.
- Across groups, the percentage of subjects with pneumococcal antibody concentrations ≥ 0.15 µg/mL was at least 96.5% except for serotypes 6B (90.3%) and 23F (92.9%) and the percentage of subjects with pneumococcal antibody concentrations ≥ 0.35 µg/mL was at least 90.1% except for serotypes 6B (70.5%) and 23F (78.1%).

Table 1: Difference between groups in percentage of subjects with titre/concentrations equal to or above the proposed cut-off one month after primary vaccination between FormA and Control groups (ATP cohort for immunogenicity)

								Difference in percentage (Control minus FormA)		
		Control			FormA				97.5% CI	
Antibody	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-D (ELISA)	**0.1 IU/mL**	**219**	**219**	**100**	**214**	**214**	**100**	**0.00**	**-2.25**	**2.30**
Anti-T	**0.1 IU/mL**	**219**	**219**	**100**	**214**	**214**	**100**	**0.00**	**-2.25**	**2.30**
Anti-HBs	**10 mIU/mL**	**209**	**205**	**98.1**	**202**	**197**	**97.5**	**0.56**	**-3.27**	**4.63**
Anti-PRP	**0.15 µg/mL**	**218**	**193**	**88.5**	**214**	**197**	**92.1**	**-3.52**	**-10.19**	**3.00**
Anti-Polio 1	8 ED50	204	199	97.5	194	189	97.4	0.13	-4.01	4.42
Anti-Polio 2	8 ED50	197	184	93.4	190	172	90.5	2.87	-3.49	9.54
Anti-Polio 3	8 ED50	186	184	98.9	192	188	97.9	1.01	-2.61	4.95

FormA = DTPa-HBV-IPV/Hib Form A + Prevenar 13 at 2, 3 and 4 months of age; Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age; N = number of subjects with available results
n/% = number/percentage of subjects with titre and concentration within the specified range; 97.5% CI = Standardized asymptotic 97.5% confidence interval; LL = lower limit, UL = upper limit; Note that rows in bold indicate the result is linked to the primary objective

Table 2. Difference between groups in percentage of subjects with titre/concentrations equal to or above the proposed cut-off one month after primary vaccination between FormB and Control groups (ATP cohort for immunogenicity)

								Difference in percentage (Control minus FormB)		
		Control			FormB				97.5% CI	
Antibody	**Type**	**N**	**n**	**%**	**N**	**n**	**%**	**%**	**LL**	**UL**
Anti-D (ELISA)	**0.1 IU/mL**	**219**	**219**	**100**	**217**	**217**	**100**	**0.00**	**-2.25**	**2.27**
Anti-T	**0.1 IU/mL**	**219**	**219**	**100**	**217**	**217**	**100**	**0.00**	**-2.25**	**2.27**
Anti-HBs	**10 mIU/mL**	**209**	**205**	**98.1**	**205**	**203**	**99.0**	**-0.94**	**-4.57**	**2.36**
Anti-PRP	**0.15 µg/mL**	**218**	**193**	**88.5**	**216**	**190**	**88.0**	**0.57**	**-6.53**	**7.70**
Anti-Polio 1	8 ED50	204	199	97.5	198	193	97.5	0.07	-4.05	4.29
Anti-Polio 2	8 ED50	197	184	93.4	191	181	94.8	-1.36	-7.19	4.37
Anti-Polio 3	8 ED50	186	184	98.9	195	191	97.9	0.98	-2.64	4.87

FormB = DTPa-HBV-IPV/Hib Form B + Prevenar 13 at 2, 3 and 4 months of age; Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age; N = number of subjects with available results; n/% = number/percentage of subjects with titre and concentration within the specified range; 97.5% CI = Standardized asymptotic 97.5% confidence interval; LL = lower limit, UL = upper limit; Note that rows in bold indicate the result is linked to the primary objective

Table 3. Adjusted ratios of antibody geometric mean concentration/titre one month after primary vaccination between FormA and Control groups (ATP cohort for immunogenicity)

					Adjusted GMC ratio (Control / FormA)		
	Control		FormA			97.5% CI	
Antibody	**N**	**Adjusted GMC**	**N**	**Adjusted GMC**	**Value**	**LL**	**UL**
Anti-D (ELISA) (IU/mL)	211	1.861	199	1.489	1.25	1.10	1.42
Anti-T (IU/mL)	211	1.987	199	1.803	1.10	0.97	1.25
Anti-PT (EL.U/mL)	**209**	**73.9**	**199**	**58.5**	**1.26**	**1.11**	**1.44**
Anti-FHA (EL.U/mL)	**208**	**207.6**	**196**	**193.0**	**1.08**	**0.94**	**1.23**
Anti-PRN (EL.U/mL)	**210**	**105.6**	**199**	**79.5**	**1.33**	**1.14**	**1.54**
Anti-HBS (mIU/mL)	209	791.6	202	634.1	1.25	0.91	1.71
Anti-Polio 1 (ED50)	190	156.4	176	124.5	1.26	0.94	1.67
Anti-Polio 2 (ED50)	171	91.1	158	77.7	1.17	0.88	1.56
Anti-Polio 3 (ED50)	175	260.0	173	211.7	1.23	0.91	1.67
Anti-PRP (µg/mL)	218	1.155	214	1.014	1.14	0.85	1.54

FormA = DTPa-HBV-IPV/Hib Form A + Prevenar 13 at 2, 3 and 4 months of age; Control = DTPa-HBV-IPV/Hib licensed + Prevenar 13 at 2, 3 and 4 months of age; Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration; N = Number of subjects with both pre- and post-vaccination results available
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Country effect and baseline concentration - pooled variance with more than 2 groups); LL = lower limit, UL = upper limit; Note that rows in bold indicate the result is linked to the primary objective

Table 4. Adjusted ratios of antibody geometric mean concentration/titre one month after primary vaccination between FormB and Control groups (ATP cohort for immunogenicity)

					Adjusted GMC ratio (Control / FormB)		
	Control		FormB			97.5% CI	
Antibody	**N**	**Adjusted GMC**	**N**	**Adjusted GMC**	**Value**	**LL**	**UL**
Anti-D (ELISA) (IU/mL)	211	1.861	210	1.694	1.10	0.97	1.24
Anti-T (IU/mL)	211	1.987	210	1.776	1.12	0.99	1.26
Anti-PT (EL.U/mL)	**209**	**73.9**	**210**	**59.0**	**1.25**	**1.10**	**1.43**
Anti-FHA (EL.U/mL)	**208**	**207.6**	**209**	**166.6**	**1.25**	**1.09**	**1.42**
Anti-PRN (EL.U/mL)	**210**	**105.6**	**208**	**66.7**	**1.58**	**1.37**	**1.84**
Anti-HBS (mIU/mL)	209	791.6	205	597.4	1.33	0.97	1.81
Anti-Polio 1 (ED50)	190	156.4	185	106.2	1.47	1.11	1.95
Anti-Polio 2 (ED50)	171	91.1	167	77.7	1.17	0.88	1.56
Anti-Polio 3 (ED50)	175	260.0	185	183.8	1.41	1.05	1.91
Anti-PRP (µg/mL)	218	1.155	216	0.776	1.49	1.11	2.01

FormB = DTPa-HBV-IPV/Hib Form B + Prevenar 13 at 2, 3 and 4 months of age; Control = DTPa-HBV-IPV/Hib licensed + Prevenar13 at 2, 3 and 4 months of age; Adjusted GMC = geometric mean antibody concentration adjusted for baseline concentration; N = Number of subjects with both pre- and post-vaccination results available
97.5% CI = 97.5% confidence interval for the adjusted GMC ratio (Ancova model: adjustment for Country effect and baseline concentration - pooled variance with more than 2 groups); LL = lower limit, UL = upper limit; Note that rows in bold indicate the result is linked to the primary objective

- Safety results

Safety / reactogenicity:

The safety analysis was performed on the Total vaccinated cohort.

Any symptom: The percentage of doses followed by a report of any symptom (solicited and unsolicited, local and general) ranged from 87.8% to 91.2% in the three groups. The majority of the symptoms were reported during the first 4 (Days 0-3) days following vaccination.

Solicited local symptoms: Injection site pain was the most frequently reported solicited local symptom in the three groups, reported following 52.9%, 52.2% and 41.8% doses in the Form A, Form B and Control groups, respectively. The most common grade 3 solicited local symptom in the three groups was swelling, reported following 7.4% doses in Form A group and 8.1% doses in the Form B and Control groups.

Solicited general symptoms: Irritability (any and grade 3) was the most frequently reported solicited general symptom in the three groups. Grade 3 fever (> 39.0 °C axillary temperature) was reported for 0.7% of subjects in Form A and Form B groups and 0.6% of subjects in the Control group.

Unsolicited symptoms: During the 31-day follow-up period, according to the overall/subject analysis, grade 3 unsolicited symptoms were reported for 7.1%, 8.7% and 6.7% of subjects in the Form A, Form B and Control groups, respectively. Unsolicited symptoms with a causal relationship to vaccination were reported for 21.7%, 21.1% and 23% of subjects in the Form A, Form B and Control groups, respectively.

Concomitant medication: The percentage of doses followed by at least one concomitant medication during the 31-day follow up period following vaccination was 60.1%, 59.2% and 52.2% in the Form A, Form B and Control groups, respectively. Prophylactic antipyretics were given after not more than 4.6% of doses in the three groups.

Serious adverse events: SAEs were reported for 9 (3.8%), 5 (2.1%) and 4 (1.7%) subjects in the Form A, Form B and Control groups, respectively. One fatal SAE was reported during the entire study period: This fatal case was described for a 2-month-old female (subject 1929) who died 17 days after Dose 1 of the Form A vaccine due to asphyxia and interstitial lung disease. The subject was co-sleeping with her parents. The majority of the SAEs reported across the groups were lower respiratory illnesses (i.e. bronchiolitis, pneumonia, etc). None of the SAEs were considered to be potentially related to vaccination by the investigator.

Withdrawals due to adverse events /serious adverse events: One death was reported during the study for a subject from the Form A group. Subject number 1929 died 17 days after receiving the first dose of the study vaccine due to asphyxia and interstitial lung disease. This event was considered by the investigator not to be related to vaccination.

Important safety information received after the data lock point (database freeze date): No safety information was received after the data lock point (database freeze date) for this study.

4.3. Discussion on clinical aspects

Inferential immunogenicity objectives (One month post primary vaccination, for each investigational group)

The primary objective of the study was not met: non-inferiority of the immunogenicity respons to Formulation A versus *Infanrix hexa* and to Formulation B versus *Infanrix hexa* was not met:

- Non-inferiority in terms of immune response to diphtheria, tetanus and hepatitis B was demonstrated since the upper limits of the standardised asymptotic 97.5% CI on the between groupdifference (Control group minus each investigational group) in terms of seroprotection rates to D, T and HBs were below the pre-defined non-inferiority margin of 10%.
- For each formulation, the upper limits of the 97.5% CI on the GMC ratio (Control group divided by each investigational group) were below 1.5, the pre-defined clinical limit for non-inferiority, in terms of immune response to PT and FHA. 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.
- For PRP, the upper limits of the standardised asymptotic 97.5% CI on the group difference (Control group minus each investigational group) for the percentage of seroprotected subjects was below 10%, the pre-defined clinical limit for non-inferiority. However, in view of the

sequential nature of analysis non-inferiority for PRP could not be concluded for both formulations.

Descriptive immunogenicity objectives:

- One month post primary vaccination, between 97.5% and 100% subjects had seroprotective antibodies against diphtheria, tetanus and hepatitis B. Between 90.5% to 97.9% subjects had seroprotective antibodies against the three poliovirus types. Anti-PRP seroprotection rates ranged from 87.9% to 92.1%. Seropositive antibody levels against pertussis were observed in 100% of the subjects in the three groups.

Safety and reactogenicity objectives:

- 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 °C per subject was higher in Form A (33.8%) and Form B (30.8) compared to the control group (18.1%).
- At least one unsolicited AE was reported for 153 (63.8%), 165 (68.2%), and 159 (66.5%) subjects in the Form A, Form B and Control groups, respectively. SAEs were reported for 9 (3.8%), 5 (2.1%) and 4 (1.7%) subjects in the Form A, Form B and Control groups, respectively. One fatal SAE was reported during the entire study period: Subject 1929 from Form A group died 17 days after Dose 1 of the study vaccine due to asphyxia and interstitial lung disease. None of the SAEs were considered to be potentially related to vaccination by the investigator.

5. Rapporteur's Overall Conclusion AND RECOMMENDATION

Overall conclusion

The MAH submitted the results of a double-blind, randomised, multicentre study 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 primary objective, i.e. non-inferiority of the immunogenicity of at least one of the novel DTPa-HBV-IPV/Hib vaccine formulations compared to the licensed Infanrix Hexa vaccine, was not met according to the criteria set for non-inferiority, as the immune response to the pertactin component of both novel formulations was not non-inferior to Infanrix Hexa. No divergent safety signals were detected in the comparison of the new formulation with the licensed Infanrix Hexa.

The MAH should continue to investigate in pertussis vaccines that offer prolonged protection compared to the currently authorised vaccines in view of the resurgence of pertussis in fully vaccinated individuals which appears to be at least partly due to waning vaccine-induced immunity (Cherry, 2012).

6. Request for supplementary information

Request for supplementary information: In view of failure to show non-inferiority for both new formulations against the approved formulation in relation to immunogenicity, the applicant should clarify backup development strategy and consequential deliverables.

Reference

Cherry, J. D. (2012). Epidemic Pertussis in 2012 — The Resurgence of a Vaccine-Preventable Disease. *New England Journal of Medicine*, 120815140022001. doi:10.1056/NEJMp1209051