EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

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/P46/0104

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

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

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I. EXECUTIVE SUMMARY

The MAH assessed the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B vaccine challenge in healthy children aged 11-12 years, previously vaccinated with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) or GSK Biologicals' DTPa-IPV/Hib and HBV (*Engerix- B*) vaccines at the ages of 3, 5 and 11 months in clinical trial DTPa-HBV-IPV-031 (217744/031). The MAH concluded that these data warrant a change in the SmPC of the product to reflect anti-HepB Ab persistence. A type II variation will be submitted in due time in order to update section 5.1 of the SmPC.

II. RECOMMENDATION[1]

The data from this study can warrant a change in the SmPC and PL to reflect the data on the long-term persistence of the antibody response following Hepatitis B vaccination.

III. INTRODUCTION

The MAH submitted a completed paediatric study for Infanrix hexa to comply with the requirements of Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. Long-term persistence of anti-hepatitis B antibodies and response to a hepatitis B vaccine were assessed in healthy children aged 11-12 years previously vaccinated with a anti hepatitis B vaccine at the ages of 3, 5 and 11 months in clinical trial DTPa-HBV-IPV-031 (217744/031).

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

One dose (0.5 ml) of *Engerix-B* (Lot no.: AHBVB720A, Expiry date: 31 March 2012) contained: 10 µg of recombinant hepatitis B surface antigen adsorbed on 0.25 mg aluminium as aluminium hydroxide.

IV.2 Clinical aspects

1. Introduction

Long-term persistence of anti-hepatitis B antibodies and response to a hepatitis B vaccine were assessed in healthy children aged 11-12 years previously vaccinated with a anti hepatitis B vaccine at the ages of 3, 5 and 11 months in clinical trial DTPa-HBV-IPV-031 (217744/031). According to the MAH these data warrant a change in the vaccine SmPC to reflect the data regarding the long-term antibody persistence.

2. Clinical study

2.1 Methods

2.1.1 Objectives

Primary:

[1] *The recommendation from section V can be copied in this section*

- To assess the anti-HB antibody response to a challenge dose of HBV vaccine in subjects aged 11-12 years, vaccinated in infancy with three doses of *Infanrix hexa* or *Engerix-B* at 3, 5 and 11 months of age.

Secondary:

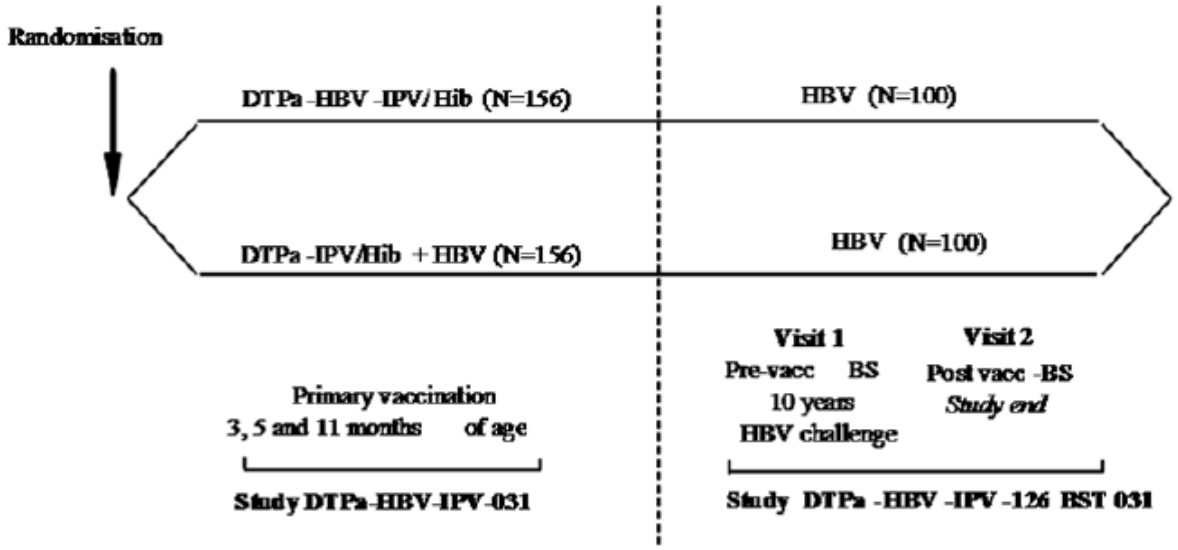
- To assess the persistence of anti-HB antibodies, 10-11 years after primary infant vaccination with three doses of *Infanrix hexa* or *Engerix-B* at 3, 5 and 11 months of age.
- To evaluate the safety and reactogenicity of a challenge dose of HBV vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

2.1.2 Study design

Phase IV, open, multi-centre, non-randomised study with the same two groups as in the primary study. All subjects previously vaccinated with three doses of DTPa-HBV-IPV/Hib or DTPa-IPV/Hib+HBV in the first year of life received a single challenge dose of GSK Biologicals' *Engerix-B* vaccine in this study.

The two treatment groups were as follows:

- **DTPa-HBV-IPV/Hib group**: Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
- **DTPa-IPV/Hib+HBV group**: Subjects who previously received DTPa-IPV/Hib + HBV (*Engerix-B*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.



N = Number of subjects planned to be enrolled

Pre-vacc BS = Pre-vaccination blood sampling, Post-vac BS = Post-vaccination blood sampling

Two blood samples were drawn: one before, and the other, one month after the challenge dose of *Engerix-B* vaccine.

2.1.3 Study population /Sample size

Subjects aged 11-12 years, previously vaccinated with three doses of *Infanrix hexa* or *Engerix-B* at 3, 5 and 11 months of age in the primary study 217744/031 (DTPa-HBV-IPV-031).

Number of subjects:			
Group	DTPa-HBV-IPV/Hib	DTPa-IPV/Hib+HBV	Total
Planned	135	129	264
Total Vaccinated Cohort (TVC)	95	90	185
Completed	95	90	185

Group	DTPa-HBV-IPV/Hib	DTPa-IPV/Hib+HBV	Total
According-to-protocol (ATP) cohort for antibody persistence	95	89	184
ATP cohort for immunogenicity	95	89	184

2.1.4 Treatments

Vaccination schedule/site: All subjects received a dose of Engerix-B as an intramuscular injection into the deltoid region of the non-dominant arm.

2.1.5 Outcomes/endpoints

Primary endpoint

Anti-HBs antibody concentrations one month after a challenge dose of HBV vaccine:

- Percentage of subjects with anti-HBs antibody concentrations ≥ 100 mIU/ml.

Secondary endpoints

Immunogenicity

Persistence and immune response to the study vaccine:

- Percentage of subjects with an anamnestic response to a challenge dose.
- Anti-HBs antibody concentrations ≥ 3.3 mIU/ml, ≥ 10 mIU/ml, and ≥ 100 mIU/ml before and one month after a challenge dose of HBV vaccine.

Safety and reactogenicity:

Solicited local and general symptoms.

- Occurrence of solicited local symptoms during the 4-day (Day 0 to Day 3) follow-up period after a challenge dose of HBV vaccine.
- Occurrence of solicited general symptoms during the 4-day (Day 0 to Day 3) follow-up period after a challenge dose of HBV vaccine.

Unsolicited adverse events.

- Occurrence of unsolicited symptoms during the 31-day (Day 0 to Day 30) follow-up period after a challenge dose of HBV vaccine.

Serious adverse events.

- Occurrence of SAEs after the challenge dose of HBV vaccine up to the study end.

2.1.6 Statistical methods, sample size

The sample size of this challenge dose study was not estimated using any power based computations. A total of 312 children aged 11-12 years, who participated in the primary study 217744/031 (DTPa-HBV-IPV-031) were expected to participate in this challenge dose study. It was assumed that a range of 15% to 10% of the subjects enrolled in the challenge dose study might be non-evaluable at the time of analysis (e.g. dropouts, noncompliance with protocol etc.). Therefore, a total of 270 or 280 evaluable subjects were expected to participate in this challenge dose study.

Total vaccinated cohort

The TVC included all subjects who received the challenge dose of the HBV vaccine. The TVC for the analysis of safety included all subjects with study vaccine administration documented. The TVC for the analysis of immunogenicity was to include all subjects who received a challenge

dose of HBV vaccine and for whom data concerning immunogenicity endpoint measures were available at the post-HBV vaccine challenge blood sampling time point.

ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e. those who met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria met during the study), who had received a challenge dose of *Engerix-B* and for whom data concerning immunogenicity endpoint measures were available at the post-HBV challenge time point. The interval between Visit 1 and Visit 2, considered for inclusion of a subject in the ATP cohort for analysis of immunogenicity was 21-48 days.

ATP cohort for antibody persistence

The ATP cohort for antibody persistence included all subjects:

- aged 11-12 years (from and including the 11th birthday up to but excluding the 13th birthday) at the time of enrolment,
- who had received three doses of the combination vaccine (*Infanrix hexa* or *Engerix-B*) in the primary study 217744/031 (DTPa-HBV-IPV-031),
- who had not received any additional dose of hepatitis B (containing) vaccine,
- with no evidence of hepatitis B infection or disease (including anti-HBc at postchallenge dose time point or abnormal increase in anti-HBs concentrations),
- for whom serological results were available at the pre-HBV vaccine challenge blood sampling time point.

Analysis of safety: Analysis was performed on the TVC.

Analysis of demography: At Visit 1, demographic characteristics (age in years and gender) were tabulated. The mean age (with the range and standard deviation) of the vaccinated subjects was calculated. The distribution of subjects among the study centres was tabulated.

2.1.7 Derived and transformed data

Immunogenicity

- A seronegative subject was a subject with anti-HB antibody concentrations below the cut-off level (< 3.3 mIU/ml).
- A seropositive subject was a subject with anti-HB antibody concentrations above the cut-off level (≥ 3.3 mIU/ml).
- A seroprotected subject was a subject with anti-HB antibody concentrations ≥ 10 mIU/ml.
- Anamnestic response to the challenge dose was defined as:
    - At least (i.e. greater than or equal to) a 4-fold rise in post-challenge dose anti-HBs antibody concentrations in subjects seropositive at the pre-challenge dose time point.
    - Post-challenge dose anti-HBs antibody concentrations ≥10 mIU/ml in subjects seronegative at the pre-challenge dose time point.
- The GMC calculations were performed by taking the anti-log of the mean of the log10 concentration transformations. Antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC calculation.
- For a given subject and a given immunogenicity measurement, missing or nonevaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

Safety/Reactogenicity

- For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced. Therefore the analysis of the solicited symptoms based on the TVC included only subjects with documented safety data.

- For the analysis of unsolicited adverse events/concomitant medication, all vaccinated subjects were to be considered and subjects who did not report an event were considered as subjects without an event.

2.2 Results

2.2.1 Demography results:

The mean age of subjects for the ATP cohort for immunogenicity was 11.3 years, with a standard deviation of 0.46 years. Male subjects constituted 57.1% of the study population.

2.2.2 Number of subjects

A total of 312 subjects were enrolled in the primary study 217744/031 (DTPa-HBV-IPV-031). A total of 185 subjects (95 subjects in the DTPa-HBV-IPV/Hib group and 90 subjects in the DTPa-IPV/Hib+HBV group) were vaccinated in this study after having been checked for the inclusion and exclusion criteria. The main reasons for non-participation in this challenge dose study were attributed to consent withdrawal (not due to AEs/SAEs) and migration of subjects from the study area. The number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion is presented in Table 9.

Table 9 Number of subjects enrolled into the study as well as the number excluded from ATP analyses with reasons for exclusion

Title	Total			DTPa-HBV-IPV/Hib		DTPa-IPV/Hib+HBV	
	n	s	%	n	s	n	s
Total cohort	264			135		129	
Study vaccine dose not administrated but subject number allocated (code 1030)	79	79		40	40	39	39
Total Vaccinated Cohort	185		100	95		90	
ATP cohort for safety	185		100	95		90	
Protocol violation (inclusion/exclusion criteria) (code 2010)	1	1		0	0	1	1
ATP cohort for immunogenicity	184		99.5	95		89	
Protocol violation (inclusion/exclusion criteria-persistence) (code 3010)	1	1		0	0	1	1
ATP cohort for antibody persistence	184		99.5	95		89	

DTPa-HBV-IPV/Hib group = Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
DTPa-IPV/Hib+HBV group = Subjects who previously received DTPa-IPV/Hib + HBV (*Engerix- B*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total Vaccinated Cohort

2.2.3 Immunogenicity results

Immunological correlate of protection: Antibodies to the HB antigen were measured using ELISA developed in-house. The cutoff of the test was set at 3.3 mIU/ml. An antibody concentration ≥ 10 mIU/ml defined seroprotection [Centre for Disease Control, 1991; World Health Organization, 1988].

Primary objective and endpoint: Assessment of the anti-HB antibody response to a challenge dose of HBV vaccine in the subjects aged 11-12 years, vaccinated in infancy with three doses of *Infanrix hexa* or *Engerix-B* at 3, 5 and 11 months of age by determination of the anti-HB antibody concentration and the percentage of subjects with anti-HB antibody concentrations ≥ 100 mIU/ml one month after the challenge dose.

Response to the HBV vaccine challenge dose one month after the challenge dose vaccination (ATP cohort for immunogenicity):

The anti-HBs immunogenicity results for the ATP cohort for immunogenicity at pre and post-challenge dose time points is presented in Table 1.

- The percentage of subjects with anti-HB antibody concentrations ≥ 10 mIU/ml was 95.8% in the DTPa-HBV-IPV/Hib group and 98.9% in the DTPa-IPV/Hib+HBV group.
- The percentage of subjects with anti-HBs antibody concentrations ≥ 100 mIU/ml was 92.6% in the DTPa-HBV-IPV/Hib Group and 96.6% in the DTPa-IPV/Hib+HBV group.
- The anti-HBs GMCs observed in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups were 2917.5 mIU/ ml and 3943.7 mIU/ ml, respectively

Table 1: Anti-HBs seropositivity rates, percentage of subjects with antibody concentrations ≥ 10 mIU/ml, ≥100mIU/ml, percentage of subjects with antibody concentrations between ≥ 10mIU/ml and 100 mIU/ml and GMCs (calculated on all subjects) at pre and post-challenge dose time point (ATP cohort for immunogenicity)

			≥ 3.3 mIU/ml				≥ 10 mIU/ml				≥ 10 and <100 mIU/ml				≥ 100 mIU/ml				GMC		
					95% CI				95% CI				95% CI				95% CI		Value	95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL		LL	UL
DTPa-HBV-IPV/Hib	Pre-C	95	69	72.6	62.5	81.3	51	53.7	43.2	64.0	40	42.1	32.0	52.7	11	11.6	5.9	19.8	12.3	8.8	17.2
	Post-C	95	93	97.9	92.6	99.7	91	95.8	89.6	98.8	3	3.2	0.7	9.0	88	92.6	85.4	97.0	2917.5	1836.3	4635.4
DTPa-IPV/Hib +HBV	Pre-C	89	67	75.3	65.0	83.8	50	56.2	45.3	66.7	43	48.3	37.6	59.2	7	7.9	3.2	15.5	13.9	9.8	19.8
	Post-C	89	88	98.9	93.9	100	88	98.9	93.9	100	2	2.2	0.3	7.9	86	96.6	90.5	99.3	3943.7	2553.4	6090.8

DTPa-HBV-IPV/Hib group = Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
DTPa-IPV/Hib+HBV group = Subjects who previously received DTPa-IPV/Hib + HBV (*Engerix-B*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-C = Pre-challenge dose time point
Post-C = Post-challenge dose time point

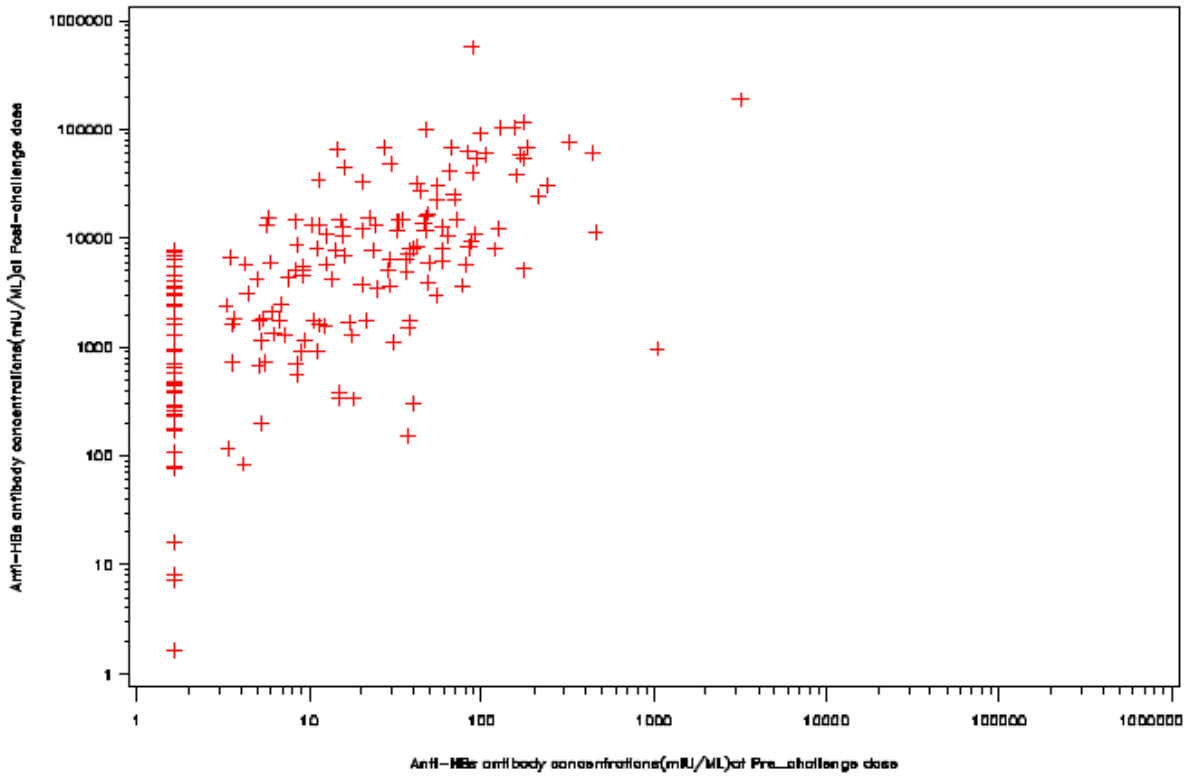
Relationship between pre-challenge serological status and response to the HBV challenge dose

The anti-HBs seropositivity rates, percentage of subjects with antibody concentrations ≥ 10 mIU/ml, ≥ 100mIU/ml and GMCs at the post-challenge dose time point in relation to their pre-challenge dose status is presented in Table 12 (of the MAH body report, not shown here) and Figure 1.

- In the DTPa-HBV-IPV/Hib (Infanrix hexa) group, the percentage of subjects with seropositivity rates increased from 72.6% to 97.9%, the percentage of subjects with anti-HBs concentrations ≥ 10 mIU/ml increased from 53.7% to 95.8% and the percentage of subjects with anti-HBs concentrations ≥ 100 mIU/ml increased from 11.6% to 92.6%, one month after the challenge dose.

- In the DTPa-IPV/Hib+HBV group, the percentage of subjects with seropositivity rates increased from 75.3% to 98.9%, the percentage of subjects with anti-HBs concentrations ≥ 10 mIU/ml increased from 56.2% to 98.9% and the percentage of subjects with anti-HBs concentrations ≥ 100 mIU/ml increased from 7.9% to 96.6%, one month after the challenge dose.

Figure 1 **Anti-HBs antibody concentrations between pre and post-challenge dose (ATP cohort for immunogenicity)**



Secondary immunogenicity objective: To assess the persistence of anti-HBs antibodies, 10-11 years after primary infant vaccination with three doses of *Infanrix hexa* or *Engerix-B* at 3, 5 and 11 months of age through

Determination of the percentage of subjects with an anamnestic response to a challenge dose.

Determination of anti-HBs antibody concentrations ≥ 3.3 mIU/ml, ≥ 10 mIU/ml, and ≥ 100 mIU/ml before and one month after a challenge dose of HBV vaccine.

Anamnestic response to the HBV vaccine challenge dose (ATP cohort for immunogenicity):
The anamnestic response to the HBV challenge dose is presented in Table 13.

- An anamnestic response to the HBV vaccine challenge dose was mounted by 95.8% and 97.8% of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.
- The percentage of subjects who were seronegative at the pre-challenge time point and who mounted an immune response were 84.6% and 95.5% in the DTPa-HBV-IPV/Hib group and the DTPa-IPV/Hib+HBV groups, respectively.

Table 13 Anamnestic response to the HBV challenge dose stratified based on the pre-challenge dose status (ATP cohort for immunogenicity)

			Anamnestic response			
					95% CI	
Group	Pre-vaccination status	N	n	%	LL	UL
DTPa-HBV-IPV/Hib	S- (<3.3 mIU/ml)	26	22	84.6	65.1	95.6
	3.3-<10mIU/ml	18	18	100	81.5	100
	≥10 mIU/ml	51	51	100	93.0	100
	Total	95	91	95.8	89.6	98.8
DTPa-IPV/Hib+HBV	S- (<3.3 mIU/ml)	22	21	95.5	77.2	99.9
	3.3-<10mIU/ml	17	17	100	80.5	100
	≥10 mIU/ml	50	49	98.0	89.4	99.9
	Total	89	87	97.8	92.1	99.7

DTPa-HBV-IPV/Hib group = Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
DTPa-IPV/Hib+HBV group = Subjects who previously received DTPa-IPV/Hib + HBV (Engerix-B) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
Stratification based in pre-challenge dose status:
<3.3 mIU/ml = subjects with antibody concentration <3.3 mIU/ml
3.3-10 mIU/ml = subjects with antibody concentration between 3.3 mIU/ml to 10 mIU/ml
≥10 mIU/ml = subjects with antibody concentration ≥10 mIU/ml
N = number of subjects with pre and post-challenge dose results available
n (%) = number (percentage) of subjects with antibody concentrations above the specified cut-off
95% CI; LL, UL = exact 95% confidence interval; lower and upper limits
S- = seronegative subjects (antibody concentration < 3.3 mIU/ml)
Response defined as:
For initially seronegative subjects, antibody concentration ≥ 10 mIU/ml one month after post-challenge dose
For initially seropositive subjects: antibody concentration at one month after post-challenge dose ≥ 4 fold the pre-vaccination antibody concentration.

Persistence of antibodies against hepatitis B at the pre-challenge dose time point (ATP cohort for persistence):

The result for the ATP cohort for persistence at the pre-challenge dose time point are presented in Table 1.

- The percentage of subjects with anti-HBs antibody concentrations ≥ 3.3 mIU/ml was 72.6%, those with anti-HBs antibody concentrations ≥ 10 mIU/ml was 53.7 % and those with anti-HBs antibody concentrations ≥ 100 mIU/ ml was 11.6 % in the DTPa-HBV-IPV/Hib group.
- The percentage of subjects with anti-HBs antibody concentrations ≥ 3.3 mIU/ml was 75.3%, those with anti-HBs antibody concentrations ≥ 10 mIU/ml was 56.2 % and those with anti-HBs antibody concentrations ≥ 100 mIU/ ml was 7.9 % in the DTPa-IPV/Hib+HBV group.
- The GMCs were 12.3 mIU/ ml and 13.9 mIU/ ml in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.

Immunogenicity conclusions

- A single dose of *Engerix-B* was shown to be immunogenic one month after the challenge dose as evidenced by the percentage of subjects with anti-HBs antibody concentrations ≥10 mIU/ml (95.8% and 98.9 % of subjects, in the DTPa-HBVIPV/Hib and DTPa-IPV/Hib+HBV groups, respectively) and anti-HBs antibody concentrations ≥ 100 mIU/ml (92.6% and 96.6% of subjects, in the DTPa-HBVIPV/Hib and DTPa-IPV/Hib+HBV groups, respectively).

- Persisting anti-HBs antibody concentrations ≥ 3.3 mIU/ml after a period of about 10 years after the primary vaccination, were observed in72.6 % and 75.3 % of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively and anti-HBs antibody concentrations ≥10 mIU/ml, were observed in 53.7 % and 56.2 % of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.
- An anamnestic response was mounted by 95.8% and 97.8% of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.

2.2.4 Safety results

Secondary safety objective: To evaluate the safety and reactogenicity of a challenge dose of HBV vaccine in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

Solicited local adverse events were pain, redness or swelling at the injection site. All sollicited local (injection site) reactions were considered causally related to vaccination.
Solicited general adverse events were fatigue, fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain) or headache.
Serious adverse events were untowarded medical occurrences that either resulted in death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation or resulted in disability/incapacity.

Solicited local adverse events
The incidence of solicited local symptoms reported during the 4-day (Day 0 to Day 3) post-vaccination period is presented in Table 16.
All local symptoms were considered to be causally related to vaccination.
- Pain at the injection site was the most frequently reported solicited local symptom in both groups, reported for not more than 31.6% of subjects during the 4-day (Day 0 to Day 3) post-vaccination follow-up period.
- Grade 3 pain was reported for one subject in each group.
- Swelling was reported for 15.8% and 8.9% of subjects in DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.

Table 16 Incidence of solicited local symptoms reported during the 4-day (Day 0 to Day 3) post-vaccination period (Total Vaccinated Cohort)

		DTPa-HBV-IPV/Hib					DTPa-IPV/Hib+HBV				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Pain	Any	95	30	31.6	22.4	41.9	90	24	26.7	17.9	37.0
	Grade 3	95	1	1.1	0.0	5.7	90	1	1.1	0.0	6.0
Redness (mm)	Any	95	25	26.3	17.8	36.4	90	22	24.4	16.0	34.6
	>50 mm	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
Swelling (mm)	Any	95	15	15.8	9.1	24.7	90	8	8.9	3.9	16.8
	>50 mm	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0

DTPa-HBV-IPV/Hib group = Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
DTPa-IPV/Hib+HBV group = Subjects who previously received DTPa-IPV/Hib + HBV (*Engerix-B*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
N= number of subjects with the documented dose,
n (%) = number (percentage) of subjects reporting the symptom at least once,
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit,
Any = Any solicited local symptom reported regardless of activity,
Grade 3 Pain: Pain that prevented normal activity.

Solicited general adverse events

The incidence of solicited general symptoms reported during the 4-day (Day 0 to Day 3) post-vaccination period is presented in Table 17.

- Fatigue was the most frequently reported solicited general symptom, reported for 24.2% and 24.4% of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.
- Solicited general symptoms of Grade 3 intensity (fatigue and headache) was reported for one subject in the DTPa-HBV-IPV/Hib group.

Table 17 Incidence of solicited general symptoms reported during the 4-day (Day 0 to Day 3) post-vaccination period (Total Vaccinated Cohort)

		DTPa-HBV-IPV/Hib					DTPa-IPV/Hib+HBV				
					95 % CI					95 % CI	
Symptom	Type	N	n	%	LL	UL	N	n	%	LL	UL
Fatigue	Any	95	23	24.2	16.0	34.1	90	22	24.4	16.0	34.6
	Related	95	12	12.6	6.7	21.0	90	10	11.1	5.5	19.5
	Grade 3	95	1	1.1	0.0	5.7	90	0	0.0	0.0	4.0
	Grade 3* Related	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
Gastrointestinal symptoms	Any	95	9	9.5	4.4	17.2	90	9	10.0	4.7	18.1
	Related	95	3	3.2	0.7	9.0	90	5	5.6	1.8	12.5
	Grade 3	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
	Grade 3* Related	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
Headache	Any	95	19	20.0	12.5	29.5	90	14	15.6	8.8	24.7
	Related	95	7	7.4	3.0	14.6	90	3	3.3	0.7	9.4
	Grade 3	95	1	1.1	0.0	5.7	90	0	0.0	0.0	4.0
	Grade 3* Related	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
Temperature (Axillary) (°C)	Any	95	1	1.1	0.0	5.7	90	3	3.3	0.7	9.4
	>37.5 - ...	95	1	1.1	0.0	5.7	90	3	3.3	0.7	9.4
	>38.0 - ...	95	1	1.1	0.0	5.7	90	0	0.0	0.0	4.0
	>38.5 - ...	95	1	1.1	0.0	5.7	90	0	0.0	0.0	4.0
	>39.0 - ...	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
	>39.0 - ...Related	95	0	0.0	0.0	3.8	90	0	0.0	0.0	4.0
	Related	95	0	0.0	0.0	3.8	90	1	1.1	0.0	6.0

DTPa-HBV-IPV/Hib group = Subjects who previously received DTPa-HBV-IPV/Hib (*Infanrix hexa*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
DTPa-IPV/Hib+HBV group = Subjects who previously received DTPa-IPV/Hib + HBV (*Engerix-B*) at 3, 5 and 11-12 months of age and received a challenge dose of HBV vaccine in this study.
N= number of subjects with the administered dose
n (%)= number (percentage) of subjects reporting the symptom at least once
95%CI= Exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Any = Any solicited general symptom reported regardless of intensity
Grade 3 = Symptoms that prevented normal activity (Grade 3 Fever = Temperature >39.0°C)
Grade 3* Related = Grade 3 symptoms related to vaccination

Unsolicited adverse events

The percentage of subjects for whom the occurrence of unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Day 0 to Day 30) post-vaccination period was reported is presented in Table 18 (not shown). The percentage of subjects who reported the occurrence of Grade 3 unsolicited symptoms classified by MedDRA Primary System Organ Class and Preferred Term during the 31-day (Day 0 to Day 30) post-vaccination period is presented in Table 19 (not shown) .

- At least one unsolicited symptom was reported for 5.3% and 7.8% of subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.

- Grade 3 unsolicited AE (Otitis media) was reported for one subject in the DTPa-IPV/Hib+HBV group.
- No unsolicited symptoms that were considered to be causally related to vaccination were reported during the 31-day follow-up period.

Serious adverse events

Fatal events: No deaths were reported during the study.

Non-fatal events: Over the entire study period (31-days), an SAE, [Infection (not specified)], was reported for subject number 287 in the DTPa-HBV-IPV/Hib group, two days after vaccination which resulted in hospitalisation and lasted for six days. The infection resolved during the course of the study and was assessed as not causally related to the vaccination, by the investigator.

Safety conclusions

- At least one unsolicited symptom was reported for not more than 7.8% of subjects across both groups.
- Grade 3 unsolicited symptom (Otitis media) was reported for one subject in the DTPa-IPV/Hib+HBV group.
- The SAE reported for one subject (infection) resolved during the course of the study and was not assessed as causally related to the vaccination by the investigator.
- No fatal SAEs were reported.

3. Discussion on clinical (immunogenicity and safety) aspects

The present study was conducted to assess anti-HBs antibody persistence and immune response to a challenge dose of HBV in children 11-12 years, previously vaccinated with GSK DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) or GSK Biologicals' DTPa-IPV/Hib and HBV (*Engerix-B*) vaccines at the age of 3, 5 and 11 months. The results demonstrate that the immune response induced by the three dose primary vaccination course in infancy persisted for at least 11 years (anti-HBs antibody concentrations $\geq$ 3.3 mIU/ml was reported in 72.6 % subjects in the DTPa-HBV-IPV/Hib group and 75.3 % subjects in the DTPa-IPV/Hib+HBV group). An anamnestic response to the HBV challenge dose, indicative of an immunological memory to the vaccine antigen, was observed in the majority of subjects (anamnestic response mounted by 95.8% subjects in the DTPa-HBVIPV/Hib group and 97.8% of subjects in the DTPa-IPV/Hib+HBV group). The data suggests that protection against hepatitis B may still be conferred through immune memory in all subjects who responded to the primary vaccination but subsequently had anti-HB antibody concentrations < 10 mIU/ml.

Hepatitis B response to the challenge dose is comparable in children who received the HBV component as part of a combination vaccine or as a monovalent vaccine in infancy.

Engerix-B was confirmed to be safe, well tolerated and immunogenic when administered as a challenge dose in subjects primed in infancy with *Infanrix hexa* or *Engerix-B*.

4. Conclusions:

- One month after the challenge dose, 92.6% and 96.6% subjects had anti-HBs antibody concentration ≥ 100 mIU/ml in DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV group, respectively.
- Approximately ten years after the primary vaccination, 72.6% in DTPa-HBV-IPV/Hib group and 75.3% subjects in DTPa-IPV/Hib+HBV group had anti-HB antibody concentration ≥3.3 mIU/ml, 53.7% in DTPa-HBV-IPV/Hib group and 56.2% subjects in DTPa-IPV/Hib+HBV group had anti-HB antibody concentration ≥10 mIU/ml.
- An anamnestic response to the hepatitis B challenge dose was mounted by 95.8% (91/95) and 97.8% (87/89) subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively.

- At least one unsolicited symptom was reported for 5.3% and 7.8% subjects in DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV group, respectively, within the 31 day (Day 0 to Day 30) follow up period after the challenge dose.
- An SAE (infection, not specified) was reported for one subject from DTPa-HBV-IPV/Hib group, which was assessed by the investigator as not causally related to vaccination. The SAE was resolved before the end of study.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
The MAH assessed the long-term persistence of antibodies against hepatitis B and the immune response to a hepatitis B vaccine challenge in healthy children aged 11-12 years, previously vaccinated with GlaxoSmithKline (GSK) Biologicals' DTPa-HBV-IPV/Hib vaccine (*Infanrix hexa*) or GSK Biologicals' DTPa-IPV/Hib and HBV (*Engerix- B*) vaccines at the ages of 3, 5 and 11 months in clinical trial DTPa-HBV-IPV-031 (217744/031).
The presented data indicate that about 75% of subjects were seropositive for anti-HB Ab and about 55% displayed seroprotective anti-HB antibody levels 10 years after the last vaccination. An anamnestic response to the hepatitis B challenge dose was mounted by 95.8% (91/95) and 97.8% (87/89) subjects in the DTPa-HBV-IPV/Hib and DTPa-IPV/Hib+HBV groups, respectively. These data highlight the persistence of the anti-HB immune response 10 year after the primary vaccination series.

Recommendation
The MAH concluded that these data warrant a change in the SmPC of the product to reflect anti-HepB Ab persistence and will submit a type II variation in due time in order to update section 5.1 of the SmPC. The corresponding Type II variation will be evaluated upon receipt.

Fulfilled:
No further action required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

None.