Public Assessment Report for paediatric studies submitted in accordance with Article 45 and Article 46 of Regulation (EC) No1901/2006, as amended

ENGERIX B Junior (r-DNA Hepatitis B surface antigen (HBsAg))

BE/W/0006/pdWS/001

Marketing Authorisation Holder:
GlaxoSmithKline Biologicals

Rapporteur:	Belgium (FAMHP)
Finalisation procedure (day 120):	28/03/2021

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Engerix B Junior
INN (or common name) of the active substance(s):	**r-DNA Hepatitis B surface antigen (HBsAg)**
MAH:	GlaxoSmithKline Biologicals
Currently approved Indication(s)	For active immunisation against hepatitis B virus infection (HBV) caused by all known subtypes in non-immune subjects of all ages. The categories within the population to be immunised are determined on the basis of official recommendations.
Pharmaco-therapeutic group (ATC Code):	J07BC01
Pharmaceutical form(s) and strength(s):	Suspension for injection. 1 dose (0.5ml): Hepatitis B virus surface antigen recombinant (S protein) adsorbed 10 micrograms per 0.5 ml

I. EXECUTIVE SUMMARY

Data from 14 studies have been assessed. These studies aimed at assessing immunogenicity and safety of the hepatitis B surface antigen (HBsAg) vaccine in children and adolescents (from birth to 18 years old). The studies are descriptive, and most have a limited sample size (all studies have an overall sample size <300 except HBV-243 [n=351], and 6 studies enrolled <50 subjects in the relevant groups). Seven of the studies have very limited documentation, and there are inconsistencies in the data presented for several of the studies. For some studies, safety data are not available. Issues with the studies were mainly for the oldest studies dating from the 1990th.

Three different dose levels have been used in the studies (5, 10, 20 µg HBsAg). The 10 µg HBsAg dose level corresponds to Engerix B Junior, which is indicated up to 15 years of age, while the 20 µg dose level corresponds to Engerix which is indicated from 16 years of age. For most of the studies, schedules are those reflected in the SmPC of Engerix Junior.

Overall, immunogenicity data are consistent with the data already presented in the SmPC. However, the assessment shows that the data with respect to the persistence of protection and the comparison of dose levels need to be updated in the SmPC.

Five studies described the immune response induced by different dose levels and schedules in children and adolescents, of which three studies compared the 10 and 20 µg HBsAg dose levels with either a 0, 1, (2), 12 or a 0, 1, 6 months schedule. These 3 studies enrolled children from 1.5 to 18 years old. The dose levels of 10 µg and 20 µg induced high and similar seroprotection rates 1 month after the completion of the vaccination schedule. Nevertheless, a trend for an higher seroprotection rate after two doses of 20 µg compared to two doses of 10 µg was noted in the three studies, and one of the studies suggest that seroprotection rate at Month 3 following two doses of 20 µg (at 0 and 1 month) is higher than that obtained following three doses of 10 µg dose (at 0, 1 and 2 month). These data suggest that protection is more rapid with the 20 µg dose level in children 1.5 to 18 years old. A more rapid protection may even be obtained with only two doses of the 20 µg as compared to three doses of 10 µg.

Six studies described the vaccine immunogenicity under different dose levels and schedules in neonates born from HBsAg -negative or -positive mothers, and generated results in line with the data presented in the SmPC (section 5.1.) and the statements in the SmPC (section 4.2.).

Three booster studies were assessed. Overall, they enrolled subjects from 12 to 16 years of age who received a priming vaccination either with Engerix B Junior or Infanrix hexa. An anamnestic response was demonstrated in all studies. These data are consistent with the literature that suggests long-term persistence and immune memory induced by vaccines against hepatitis B, extending up to at least 20 years after primary vaccination and a low frequency of breakthrough cases. However, the immunogenicity results of study HBV-319, which are relevant to infants primed with Engerix B are not described under the section 5.1 of the Engerix B Junior SmPC.

Overall, there was no safety issue revealed by these studies. Most of the adverse reactions are reported under the section 4.8. of the SmPC of Engerix B Junior and Engerix B. Nodule formation described in the study HBV-104 and the low haemoglobin values grade 4 (n=1) and 3 (n=3) recorded in the Malaria-057 study are however not listed in the summary table under section 4.8 of the Engerix B Junior SmPC.

No clinically significant trend toward a higher frequency of AE was noted with the 20 vs. the 10 µg dose level, which is consistent with the statement in section 4.9. of the SmPC.

II. RECOMMENDATION

The MAH is requested to update, via the submission of a type II variation, the section 5.1 of the SmPC with data of the HBV-319 study.

The MAH is invited to take the opportunity to verify that the SmPCs are still harmonized across EC countries and to harmonize them if applicable.

III. INTRODUCTION

On 28/04/2016, the MAH submitted completed paediatric studies for Engerix B in accordance with Article 45 and Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. Several additional studies were submitted by the MAH on 25/10/17 and 08/05/2018. A total of 14 studies are included in these submissions.

A short critical expert overview has also been provided with each submission.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Engerix B and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Each dose (0.5 ml) of Engerix B vaccine contained 10 µg HBsAg adsorbed on 250 µg Aluminium as aluminium hydroxide.
In one study (HBV-405), a group of subjects received half of the formulation whereas in studies HBV -079, -217, and -243, a group received the double dose.

IV.2 Clinical aspects

Seroprotection (SP) has been defined as anti-HBs titers ≥10.0 mIU/Ml in all the studies, which is considered as an established correlate of protection.

1. Introduction

The MAH submitted final reports for:

Article 46

- **Malaria-057** (111315 – Eudra CT number 2012-005718-20)
Study title: A Phase II randomized, open, controlled multi-center study to evaluate the safety and immunogenicity of 7 infant immunization schedules of the RTS, S/AS01 E candidate vaccine against P.falciparum

- **DTPa-HBV-IPV-114** (106793 – Eudra CT number 2013-002821-41)

Study title: An open-label, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a single dose hepatitis B (Engerix B kinder) vaccine challenge in adolescents aged 12-13 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa) vaccine

- **HBV-319** (116722 – Eudra CT number 2012-003950-10)

Study title: An open, phase IV, single-group, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a challenge dose of Engerix B Kinder in adolescents 15-16 years of age who were vaccinated in infancy with three doses of Engerix B Kinder

- **DTPa-HBV-IPV-115** (EudraCT number : 2015-003391-74)

Other studies:

Article 45

1) **103860/005 – HBV 104**
   Comparative study of the immunogenicity and safety of two dosing schedules in neonates
2) **103860/013 – HBV 079**
   A comparative study of two different doses of Smith Kline-RIT rec-DNA Hepatitis B vaccine (10 mcg and 20 mcg)
3) **103860/018 – HBV 153**
   Immunogenicity and protective efficacy of Smith Kline RIT's rec-DNA Hepatitis B vaccine in newborns of HbsAg positive or negative mothers
4) **103860/021 – HBV 177**
   Immunogenicity and protective efficacy of Smith Kline RIT's rec-DNA Hepatitis B vaccine in newborns of HbsAg positive or negative mothers
5) **103860/023 – HBV 155**
   Immunogenicity and protective efficacy of Smith Kline RIT's rec-DNA Hepatitis B vaccine in newborns of HbsAg positive or negative mothers
6) **103860/034 – HBV 154**
   Immunogenicity and protective efficacy of Smith Kline RIT's rec-DNA Hepatitis B vaccine in newborns of HbsAg positive or negative mothers
7) **103860/035 – HBV 156**
   Immunogenicity and protective efficacy of Smith Kline RIT's rec-DNA Hepatitis B vaccine in newborns of HbsAg positive or negative mothers
8) **103860/065 – HV 405**
   Comparative study of the immunogenicity and safety of two doses of Engerix-B administered to healthy infants at 2, 4 and 6 months of age
9) **103860/093 – HBV 217**
   A comparative, Single-Blind, Randomised Study of the Immunogenicity and Safety of Engerix-B administered at two different dose levels
10) **103860/090 – HBV 243**
    Open, randomized study to evaluate the immunogenicity of Engerix®-B when administered according to a vaccination schedule of 0, 1 and 12 months to healthy adolescents at two different doses (10 µg vs 20 µg)

2. Clinical studies

MALARIA-057 (111315-Eudra CT number 2012-005718-20)

➢ Description

A phase 2, open, randomized, controlled, multi-center study to evaluate the safety and immunogenicity of 7 infant immunization schedules of the RTS,S/AS01E candidate vaccine against P. falciparum.

Study initiation and completion: from January 2011 to December 2014

➢ Methods

- Objective(s)

1. Co-Primary

Safety: To describe the safety of 7 infant immunization schedules of RTS,S/AS01E integrated with an EPI regimen comprising OPV, BCG, DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) from study start until month 10.

Immunogenicity: To describe the anti-CS antigen response induced by 7 infant immunization schedules of RTS,S/AS01E, integrated with an EPI regimen comprising OPV, BCG, DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax), with and without a neonatal dose of hepatitis B (Engerix-B), at 1 month post Dose 3 of RTS,S/AS01E.

2. Secondary

Safety: To describe the safety and reactogenicity of 7 infant immunization schedules of RTS,S/AS01E integrated with an EPI regimen comprising OPV, BCG, DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) from study start until Month 10.

Immunogenicity : **(i)** To describe the anti-CS antigen response induced by 7 infant immunization schedules of RTS,S/AS01E integrated with an EPI regimen comprising OPV, BCG, DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) until Month 10. **(ii)** To describe the anti-HBs antigen response induced by 7 infant immunization schedules of RTS,S/AS01E integrated with an EPI regimen comprising OPV, BCG, DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) until Month 10. **(iii)** To describe the antibody responses to diphtheria, tetanus, whole-cell pertussis, polio serotypes 1, 2 and 3 and Haemophilus influenzae type b, induced when RTS,S/AS01E on 7 schedules is integrated with an EPI regimen comprising OPV, BCG and DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) at 1 month post Dose 3 of Tritanrix HepB/Hib (Month 5). **(iv)** To describe the antibody responses to measles induced when RTS,S/AS01E is integrated with an EPI regimen comprising OPV, BCG and DTPwHepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of hepatitis B (Engerix-B) at 1 month post dose of measles vaccine (Month 10).

- Study design

Experimental design: phase 2, open, randomized (1: 1: 1: 1: 1: 1: 1: 1 ratio), controlled trial conducted at 1 study site with 8 groups (7 investigational regimens and 1 comparator regimen which is a recognized EPI schedule).

- Study population and sample size

Healthy male or female infants between 1 and 7 days (inclusive) of age (where Day 1 is day of birth), born after a normal gestation period (between 37 and 42 weeks) and born to a mother negative for HIV antibody and hepatitis B surface antigen. Subjects were ineligible if they had previously received diphtheria, tetanus, pertussis (whole-cell or acellular), Haemophilus influenzae type b, hepatitis B, BCG tuberculosis, measles or oral polio vaccines.

Table 1 Group labelling and definitions

Group label in tables	Group definition for footnote	Pooled groups label in tables
NEO_10W_14W	RTS,S/AS01$_E$ at ≤7 days, 10 weeks and 14 weeks	NEO_RTS
NEO_10W_6M	RTS,S/AS01$_E$ at ≤7 days, 10 and 26 weeks	NEO_RTS
6W_10W_14W	RTS,S/AS01$_E$ at 6, 10 and 14 weeks	Not applicable
6W_10W_6M	RTS,S/AS01$_E$ at 6, 10 weeks and 26 weeks	Not applicable
P_6W_10W_6M	HB (*Engerix-B*) at ≤7 days, and RTS,S/AS01$_E$ at 6, 10 and 26 weeks	NEO_HBS
10W_14W_6M	RTS,S/AS01$_E$ at 10, 14 and 26 weeks	Not applicable
14W_6M_9M	RTS,S/AS01$_E$ at 14, 26 weeks and 9 months	Not applicable
Control	HB (*Engerix-B*) at ≤7 days	NEO_HBS

All groups received BCG plus OPV at ≤7 days, Tritanrix HepB/Hib plus OPV at 6, 10 and 14 weeks and Rouvax at 9 months
HB = hepatitis B vaccine
Pooled group labels in tables:
NEO_RTS = Subjects who received neonatal dose of RTS,S
NEO_HBS = Subjects who received neonatal dose of HepB

In total, 653 subjects were screened, 480 enrolled. 479 subjects were vaccinated. Final ATP cohort for immunogenicity, n= 48 in NEO_10W_14W, 46 in NEO_10W_6M, 47 in 6W_10W_14W, 48 in 6W_10W_6M, 47 in P_6W_10W_6M, 44 in 10W_14W_6M, 54 in 14W_6M_9M, and 48 in Control groups.

Groups of interest for the present assessment are those who received a dose of Engerix B within the first 7 days of life (P_6W_10W_6M and control groups) and the group 6W_10W_6M with comparable schedule RTS,S vaccination.

- Treatments

Vaccine: 0.5ml of Engerix-B kinder (10µg HBsAg adsorbed on 250 µg Aluminium as aluminium hydroxide)

Table 2 Study groups and vaccination schedules

Study group in protocol	Vaccine	Schedule					
		≤ 7d	6w	10w	14w	26w	9M
≤ 7d, 10, 14	RTS,S/AS01$_E$	•		•	•		
≤ 7d, 10, 26	RTS,S/AS01$_E$	•		•		•	
6, 10, 14	RTS,S/AS01$_E$		•	•	•		
6, 10, 26	RTS,S/AS01$_E$		•	•		•	
6, 10, 26 and HB	RTS,S/AS01$_E$		•	•		•	
	Engerix-B	•					
10, 14, 26	RTS,S/AS01$_E$			•	•	•	
14, 26, 9M	RTS,S/AS01$_E$				•	•	•
Control	*Engerix-B*	•					
All subjects	*Tritanrix HepB/Hib*		•	•	•		
	BCG	•					
	OPV	•	•	•	•		
	Rouvax						•

d = day; w = week; M = month
Engerix-B = hepatitis B vaccine (GSK Biologicals)
Tritantrix HepB/Hib = diphtheria, tetanus, whole-cell pertussis, hepatitis B and *Haemophilus influenzae* type b vaccine (GSK Biologicals)
OPV = oral poliovirus vaccine (*Polio Sabin,* GSK Biologicals)
BCG = Bacillus Calmette-Guérin (BCG) (tuberculosis) vaccine (Statens Serum Institute)
Rouvax = attenuated measles vaccine (Aventis Pasteur)

The duration of the study was approximately 18 months per child: 10 months for the primary study, plus a follow-up period of 8 months.

- Outcomes/endpoints

1. Co-primary endpoints

Safety: Occurrence of serious adverse events (SAEs) from study start until Month 10.
Immunogenicity: Anti-CS antibody concentrations at 1 month post Dose 3 of RTS,S/AS01E.

2. *Secondary endpoints*

Safety: (i) Occurrence of unsolicited adverse events (AEs) after each vaccine administration over a 30 day follow-up period (day of vaccination and 29 subsequent days).(ii) Occurrence of solicited general and local reactions over a 7-day follow-up period (day of vaccination and 6 subsequent days) after each vaccine administration.(iii) Occurrence of parameters of hematological and biochemical monitoring according to a toxicity grading scale.

Immunogenicity: (i) Anti-CS antibody concentrations on blood collected until Month 10. (ii) Anti-HBs antibody concentrations on blood collected until Month 10. (iii) Anti-diphtheria antibody, anti-tetanus antibody, anti-PRP antibody and anti-BPT antibody concentrations, and anti-polio types 1, 2 and 3 antibody*titers on blood collected at Month 5. (iv) Anti-measles antibody concentrations on blood collected at Month 10.

- Statistical Methods

Demography:

The number and percentage of subjects included in the Total vaccinated cohort and in the ATP cohort for immunogenicity and the reason for elimination were tabulated by group and overall. For each group, the number of subjects who were absent and the number of subjects who came back at each visit was described. In addition, a study flow diagram (consort) was generated to present the number of subjects screened, randomized, receiving doses and included in ATP analyses. Demographic characteristics (heightfor- age z-score [HAZ], weight-for-age z-score [WAZ], gender, ethnicity, age in days at screening [Visit 1]) and hemoglobin at screening visit were summarized by group using descriptive statistics. Demography analysis was also performed by pooling the neonatal groups (NEO_RTS and NEO_HBS). The continuous variables of age, HAZ, WAZ, and hemoglobin value were described with mean, standard deviation, minimum and maximum values. For continuous variables, the number of subjects contributing to the calculations was shown as well as the number of missing values. Categorical variables, gender and ethnicity were described by number and percentage in each category.

Safety:

The analysis of safety was based on the Total Vaccinated cohort. All analyses were performed by group and pooling neonatal groups: NEO_RTS (NEO_10_14W and NEO_10W_6M) and NEO_HBS (P_6W_10W_6M and Control).

For the primary objective, the analysis focused on safety (SAEs) from Month 0 to Month 10 for each schedule. A second analysis included SAEs, related SAEs, and fatal SAEs until Month 18 (tertiary objective). All SAEs occurring within 30 days of vaccination following 3 doses of RTS,S/AS01E or Tritanrix HepB/Hib and SAEs (SAEs, related SAEs and fatal SAEs) during 30 days follow-up post neonatal dose for neonatal pooled groups (NEO_RTS and NEO_HBS), were tabulated. The proportion of subjects with at least one SAE/fatal SAE/related SAE, classified by the by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term level, was tabulated with exact 95% confidence interval (CI).

For the secondary objectives, the analysis comprised:

(i) Safety of the different schedules, selecting the AEs of specific interest: pIMDs over the period from Month 0 to Month 18, and meningitis, seizures (generalised convulsive), rashes and mucocutaneous lesions occurring within 30 days of vaccination.

(ii) Safety of the different schedules, (SAEs, related SAEs, fatal SAEs, unsolicited AEs) occurring within 30 days of vaccination following 3 doses of RTS,S/AS01E (7 co-administration study groups) or 3 doses of Tritanrix HepB/Hib alone (Engerix-B control group).

(iii) Safety of the different schedules, selecting unsolicited AEs occurring during the 30 day follow-up period post vaccination by group.

(iv) Reactogenicity of the different schedules, selecting solicited AEs occurring during the 7-day followup period of each dose of RTS,S/AS01E or Tritanrix HepB/Hib.

(v) For neonatal pooled groups (NEO_RTS and NEO_HBS), SAEs (all SAEs, related SAEs and fatal SAEs) and unsolicited AEs during 30 days follow-up post neonatal dose (RTS,S/AS01E, HepB and BCG).

(vi) Reactogenicity of the neonatal dose (RTS,S/AS01E, HepB and BCG) selecting solicited AEs occurring during the 7-day follow-up period after the neonatal dose administration by group, and pooling the neonatal groups.

(vii) The proportion of subjects with at least one AE of specific interest for safety monitoring, which included pIMDs, and generalised convulsive seizures, meningitis, rashes and mucocutaneous lesions within 30 days of vaccination, classified by the MedDRA preferred term level were tabulated with exact 95% CI. Similar tables were produced for the neonatal pooled groups (NEO_RTS and NEO_HBS).

(viii) For biochemistry (alanine aminotransferase [ALT], bilirubin, creatinine) and hematology (hemoglobin, white blood cells [WBC], platelets) parameters, the frequency distribution of results by toxicity grade at 7 days post Dose 1 and 30 days post Dose 3 were tabulated by group. Hemoglobin values at all time points were described. For the pooled neonatal groups (NEO_RTS and NEO_HBS), the frequency distribution of results by toxicity grade at 7 days post Dose 1 were tabulated; hemoglobin values at all time points were described.

(ix) The number and percentage of subjects with any antipyretic concomitant medication, prophylactic antipyretic concomitant medication and non-prophylactic antipyretic concomitant medication within 7 days post-vaccination of RTS,S/AS01E (Day 0 to Day 6) were tabulated with exact 95% CI

Immunogenicity:

The analysis of immunogenicity was based on the ATP cohort for immunogenicity.

Antibodies against CS:

The percentage of subjects with seropositive levels of anti-CS antibodies with 95% CI was determined at each time point post dose of RTS,S/AS01E. Antibody concentrations were summarized by geometric mean concentration (GMC) with 95% CI at all time points where data were available. These summaries were also produced by pre-vaccination status. Anti-CS antibody concentrations at 1 month post Dose 2 of RTS,S/AS01E, and at 1 month post Dose 3 of RTS,S/AS01E were presented using reverse cumulative curves.

Kinetics for anti-CS antibody responses according to the different schedules to Month 10 were tabulated and presented in a reverse cumulative curve at Month 10 and Month 18.

Antibodies against HBs:

The percentage of subjects with seroprotective levels of anti-HBs antibodies with 95% CI was determined at each blood sampling time point. Antibody concentrations were summarized by GMC with 95% CI at all time points where data were available. Anti-HBs antibody concentrations at 1 month post Dose 3 of RTS,S/AS01E were presented using reverse cumulative curves.

Between-group comparisons:

In addition, specific between-group comparisons based on adjusted GMC ratio (point estimate and associated 95% CI) and difference in seropositivity/seroprotective rates (point estimate and associated 95% CI) were performed: To assess the impact of the HepB vaccine dose during the first days of life on anti-CS antibodies immunogenicity by comparing anti-CS immunogenicity at 1 month post Dose 3 of RTS,S/AS01E between P_6W_10W_6M vs 6W_10W_6M.

- **Results**

  - Recruitment and number analysed

In total, 653 subjects were screened, 480 enrolled. 479 subjects were vaccinated. Final ATP cohort for immunogenicity, n= 48 in NEO_10W_14W, 46 in NEO_10W_6M, 47 in 6W_10W_14W, 48 in 6W_10W_6M, 47 in P_6W_10W_6M, 44 in 10W_14W_6M, 54 in 14W_6M_9M, and 48 in Control groups.

Groups of interest: 6W_10W_6M (n=48), P_6W_10W_6M (n=47) and control groups (n=48).

  - Baseline data

Demographic characteristics are detailed in the Table below.

Table 3 Demographic characteristics

		NEO_10W_14W N = 60		NEO_10W_6M N = 59		6W_10W_14W N = 60		6W_10W_6M N = 60		P_6W_10W_6M N = 60		10W_14W_6M N = 60		14W_6M_9M N = 60		Control N = 60		Total N = 479	
Characteristics	Parameters or Categories	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%	Value or n	%
Age at screening in days	Mean	0.4	-	0.4	-	0.2	-	0.2	-	0.5	-	0.2	-	0.2	-	0.4	-	0.3	-
	SD	1.1	-	1.2	-	1.0	-	0.8	-	1.4	-	0.8	-	0.9	-	1.2	-	1.1	-
	Median	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-
	Minimum	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-
	Maximum	4.0	-	6.0	-	5.0	-	4.0	-	5.0	-	4.0	-	4.0	-	6.0	-	6.0	-
Gender	Female	30	50.0	32	54.2	28	46.7	35	58.3	31	51.7	29	48.3	24	40.0	28	46.7	237	49.5
	Male	30	50.0	27	45.8	32	53.3	25	41.7	29	48.3	31	51.7	36	60.0	32	53.3	242	50.5
Hemoglobin[g/dL]	N	60	-	59	-	60	-	60	-	60	-	60	-	60	-	60	-	479	-
	Mean	16.3	-	15.5	-	15.4	-	15.8	-	16.0	-	15.4	-	15.7	-	15.5	-	15.7	-
	SD	2.1	-	1.6	-	1.4	-	1.9	-	1.9	-	2.0	-	1.7	-	1.6	-	1.8	-
	Minimum	13.1	-	13.1	-	13.1	-	13.2	-	13.2	-	13.1	-	13.1	-	13.1	-	13.1	-
	Maximum	23.4	-	19.6	-	19.2	-	21.7	-	22.3	-	21.0	-	21.5	-	19.7	-	23.4	-
	Missing	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-

NEO_10W_14W = RTS,S/AS01$_E$ at ≤7 days, 10 weeks and 14 weeks
NEO_10W_6M = RTS,S/AS01$_E$ at ≤7 days, 10 and 26 weeks
6W_10W_14W = RTS,S/AS01$_E$ at 6, 10 and 14 weeks
6W_10W_6M = RTS,S/AS01$_E$ at 6, 10 and 26 weeks
P_6W_10W_6M = HB (*Engerix-B*) at ≤7 days, and RTS,S/AS01$_E$ at 6, 10 and 26 weeks
10W_14W_6M = RTS,S/AS01$_E$ at 10, 14 and 26 weeks
14W_6M_9M = RTS,S/AS01$_E$ at 14, 26 weeks and 9 months
Control = HB (*Engerix-B*) at ≤7 days
N = number of subject number
n = number of subject number in a given category
Value = value of the considered parameter
% = n / Number of subject number with available results x 100

- Immunogenicity results

1. Effect of Engerix B on anti-CS antibodies titers (P_6W_10W_6M vs 6W_10W_6M)
A neonatal dose of Engerix-B did not increase (or decrease) the anti-CS response: 6W_10W_6M : P_6W_10W_6M, GMC ratio 0.92; 95% CI: 0.51, 1.66.

Table 4 Seropositivity rates and GMCs for anti-CS antibodies at one month PD3 of RTS,S/AS01E

Group	Timing	N	≥ 0.5 EU/ML				GMC			Min	Max
					95% CI			95% CI			
			n	%	LL	UL	value	LL	UL		
NEO_10W_14W	PIV(M5)	47	47	100	92.5	100	128.2	92.2	178.2	5.1	807.9
NEO_10W_6M	PV(M7)	43	43	100	91.8	100	136.6	93.0	200.7	12.5	1369.0
6W_10W_14W	PIV(M5)	45	45	100	92.1	100	218.3	160.1	297.6	3.4	1126.7
6W_10W_6M	PV(M7)	46	46	100	92.3	100	156.5	100.4	244.0	0.9	1451.0
P_6W_10W_6M	PV(M7)	43	43	100	91.8	100	170.6	114.6	254.1	2.6	4383.9
10W_14W_6M	PV(M7)	41	41	100	91.4	100	392.6	323.3	476.7	94.0	1406.4
14W_6M_9M	PVI(M10)	47	46	97.9	88.7	99.9	269.9	183.3	397.5	<0.5	1693.1
Control	PIV(M5)	48	0	0.0	0.0	7.4	0.3	0.3	0.3	<0.5	<0.5

Similar seropositivity rates and GMC were also seen at screening, M4, M10, and M18.

2. Effect of RTS,S on anti-HBs antibodies titers (P_6W_10W_6M vs control)

On assessing a neonatal dose of hepatitis B vaccine, at Month 7, anti-HBs antibody response in the P_6W_10W_6M group was 34589.1 mIU/mL (95% CI: 21299.2, 56171.6) and in the 6W_10W_6M group was 29839.9 mIU/mL (95% CI: 20731.1, 42951.0). At month 18, GMC were similar for both groups and 100% of the subjects had antibody titers higher than 10 mIU/ml.

3. Effect of Engerix B on the EPI vaccine-induced immune responses (P_6W_10W_6M vs 6W_10W_6M)

No major effect were demonstrated of Engerix B on anti -diphteria, -tetanus, -*haemophilus influenzae* type b, -pertussis, -polio humoral immune responses (Tables 5, 6, 7 and 8). No data for anti-measles immune responses for these groups are given.

Table 5 Seropositivity rates and GMCs for anti-diphteria and anti-tetanus antibodies concentration at month 5

				≥ 0.1 IU/ML				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
Anti-diphtheria	NEO_10W_14W	PIV(M5)	48	47	97.9	88.9	99.9	3.1	2.2	4.5	<0.1	18.6
	NEO_10W_6M	PIV(M5)	46	46	100	92.3	100	3.9	2.9	5.3	0.1	46.8
	6W_10W_14W	PIV(M5)	45	45	100	92.1	100	3.2	2.5	4.0	0.6	15.1
	6W_10W_6M	PIV(M5)	48	48	100	92.6	100	4.0	3.2	5.1	0.8	19.5
	P_6W_10W_6M	PIV(M5)	47	47	100	92.5	100	3.6	2.7	4.8	0.5	20.9
	10W_14W_6M	PIV(M5)	44	44	100	92.0	100	4.3	3.2	5.8	0.2	18.4
	14W_6M_9M	PIV(M5)	54	54	100	93.4	100	4.3	3.4	5.5	0.6	41.8
	Control	PIV(M5)	47	47	100	92.5	100	4.6	3.7	5.6	0.7	21.2
Anti-tetanus	NEO_10W_14W	PIV(M5)	48	48	100	92.6	100	3.5	2.6	4.6	0.5	18.2
	NEO_10W_6M	PIV(M5)	46	46	100	92.3	100	3.2	2.3	4.4	0.3	23.1
	6W_10W_14W	PIV(M5)	45	45	100	92.1	100	3.7	2.8	4.8	0.7	76.2
	6W_10W_6M	PIV(M5)	48	48	100	92.6	100	2.8	2.2	3.7	0.3	14.6
	P_6W_10W_6M	PIV(M5)	47	47	100	92.5	100	3.3	2.4	4.4	0.2	18.3
	10W_14W_6M	PIV(M5)	44	44	100	92.0	100	3.3	2.4	4.6	0.2	30.8
	14W_6M_9M	PIV(M5)	54	54	100	93.4	100	3.5	2.6	4.6	0.2	31.8
	Control	PIV(M5)	47	47	100	92.5	100	4.6	3.5	6.0	0.5	22.5

Table 6 Seropositivity rates and GMCs for anti-PRP antibody concentration at month 5

				≥ 0.15 UG/ML				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-PRP	NEO_10W_14W	PIV(M5)	47	46	97.9	88.7	99.9	6.8	4.5	10.3	<0.2	61.8
	NEO_10W_6M	PIV(M5)	44	44	100	92.0	100	11.1	7.5	16.5	0.3	116.6
	6W_10W_14W	PIV(M5)	44	43	97.7	88.0	99.9	11.4	7.3	17.8	<0.2	215.9
	6W_10W_6M	PIV(M5)	48	48	100	92.6	100	13.6	9.6	19.3	0.4	225.2
	P_6W_10W_6M	PIV(M5)	47	47	100	92.5	100	10.9	7.4	16.0	0.7	125.0
	10W_14W_6M	PIV(M5)	43	43	100	91.8	100	11.0	7.1	16.9	0.7	87.1
	14W_6M_9M	PIV(M5)	52	52	100	93.2	100	15.6	10.6	22.8	0.5	504.4
	Control	PIV(M5)	47	47	100	92.5	100	13.8	9.7	19.5	0.5	111.4

Table 7 Seropositivity rates and GMCs for anti-BPT antibody concentration at month 5

				≥ 15 EU/ML				GMC				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
anti-BPT	NEO_10W_14W	PIV(M5)	43	42	97.7	87.7	99.9	82.9	69.9	98.4	<15.0	198.0
	NEO_10W_6M	PIV(M5)	42	42	100	91.6	100	102.3	84.9	123.4	30.0	393.0
	6W_10W_14W	PIV(M5)	41	41	100	91.4	100	86.7	72.5	103.7	21.0	246.0
	6W_10W_6M	PIV(M5)	46	45	97.8	88.5	99.9	81.2	66.7	98.8	<15.0	265.0
	P_6W_10W_6M	PIV(M5)	42	42	100	91.6	100	99.2	82.6	119.1	20.0	267.0
	10W_14W_6M	PIV(M5)	42	42	100	91.6	100	86.1	71.7	103.4	25.0	244.0
	14W_6M_9M	PIV(M5)	50	50	100	92.9	100	91.0	75.9	109.0	18.0	334.0
	Control	PIV(M5)	41	40	97.6	87.1	99.9	109.8	89.7	134.4	<15.0	276.0

Table 8 Seropositivity rates and GMCs for anti-polio types 1, 2 and 3 antibody concentration at month 5

				≥ 8 ED_{50}				*GMT*				
						95% CI			95% CI			
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL	Min	Max
POLIO 1 AB	NEO_10W_14W	PIV(M5)	25	25	100	86.3	100	27.6	16.5	46.0	<8.0	286.7
	NEO_10W_6M	PIV(M5)	13	13	100	75.3	100	21.6	10.3	45.2	<8.0	71.7
	6W_10W_14W	PIV(M5)	20	20	100	83.2	100	31.7	17.2	58.7	<8.0	286.7
	6W_10W_6M	PIV(M5)	14	14	100	76.8	100	47.1	21.5	102.8	<8.0	286.7
	P_6W_10W_6M	PIV(M5)	13	12	92.3	64.0	99.8	19.9	4.0	98.3	<8.0	286.7
	10W_14W_6M	PIV(M5)	20	18	90.0	68.3	98.8	23.6	8.4	66.5	<8.0	286.7
	14W_6M_9M	PIV(M5)	20	20	100	83.2	100	16.7	7.9	35.4	<8.0	286.7
	Control	PIV(M5)	19	18	94.7	74.0	99.9	45.4	18.9	109.4	<8.0	286.7
POLIO 2 AB	NEO_10W_14W	PIV(M5)	31	31	100	88.8	100	27.5	16.8	45.1	<8.0	696.3
	NEO_10W_6M	PIV(M5)	16	15	93.8	69.8	99.8	35.1	14.9	82.4	<8.0	348.2
	6W_10W_14W	PIV(M5)	25	25	100	86.3	100	56.6	32.8	97.7	<8.0	696.3
	6W_10W_6M	PIV(M5)	25	23	92.0	74.0	99.0	37.9	17.0	84.6	<8.0	696.3
	P_6W_10W_6M	PIV(M5)	19	19	100	82.4	100	42.0	21.6	81.6	<8.0	246.2
	10W_14W_6M	PIV(M5)	29	25	86.2	68.3	96.1	27.6	12.6	60.4	<8.0	696.3
	14W_6M_9M	PIV(M5)	25	25	100	86.3	100	40.1	24.1	66.6	<8.0	696.3
	Control	PIV(M5)	30	30	100	88.4	100	25.9	16.4	40.7	<8.0	246.2
POLIO 3 AB	NEO_10W_14W	PIV(M5)	27	23	85.2	66.3	95.8	3.6	1.6	7.9	<8.0	72.4
	NEO_10W_6M	PIV(M5)	11	9	81.8	48.2	97.7	2.3	0.6	8.7	<8.0	72.4
	6W_10W_14W	PIV(M5)	23	21	91.3	72.0	98.9	5.1	2.6	10.2	<8.0	51.2
	6W_10W_6M	PIV(M5)	18	15	83.3	58.6	96.4	3.3	1.3	8.4	<8.0	36.2
	P_6W_10W_6M	PIV(M5)	16	15	93.8	69.8	99.8	5.6	2.6	12.2	<8.0	36.2
	10W_14W_6M	PIV(M5)	24	19	79.2	57.8	92.9	2.6	1.2	5.7	<8.0	36.2
	14W_6M_9M	PIV(M5)	24	22	91.7	73.0	99.0	3.0	1.6	5.5	<8.0	18.1
	Control	PIV(M5)	26	25	96.2	80.4	99.9	6.0	3.3	10.8	<8.0	144.8

- Safety results

The incidence of solicited local AE following a neonatal dose of RTS,S or Engerix B within the 7-day post-vaccination period was similar for both vaccines. No grade 3 solicited local AE was reported.
Solicited general AE following a neonatal dose of RTS,S or Engerix B within the 7-day post-vaccination period were reported in more than one subject following administration of both vaccines. Fever >37.5°C was reported after 14.3% (95% CI:8.5-21.9) and 6.7% (95%CI:2.9-12.8) of neonatal doses or RTS,S and Engerix-B respectively. No grade 3 solicited general AE was reported.

Unsolicited AE during the 30-days post-vaccination period were 21.8% (95% CI:14.8-30.4) and 27.5% (95% CI:19.7-36.4) of subjects receiving RTS,S and Engerix B respectively. One unsolicited AE was a grade 3 following RTS,S vaccination (meningitides). No unsolicited AE within 30 days of the neonatal dose of RTS,S/AS01E or Engerix-B was considered to be causally related to vaccination.
Serious AE during the 30-day post-vaccination period were reported in 1.7% (95% CI:0.2-5.9) and 2.5% (95% CI:0.5-7.1) of subjects receiving RTS,S or Engerix-B respectively.No SAE was considered to be causally related to vaccination and none was fatal.
At day 7 post-vaccination, haemoglobin values graded 3 were recorded in 3 recipients of Engerix-B and graded 4 in 1 recipient of RTS,S and 1 of Engerix-B. Platelet values graded 4 were recorded in 1 recipient of RTS,S.

Assessor's comment:

MAL-057 study is a phase 2, open, randomized, controlled, multi-center study to evaluate the safety and immunogenicity of 7 infant immunization schedules of the RTS,S/AS01E candidate vaccine against *P. falciparum* in healthy neonates between 1 and 7 days of age. The 7 infant immunization schedules of RTS,S/AS01E were integrated with an EPI regimen comprising OPV, BCG, DTPw/HepB/Hib (Tritanrix HepB/Hib) and measles (Rouvax) with and without a neonatal dose of Engerix-B kinder. An additional group received a comparator regimen which is a recognized EPI schedule.

Groups of interest for the present assessment are the two groups who received Engerix-B kinder (P_6W_10W_6M and control groups, n=47 in each group). It was administered within the first 7 days of life in both groups. All children received BCG and OPV at the same timepoint.

The neonatal dose of Engerix-B did not increase or decrease the anti-CS response and had no major effect on anti -diphteria, -tetanus, -haemophilus influenzae type b, -pertussis, -polio humoral immune responses. Conversely, the RTS,S/AS01E candidate vaccine had no major effect on anti-HBs antibody responses.

Data on coadministration with RTS,S/AS01E are of little relevance to the SmPC of Engerix Junior in Europe.

Engerix B was well tolerated. Low haemoglobin values grade 4 and 3 were however recorded in the control group.

As only one neonatal dose was given, this schedule does not correspond to the posology of Engerix B described in the SmPC. Nevertheless, safety data of one neonatal dose of Engerix are relevant, as Engérix B Junior is indicated from birth.

The low haemoglobin level observed following neonatal administration of Engerix should be discussed in the next PSUR.

DTPa-HBV-IPV-114 (106793- Eudra CT number 2013-002821-41)

- **Description**

An open-label, phase IV, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a single dose hepatitis B (Engerix™-B Kinder) vaccine challenge in adolescents aged 12-13 years, previously primed and boosted in

the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix™ hexa) vaccine.

Study initiation and completion: from February 2014 to September 2014.

- **Methods**

  - Objective(s)

1. Primary:

Immunogenicity: The anti-HBs antibody response, in terms of subjects with antibody concentrations ≥ 100 mIU/ml, to a single challenge dose of HBV vaccine (Engerix-B Kinder) in subjects 12–13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed.

2. Secondary:

Immunogenicity: (i) The persistence of anti-HBs antibodies, in terms of seroprotection status and antibody concentrations, in subjects 12–13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed. (ii) The immunological response to the hepatitis B antigen, in terms of seroprotection status and antibody concentrations, one month after the single challenge dose of the HBV vaccine in subjects 12–13 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life, was assessed.
Safety: The safety and reactogenicity of a single challenge dose of HBV vaccine (Engerix-B Kinder) in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs), was evaluated.

  - Study design

A Phase IV, open-label, non-randomised, multicentre, single-country study with a single group. All subjects receiving a single challenge dose of HBV vaccine. Two blood samples were collected in this study, one before the administration of the single challenge dose of HBV vaccine and a second sample approximately one month after the single challenge dose of HBV vaccine. Safety data was collected up to 30 days after administration of the study vaccine.

  - Study population /Sample size

A healthy male or female between 12 to 13 years of age (from and including the 12th birthday, up to but excluding the 14th birthday) at the time of enrolment, with documented evidence of previous vaccination with Infanrix hexa that included three doses of primary vaccination received by 9 months of age and one booster dose received between 11 and 18 months of age were included in the study. Subjects with written informed consent obtained from the parent(s)/legally acceptable representative [LAR(s)] of the subject and with written informed assent (when applicable) from the subject were included in the study. Evidence of previous hepatitis B booster vaccination since administration of the fourth dose of Infanrix hexa as a booster in the second year of life or history of hepatitis B disease or intercurrent hepatitis B disease or hepatitis B vaccination at birth excluded subjects from the study. Females of childbearing potential were enrolled in the study if the subject had practiced adequate contraception 30 days prior to the vaccination, had a negative pregnancy test on the day of vaccination and had agreed to continue adequate contraception during the study and for 3 months after the completion of the vaccination.

- Treatments

A single dose of HBV vaccine was administered to all subjects, who were previously primed and boosted with four doses of Infanrix hexa in the first two years of life.
0.5ml of Engerix-B kinder (10µg HBsAg adsorbed on 250 µg Aluminium as aluminium hydroxide) was administered intra-muscularly in the deltoid region of arm.
A blood sample was collected before and one month post-HBV vaccination.

- Outcomes/endpoints

1. Primary endpoint:

Immunogenicity: Anti-HBs immune response: Anti-HBs antibody concentrations ≥ 100 mIU/ml, one month after the single challenge dose of HBV vaccine.

2. Secondary endpoints:

Immunogenicity: (i) Anti-HBs antibody persistence at 12-13 years of age, after previous vaccination with Infanrix hexa: Anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml, 10 to < 100 mIU/ml, ≥ 100 mIU/ml and anti-HBs antibody concentrations before the single challenge dose of HBV vaccine. (ii) Anti-HBs immune response: Anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml and anti-HBs antibody concentrations one month after the single challenge dose of HBV vaccine. Anamnestic response to the single challenge dose of HBV vaccine. An anamnestic response to the single challenge dose was defined as: At least (i.e. greater than or equal to) 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point. Post-vaccination, anti-HBs antibody concentrations ≥ 10 mIU/ml in subjects seronegative at the pre-vaccination time point.

Safety: (i) Solicited local and general symptoms: Occurrence of each solicited local and general symptoms during the 4-day (Day 0-3) follow-up period after the single challenge dose of HBV vaccine. (ii) Unsolicited Adverse Events (AEs): Occurrence of unsolicited AEs during the 31-day (Day 0-30) follow-up period after the single challenge dose of HBV vaccine. (iii) SAEs: Occurrence of SAEs after the single challenge dose of HBV vaccine up to study end.

- Statistical Methods

The analysis for antibody persistence was performed on the according-to-protocol (ATP) cohort for analysis of antibody persistence. The analysis for response to challenge dose was based on the ATP cohort for analysis of immunogenicity. The primary analysis of safety and reactogenicity was based on the Total Vaccinated Cohort (TVC). Analyses were performed as planned in the protocol and Statistical Analysis Plan (SAP).

Analysis of demographics:
Demographic characteristics (age at study entry, gender, geographic ancestry, height [in cm] and weight [kg]), cohort description and lost to follow-up details were summarised using descriptive statistics:
(i) Frequency tables were generated for categorical variable such as centre.
(ii) Mean, median, standard deviation was provided for continuous variable such as age.

Analysis of immunogenicity:
The primary analysis of immunogenicity was performed on the ATP cohort for immunogenicity.
Analysis for antibody persistence: Prior to the single challenge dose of HBV vaccine.

The analysis for antibody persistence was performed on the ATP cohort for analysis of antibody persistence.
(i) Percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml, ≥ 10 mIU/ml to < 100 mIU/ml, and ≥ 100 mIU/ml, with exact 95% confidence interval (CI) was calculated. (ii) Geometric Mean Concentrations (GMCs) with 95% CI were calculated for anti-HBs antibodies. (iii) The distribution of anti-HBs antibody concentrations was displayed using reverse cumulative curves (RCCs).
Response to challenge dose: One month after the single challenge dose of HBV vaccine.
The primary analysis was based on the ATP cohort for analysis of immunogenicity. Since the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was not more than 5%, a second analysis based on the TVC was not performed to complement the ATP analysis.
(i) Percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml and ≥ 100 mIU/ml, with exact 95% CI was calculated. (ii) GMCs with 95% CI were calculated for anti-HBs antibodies. The distribution of anti-HBs antibody concentrations were displayed using RCCs. (iii) The percentage of subjects with anti-HBs concentrations ≥ 6.2 mIU/ml, ≥ 10 mIU/ml, and ≥ 100 mIU/ml (with exact 95% CI) and GMCs (with 95% CI) at the post-HBV challenge dose time point, in relation to their pre-challenge dose status (< 6.2 mIU/ml, < 10 mIU/ml, ≥ 10 mIU/ml) were tabulated. (iv) The percentage of subjects (with 95% CI) who mounted an anamnestic response to the single challenge dose of HBV vaccine was calculated overall and in relation to their pre-vaccination status (<10mIU/ml, ≥ 10 mIU/ml). (v)The relationship between the anti-HBs antibody concentrations observed after the single challenge dose of HBV vaccine (given as part of this study) and the anti-HBs antibody concentrations observed at the pre-challenge dose time point was presented graphically**.**

Analysis of safety:
The primary analysis of safety and reactogenicity was based on the TVC. Since the percentage of subjects excluded from the ATP cohort for analysis of safety was not more than 5%, a second analysis based on this ATP cohort was not performed to complement the TVC analysis.
(i) The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 4-day (Day 0 to Day 3) follow-up period after the vaccination was tabulated with exact 95% CI. The same calculations were performed for any Grade 3 (solicited or unsolicited) symptoms and any symptoms requiring medical attention.
(ii) The percentage of subjects reporting each individual solicited symptom during the 4-day follow-up period with exact 95% CI, by type of adverse event; by severity (any grade, Grade 3); by relationship to vaccination as assessed by the investigator (any relationship, related) was tabulated.
(iii) The occurrence of fever was tabulated per 0.5°C cumulative increments as well as the occurrence of Grade 3 fever (> 39.0 °C axillary temperature) with causal relationship to vaccination as assessed by the investigator.
(iv) The percentage of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported within the 31-day (Day 0 to Day 30) follow-up period after vaccination was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs with a causal relationship to vaccination as assessed by the investigator.
(v) The percentage of subjects who started receiving at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day and 31-day followup period after vaccination was tabulated (with exact 95% CI).
(vi) SAEs and withdrawals due to AEs and SAEs reported during the study were described in detail.

➢ Results

- Recruitment/ Number analysed

A total of 300 subjects were vaccinated and all subjects completed the study. Of these, 293 subjects were included in the ATP cohort for analysis of immunogenicity and ATP cohort for analysis of antibody persistence.

- Baseline data

Demographic characteristics are detailed in the Table below. Out of the 293 subjects, 148 were males and the majority were Caucasian. Mean age was 12.3 years (SD:0.5).

Table 9 Demographic characteristics

Study population (ATP Cohort for analysis of immunogenicity)	
Number of subjects	**HBV Group**
Planned, N	300
N (ATP Cohort for analysis of immunogenicity)	293
Completed, n (%)	293 (100)
Demographics	**HBV Group**
N (ATP Cohort for analysis of immunogenicity)	293
Females: Males	145:148
Mean Age (At challenge dose), years (SD)	12.3 (0.5)
Median Age, years (minimum, maximum)	12 (12, 14)
White - Caucasian / European Heritage, n (%)	290 (99.0)
Other*, n (%)	2 (0.7)
White - Arabic / North African Heritage, n (%)	1 (0.3)
HBV Group = Subjects who previously received *Infanrix hexa* and received a challenge dose of HBV vaccine in this study, SD=Standard Deviation, N=Total number of subjects enrolled in the study, n/%=Number/percentage of subjects in a given category, * Other includes African-Caucasian.	

- Immunogenicity results

Persisting seroprotective anti-HBs antibody concentrations (≥10mIU/ml) were observed in 60.5% of the children who were vaccinated in infancy with 4 doses of Infanrix hexa.
An anamnestic response to the hepatitis challenge dose of HBV vaccine was demonstrated; Respectively 97.6% and 94.1% of the subjects had anti-HBs antibody titers ≥10 mIU/ml and ≥100 mIU/ml and the anti-HBs GMC was 3502.6 mIU/ml.

Table 10 Seropositivity rates (S+), percentages of subjects with anti-HBS antibody titers higher than different thresholds.

			S+				**≥ 10 mIU/ml**				**≥ 100 mIU/ml**				**GMC**		
					95% CI				**95% CI**				**95% CI**			**95% CI**	
Group	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
HBV Group	Pre	291	203	69.8	64.1	75.0	176	60.5	54.6	66.1	61	21.0	16.4	26.1	22.4	18.2	27.5
	Post	289	283	97.9	95.5	99.2	282	97.6	95.1	99.0	272	94.1	90.7	96.5	3502.6	2672.0	4591.5
HBV Group = Subjects who previously received *Infanrix hexa* 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, S+=Seropositive for anti-HBs antibodies (concentrations above the assay cut-off 6.2 mIU/ml), 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit, Pre=Blood sampling at pre-challenge dose time point, Post=Blood sampling one month after the challenge dose.																	

- Safety results

During the 4-day post-challenge period, at least one symptom (solicited or unsolicited, local or general) was reported for 67.0% of the subjects.
The most frequently reported solicited symptoms were: pain at the injection (44.0% of the subjects), swelling as a grade 3 solicited local symptom (0.7% of the subjects), fatigue (24.3% of the subjects) and headache grade 3 (2.3% of the subjects).
Unsolicited symptoms during the 31-day follow-up period were reported for 14.7% of the subjects and the most frequent was upper respiratory tract infection (3.3% of the subjects). Grade 3 unsolicited symptoms were abdominal pain, pyrexia, gastrointestinal infection, contusion, headache and cough (1.7% of the subjects). One instance of vertigo and one of urticarial were considered to be causally related to vaccination.
SAE were reported for 2 subjects but were not related to the vaccination (contusion of lumbar spine and fracture of right forearm). No fatal events were reported during the study.

Assessor's comment:

DTPa-HBV-IPV-114 is a Phase IV open label multicentre study that assessed the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of Engerix in children aged 12-13 years old who were primed and boosted in the first two years of live with four doses of the DTPa-HBV-IPV/Hib (Infanrix hexa). This is the last third of a series of four studies that assessed the persistence of antibodies against hepatitis B in children of respectively 4-5, 7-8, 12-13 and 14-15 years old who received Infanrix hexa in the first two years of live, as part of routine vaccination in infancy, in Germany.
Of 293 children vaccinated in infancy with Infanrix, 60.5% had anti-HBs antibody concentration ≥10 mIU/mL (seroprotective levels) at 12-13 years of age. One month after the challenge dose of HBV vaccine, 97.6% and 94.1% of the children had anti-HBs antibody concentration respectively ≥10 mIU/mL (seroprotective levels) and ≥100 mIU/mL.

For interpretation, see DTPa-HBV-IPV-115.

HBV-319 (116722 – Eudra CT number 2012-003950-10)

- **Description**

An open, phase IV, single-group, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a challenge dose of Engerix™- B Kinder in adolescents 15-16 years of age who were vaccinated in infancy with three doses of Engerix™-B Kinder.

Study initiation and completion: from July 2013 to February 2014.

- **Methods**

  - Objective(s)

1. Primary:

Immunogenicity: To assess the anti-HBs antibody response to a challenge dose of Engerix-B Kinder in subjects 15-16 years of age vaccinated with three doses of Engerix-B Kinder in infancy.

2. Secondary:

Immunogenicity: To assess the persistence of anti-HBs antibodies in subjects 15-16 years of age vaccinated with three doses of Engerix-B Kinder in infancy.
Safety: To evaluate the safety and reactogenicity of challenge dose of Engerix-B Kinder in terms of solicited symptoms, unsolicited symptoms and serious adverse events (SAEs).

- Study design

The study was conducted as a phase IV, open-label, non-randomised, multi-centric, single-country study with a single group. The study started at Visit 1 (Day 0) and ended at Visit 2 (Month 1). The study involved only one group (HBV group) with 303 subjects, 15-16 years of age. Two blood samples (approximately 3.5 ml each) were taken from each subject–one before the challenge dose and the other, one month after the challenge dose.

- Study population /Sample size

Healthy male or female subjects between 15 to 16 years of age for whom investigator believed that their parent(s)/LAR(s) could and would comply with the protocol requirements were enrolled in the study. Written informed consent was to be obtained from the subjects' parent(s)/LAR(s).

The subjects who used any investigational or non-registered product (drug or vaccine) other than the study vaccine within 30 days preceding the dose of the study vaccine, who were administered immunosuppressants or other immune-modifying drugs within six months prior to the vaccine dose, who had previous hepatitis-B vaccination history since administration of the third dose of Engerix B Kinder, were excluded from the study.

- Treatments

All subjects received one dose of Engerix-B Kinder vaccine at Visit 1, i.e. 0.5ml of Engerix-B kinder (10µg HBsAg adsorbed on 250 µg Aluminium as aluminium hydroxide) administered intra-muscularly in the deltoid region of arm.
A blood sample was collected before and one month post-HBV vaccination.

- Outcomes/endpoints

1. Primary endpoint:

Immunogenicity: Percentage of subjects with anti-HBs antibody concentrations ≥ 100 mIU/ml, one month after the challenge dose.

2. Secondary endpoints:

Immunogenicity: (i) Anti-HBs immune status, (ii) Percentage of subjects with an anamnestic response to the challenge dose, (iii) Anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥10 mIU/ml and ≥100 mIU/ml, before and one month after the challenge dose, (iv) Geometric Mean Concentration (GMC) of anti-HBs antibodies, before and one month after the challenge dose.
Safety: (i) Solicited local and general symptoms: Occurrence of solicited local symptoms during the 4-day (Days 0-3) follow-up period after the challenge dose. Occurrence of solicited general symptoms during the 4-day (Days 0-3) follow-up period after the challenge dose. (ii) Unsolicited adverse events: Occurrence of unsolicited symptoms during the 31-day (Days 0-30) follow-up

period after the challenge dose. (iii) Serious adverse events: Occurrence of SAEs after the challenge dose, up to the study end.

- Statistical Methods

Analysis of demographics/baseline characteristics

The demographic characteristics (age in years at challenge dose, gender, geographic ancestry, height and weight) at Visit 1, cohort description, withdrawal status was summarized using descriptive statistics.
(i) Mean, median and standard deviation were provided for continuous variable such as age.
(ii) Frequency tables were generated for categorical variables such as centre.

Analysis of immunogenicity
The primary analysis on the response to the challenge dose was performed on the ATP cohort for analysis of immunogenicity.
Prior to and one month after the challenge dose: (i) The percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/ml, ≥10mIU/ml, ≥100 mIU/ml, and between ≥10 mIU/ml and <100 mIU/ml, with exact 95% CIs was calculated. (ii) GMCs with 95% CI were calculated for anti-HBs antibodies. The distribution of anti-HBs antibody concentrations was displayed using reverse cumulative distribution curve (RCC). (iii) Relationship between pre and post-vaccination results was presented by graph. (iv) The percentage of subjects with anti-HBs concentrations ≥ 6.2 mIU/ml, ≥10 mIU/ml and ≥ 100 mIU/ml (with 95% CI) at the post-vaccination time point, in relation to their pre-vaccination status (overall, <6.2 mIU/ml, ≥6.2-10 mIU/ml, <10 mIU/ml and ≥10 mIU/ml) was tabulated. (v) The percentage of subjects (with 95% CI) that demonstrated an anamnestic response was calculated overall and in relation to their pre-vaccination status (< 6.2 mIU/ml, ≥ 6.2-10 mIU/ml, <10 mIU/ml and ≥10 mIU/ml).

Analysis of safety
The primary analysis was performed on the TVC.
(i) The percentage of subjects who reported at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 4-day (Days 0-3) follow-up period after the vaccination was tabulated with exact 95% CI. The same calculations were performed for any Grade 3 (solicited or unsolicited) symptoms and any symptoms requiring medical attention.
(ii) The percentage of subjects reporting each individual solicited symptom during the 4- day (Days 0- 3) follow-up period with exact 95% CI, by type of AE; by severity (any Grade, Grade 3 only); by relationship to vaccination (any relationship, related only) was tabulated.
(iii) The occurrence of fever was tabulated per 0.5°C cumulative increments as well as the occurrence of Grade 3 fever (> 39.0 °C axillary temperature) with causal relationship to vaccination.
(iv) The percentage of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported within the 31-day (Days 0-30) follow-up period after vaccination was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited AEs and for unsolicited AEs with a causal relationship to vaccination.
(v) Percentage of subjects with the incidence of concomitant medication during the 31-day (Day 0-Day 30) follow up period after vaccination was tabulated with exact 95%CI.
(vi) SAEs during the entire study period and withdrawals due to AEs and SAEs reported during the 31- day follow-up period after the challenge dose was described in detail.

➢ Results

- Recruitment/ Number analysed

A total of 300 subjects aged 15-16 years at the first vaccination visit were planned to be enrolled into the study to provide 270 evaluable subjects at the time of analysis. The ATP cohort for immunogenicity comprises 293 subjects.

- Baseline data

Demographic characteristics are detailed in the Table below. Of the 293 subjects, 157 were males and the majority were Caucasian. Mean age was 15.3 years (SD:0.5).

Table 11 Inclusion and demographic characteristics

Study population (ATP cohort for immunogenicity)	
Number of subjects	**HBV group**
Planned, N	300
N (ATP Cohort for immunogenicity)	293
Completed, n (%)	293 (100)
Demographics	**HBV group**
N (ATP Cohort for immunogenicity)	293
Females: Males	136:157
Mean Age, years (SD)	15.3 (0.5)
Median Age, years	15
White - Caucasian / European Heritage, n (%)	289 (98.6)
Asian - Central/South Asian Heritage, n (%)	2 (0.7)
Asian - South East Asian Heritage, n (%)	1 (0.3)
White - Arabic / North African Heritage, n (%)	1 (0.3)

HBV group = Subjects who received 3 doses of *Engerix B Kinder* as primary vaccination in infancy
SD=Standard Deviation
N=Total number of subjects enrolled in the study
n/%=Number/percentage of subjects in a given category

- Efficacy results

Fourteen years after primary vaccination with 3 doses of Engerix-B at infancy, 65.4% of the subjects had anti-HBs antibody concentrations ≥10 mIU/ml. One month after the administration of the booster dose, 97.9% of the subjects had anti-HBs antibody titers ≥10 mIU/ml and 90.8% subjects had anti-HBs antibody titers ≥100 mIU/ml (Table 12). 96.9% of the subjects mount an anamnestic response (Table 13). The GMC increased by 156-fold in response to the challenge dose.

Table 12 Percentages of subjects according to anti-HBs antibody titers pre- and post-vaccination.

				≥ 6.2 mIU/mL				≥ 10 mIU/mL				≥ 10 mIU/mL and < 100 mIU/mL				≥ 100 mIU/mL				GMC		
						95% CI				95% CI				95% CI				95% CI				95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
anti-HBs antibody	HBV group	Pre-BS	292	208	71.2	65.7	76.4	191	65.4	59.6	70.9	123	42.1	36.4	48.0	68	23.3	18.6	28.6	26.5	21.4	32.8
		Post-BS	292	287	98.3	96.0	99.4	286	97.9	95.6	99.2	21	7.2	4.5	10.8	265	90.8	86.8	93.8	4134.9	3114.2	5490.1

HBV group = Subjects who received 3 doses of *Engerix B Kinder* as primary vaccination in infancy
Seropositive=anti-HBs antibody concentration ≥6.2 mIU/mL
Seroprotection= anti-HBs antibody concentration ≥10 mIU/mL
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified cut-off
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-BS = Blood sample collected before the administration of the challenge dose
Post-BS = Blood sample collected one month after the administration of the challenge dose

Table 13 Anamnestic response for anti-HBs antibody concentrations

				Anamnestic response			
						95% CI	
Group	Sub-group	Pre-vaccination status	N	n	%	LL	UL
HBV group	<6.2mIU/mL	S-	84	78	92.9	85.1	97.3
		Total	84	78	92.9	85.1	97.3
	≥6.2mIU/mL	S+	207	204	98.6	95.8	99.7
		Total	207	204	98.6	95.8	99.7
	≥6.2-<10mIU/mL	S+	17	17	100	80.5	100
		Total	17	17	100	80.5	100
	<10mIU/mL	S-	84	78	92.9	85.1	97.3
		S+	17	17	100	80.5	100
		Total	101	95	94.1	87.5	97.8
	≥10mIU/mL	S+	190	187	98.4	95.5	99.7
		Total	190	187	98.4	95.5	99.7
	Overall	S-	84	78	92.9	85.1	97.3
		S+	207	204	98.6	95.8	99.7
		Total	291	282	96.9	94.2	98.6

HBV group = Subjects who received 3 doses of *Engerix-B Kinder* as primary vaccination in infancy
S- = seronegative subjects (antibody concentration < 6.2 mIU/mL for anti-HBs antibody) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 6.2 mIU/mL for anti-HBs antibody) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
Anamnestic response to the challenge dose is defined as:
- At least (i.e. greater than or equal to) 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point
- Post-vaccination anti-HB antibody concentrations ≥10 mIU/mL in subjects seronegative at the pre-vaccination time point

- Safety results

The most frequently reported solicited symptoms during the 4-day post-vaccination follow-up period were: pain at the injection (26.8% of the subjects with one subject reporting pain of grade 3 intensity) and fatigue (27.8% of the subjects, 15.6% being considered causally related to vaccination) for local and general AE respectively.
At least one unsolicited AE was reported for 15.2% of the subjects within 31-day post-vaccination period. Headache was the most frequent (1.7% of the subjects). Causal relationship to vaccination were reported for 3 vaccinees. At least one grade 3 unsolicited symptom was reported for 5 subjects.
Two subjects reported SAE (lower limb fracture and arthralgia) but none was considered to be causally related to vaccination.

Assessor's comment:

HBV-319 is a Phase IV, open label, single-group, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immune response to a challenge dose of Engerix™- B Kinder in adolescents 15-16 years of age who were vaccinated in infancy with three doses of Engerix™-B Kinder.

All 293 children recruited received a single challenge dose of HBV vaccine. A blood sample was taken before and one month after the single challenge dose to evaluate the ability to mount an anamnestic response to the single HBV challenge dose. The safety and reactogenicity of the single challenge dose of HBV vaccine were also evaluated. Fourteen years after Engerix-B primary vaccination at infancy, 65.4% of the subjects had anti-HBs antibody concentrations ≥10 mIU/ml (seroprotection level). One month after the administration of the booster dose, 97.9% of the subjects had anti-HBs antibody titers ≥10 mIU/ml and 96.9% of the subjects mount an anamnestic response. Vaccination was overall well tolerated.

Data from this study suggest that adolescents who were vaccinated in infancy with three doses of Engerix™-B Kinder and who do not have seroprotective antibody levels are likely to develop

an anamnestic response in the context of an HBV infection. These data are consistent with the literature that suggests long-term persistence and immune memory induced by vaccines against hepatitis B, extending up to at least 20 years after primary vaccination and with a low frequency of breakthrough cases (Van Damme P and Van Herck K. A review of the long-term protection after hepatitis vaccination. Medicine and Infectious Disease 2007; 5:79–8. Red Book. Hepatitis B vaccines: WHO position paper – July 2017).

The SmPC presents data from a study with a similar design, but this study enrolled younger children (12-13 years old). Immunogenicity data of HBV-319 are considered relevant and have to be included in the Engerix B Junior PI along with other studies showing long term persistence of protection after administration of Engerix.

DTPa-HBV-IPV-115 (Eudra CT number 2015-003391-74)

- **Description**

A phase IV, open-label, multicentre study to assess the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of hepatitis B vaccine (Engerix-B Kinder SKF103860) in children aged 14-15 years, previously primed and boosted in the first two years of life with four doses of GSK Biologicals' DTPa-HBV-IPV/Hib (Infanrix hexa SB217744) vaccine.

Study initiation and completion: from August 2016 to July 2017.

- **Methods**

  - Objective(s)

1. Primary:

Immunogenicity: To assess the immunological response to hepatitis B surface antigen, in terms of antibody concentrations ≥ 100 mIU/mL, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.

2. *Secondary*:

Immunogenicity: (i) To assess the persistence of antibodies against hepatitis B surface antigen (anti-HBs antibodies), in terms of seroprotection status and antibody concentrations, in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life. (ii) To assess the immunological response to hepatitis B surface antigen, in terms of anamnestic response, one month after the single challenge dose of the hepatitis B virus (HBV) vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life. (iii) To assess the immunological response to the hepatitis B surface antigen, in terms of seroprotection status and antibody concentrations, one month after the single challenge dose of the HBV vaccine in subjects 14-15 years of age, previously vaccinated with four doses of Infanrix hexa in the first two years of life.
Safety: To evaluate the safety and reactogenicity of a single challenge dose of HBV vaccine (Engerix-B Kinder) in terms of solicited symptoms (local and general), unsolicited symptoms and serious adverse events (SAEs).

- Study design

A Phase IV, open-label, non-randomised, multicentre, single-country study with a single group. Two blood samples were collected: one sample before, and the other sample one month after the challenge dose of HBV vaccine.

- Study population /Sample size

A healthy male or female between 14 to 15 years of age (from and including the 14th birthday, up to but excluding the 16th birthday) at the time of enrolment, with documented evidence of previous vaccination with Infanrix hexa that included three doses of primary vaccination received by 9 months of age and one booster dose received between 11 and 18 months of age were included in the study. Subjects with written informed consent obtained from the parent(s)/legally acceptable representative (LAR[s]) of the subject and with written informed assent were included in the study. Evidence of previous hepatitis B booster vaccination since administration of the fourth dose of Infanrix hexa as a booster in the second year of life or history of hepatitis B disease or intercurrent hepatitis B disease or hepatitis B vaccination at birth excluded subjects from the study. Females of childbearing potential were enrolled in the study if the subject had practiced adequate contraception 30 days prior to the vaccination, had a negative pregnancy test on the day of vaccination and had agreed to continue adequate contraception during the study and for three months after the completion of the vaccination.

- Treatments

A single dose of HBV vaccine was administered to all subjects, who were previously primed and boosted with four doses of Infanrix hexa in the first two years of life. 0.5ml of Engerix-B kinder (10µg HBsAg adsorbed on 250 µg Aluminium as aluminium hydroxide) was administered intra-muscularly in the deltoid region of arm.
A blood sample was collected before and one month post-HBV vaccination.

- Outcomes/endpoints

1. Primary endpoint:

Immunogenicity to components of the study vaccine: Anti-HBs antibody concentrations ≥ 100 mIU/mL, one month after the single challenge dose of HBV vaccine.

2. Secondary endpoints:

Immunogenicity: (i) Anti-HBs antibody persistence after previous vaccination with Infanrix hexa: Anti-HBs antibody concentrations ≥ 10 mIU/mL, ≥ 100 mIU/mL and anti-HBs antibody concentrations before the single challenge dose of HBV vaccine. (ii) Immunogenicity to the components of the study vaccine: (A) Anti-HBs antibody concentrations ≥ 10 mIU/mL and anti-HBs antibody concentrations one month after the single challenge dose of HBV vaccine; (B) Anamnestic response to the single challenge dose of HBV vaccines. (Anamnestic response to the single challenge dose was defined as: At least (i.e. greater than or equal to) 4-fold rise in post-vaccination anti-HBs antibody concentrations in subjects seropositive at the pre-vaccination time point or post-vaccination anti-HBs antibody concentrations ≥ 10 mIU/mL in subjects seronegative at the pre-vaccination time point).
Safety: (i) Solicited local and general symptoms: Occurrence of each solicited local and general symptom during the 4-day (Day 0–3) followup period after the single challenge dose of HBV vaccine. (ii) Unsolicited adverse events: Occurrence of unsolicited AEs during the 31-day (Day 0–30) follow-up period after the single challenge dose of HBV vaccine. (iii) Serious adverse

events: Occurrence of serious adverse events after the single challenge dose of HBV vaccine up to study end.

- Statistical Methods

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

Analysis of demographics:
Demographic characteristics (age at challenge dose [in years], gender, geographic ancestry, height [in cm] and weight [in kg]), reason for drop-outs or elimination from ATP cohort were summarised using descriptive statistics: (i) Frequency tables were generated for categorical variable such as centre. (ii) Mean, median and standard deviation were provided for continuous variable such as age.

Analysis of immunogenicity:
The primary analyses were based on the ATP cohort for analyses of immunogenicity. If the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analyses of immunogenicity was 5% or more, a second analyses based on the TVC was to be performed to complement the ATP analyses.
Prior to the single dose of HBV vaccine and one month after the single challenge dose of HBV vaccine: (i) Percentage of subjects with anti-HBs antibody concentrations ≥ 6.2 mIU/mL (seropositive), 10 mIU/mL and ≥ 100 mIU/mL, with exact 95% confidence interval (CI) was calculated. (ii) Geometric mean concentrations (GMCs) with 95% CI was calculated for anti-HBs antibodies. (iii) The distribution of anti-HBs antibody concentrations was displayed using reverse cumulative curves (RCCs). (iv) The percentage of subjects with anti-HBs concentrations ≥ 6.2 mIU/mL, ≥ 10 mIU/mL, and ≥ 100 mIU/mL (with exact 95% CI) and GMCs (with 95% CI) at the post-HBV challenge dose time-point, in relation to their pre-challenge dose status (< 6.2 mIU/mL, ≥ 6.2 mIU/mL - < 10 mIU/mL, ≥ 10 mIU/mL) were tabulated. (v) Percentage of subjects (with 95% CI) who mounted an anamnestic response to the single challenge dose of HBV vaccine was calculated overall and in relation to their pre-vaccination status (< 6.2 mIU/mL, ≥ 6.2 mIU/mL - < 10 mIU/mL, ≥ 10 mIU/mL). (vi) Post-challenge anti-HBs antibody concentrations as a function of pre-challenge concentrations, with regression line were computed using linear regression method for ATP cohort for immunogenicity. The model included pre-challenge log transformed concentrations as regressor (independent or explanatory variable) and post-challenge log-transformed concentrations as an outcome (dependent or response) variable. (vii) Antibody concentrations observed at the pre-challenge dose time point was to be presented graphically.

Analysis of safety:
The primary analyses of safety and reactogenicity were based on the Total Vaccinated Cohort (TVC).
(i) The percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited) and with any AE during the 4-day (Day 0 to Day 3) followup period after the vaccination was tabulated with exact 95% CI. The same calculations were performed for any Grade 3 (solicited or unsolicited) AEs, for causally related AEs with a relationship to the vaccination and for any AEs requiring medical attention.
(ii) The percentage of subjects reporting each individual solicited symptom during the 4-day follow-up period with exact 95% CI, by type of adverse event (AE) (any grade, Grade 3 only, causally related to vaccination and requiring medical attention respectively) was tabulated.
The occurrence of fever was tabulated per 0.5°C cumulative increments as well as the occurrence of fever causally related, the occurrence of Grade 3 fever (> 39.0 °C axillary temperature) with causal relationship to vaccination and the occurrence of fever requiring medical attention.

(iii) The percentage of subjects with at least one report of unsolicited AE classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported within the 31-day (Day 0 to Day 30) follow-up period after vaccination was tabulated with exact 95% CI. The same tabulation was performed for Grade 3 unsolicited AEs, for unsolicited AEs with a causal relationship to vaccination and for unsolicited AEs requiring medical attention.
(iv) The percentage of subjects who started receiving at least one concomitant medication (i.e. any medication, antipyretic medication, prophylactic antipyretics) during the 4-day and 31-day followup period after vaccination was tabulated (with exact 95% CI).
(v) SAEs and withdrawals due to AEs and SAEs reported during the study were described in detail.

➢ **Results**

- Recruitment and number analysed

A total of 300 subjects aged 14-15 years at the first vaccination visit were planned to be enrolled into the study. 302 subjects were included and completed the study. The ATP cohort for immunogenicity comprises 268 subjects.

- Baseline data

Demographic characteristics are detailed in the Table below. Of the 302 subjects included, 160 were males and the majority were Caucasian. Mean age was 14.4 years (SD:0.5).

Table 14 Demographic characteristics

Study population	
Number of subjects	**HBV Group**
Planned, N	300
Total Vaccinated Cohort	302
Completed, n (%)	302 (100)
Demographics	**HBV Group**
N (Total Vaccinated Cohort)	302
Females: Males	142:160
Mean Age, years (SD)	14.4 (0.5)
Median Age, years (minimum, maximum)	14 (13, 16)
White - Caucasian / European Heritage, n (%)	293 (97.0)
White - Arabic / North African Heritage, n (%)	4 (1.3)
African Heritage / African American, n (%)	2 (0.7)
Asian - Central/South Asian Heritage, n (%)	1 (0.3)
Asian - South East Asian Heritage, n (%)	1 (0.3)
OTHER: Caucasian/North African Mixture, n (%)	1 (0.3)

HBV Group = Subjects who previously received 4 doses of *Infanrix hexa* in first two years of life and received a challenge dose of HBV vaccine in this study
SD = Standard Deviation
N = Total number of subjects enrolled in the study
n/% = number / percentage of subjects in a given category
Note that since only month and year of the birthdate are available, the derived age may be incorrect by 1 year
Source: Table 14.1.8.1

- Immunogenicity results

Around twelve years after primary vaccination with four doses of Infanrix hexa in the first two years of life, 53.7 % of the subjects had anti-HBs antibody concentrations ≥10 mIU/ml. One month after the administration of the booster dose, 93.3% of the subjects had anti-HBs antibody titers ≥10 mIU/ml and 87.3% subjects had anti-HBs antibody titers ≥100 mIU/ml (Table 15). 92.5% of the subjects mounted an anamnestic response. The GMC increased by 127-fold in response to the challenge dose.

Table 15 Percentages of subjects according to anti-HBs antibody titers pre- and post-vaccination

			≥ 6.2 mIU/mL				≥ 10 mIU/mL				≥ 100 mIU/mL				GMC		
					95% CI				95% CI				95% CI			95% CI	
Group	Timing	N	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	value	LL	UL
HBV	Pre	268	163	60.8	54.7	66.7	144	53.7	47.6	59.8	45	16.8	12.5	21.8	15.6	12.8	19.1
Group	P1(D30)	268	255	95.1	91.8	97.4	250	93.3	89.6	96.0	234	87.3	82.7	91.1	1975.7	1436.1	2718.1

HBV Group = Subjects who previously received 4 doses of *Infanrix hexa* in first two years of life 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: Blood sampling at pre-challenge dose time point
P1(D30): Blood sampling one month after the challenge dose

- Safety results

The most frequently reported solicited symptoms during the 4-day post-vaccination follow-up period were: pain at the injection (33.6% of the subjects with 1% of the subjects reporting pain of grade 3 intensity) for the local solicited AE and fatigue 30.2% of the subjects for the general AE. Headache was the most frequently reported grade 3 solicited general symptom (4.3% of the subjects).
At least one unsolicited AE was reported for 18.2% of the subjects within 31-day post-vaccination period. At least one unsolicited adverse event of Grade 3 intensity was reported for 2.3% of the subjects. The following unsolicited adverse events were considered to be causally related to vaccination: dizziness (0.7 % of subjects) and injection site pruritus, malaise, pain and pain in extremity (each reported for 0.3% of subject).
Two subjects reported SAE (meniscus injury and eating disorder) but none was considered to be causally related to vaccination.

Assessor's comment:

DTPa-HBV-IPV-115 is a Phase IV open label multicentre study that assessed the long-term persistence of antibodies against hepatitis B and the immunogenicity and safety of a challenge dose of Engerix in children aged 14-15 years old who were primed and boosted in the first two years of live with four doses of the DTPa-HBV-IPV/Hib (Infanrix hexa). This is the last study of a series of four studies that assessed the persistence of antibodies against hepatitis B in children of respectively 4-5, 7-8, 12-13 and 14-15 years old who received Infanrix hexa in the first two years of live, as part of routine vaccination in infancy, in Germany.
All children recruited received a single challenge dose of HBV vaccine. A blood sample was taken before and one month after the single challenge dose to evaluate the ability to mount an

anamnestic response to the single HBV challenge dose. The safety and reactogenicity of the single challenge dose of HBV vaccine were also evaluated.
Of 268 children vaccinated in infancy with Infanrix, 53.7% had anti-HBs antibody concentration ≥10 mIU/mL (seroprotective levels) at 14-15 years of age. One month after the challenge dose of HBV vaccine, 93.3% and 87.3% of the children had anti-HBs antibody concentration respectively ≥10 mIU/mL (seroprotective levels) and ≥100 mIU/mL. In addition, an anamnestic response to the hepatitis B vaccine challenge dose was mounted by 92.5% of the children.
Data from this study, as those of the previous studies related to challenge vaccine after primary immunisation with Infanrix hexa, suggest that children/adolescents who do not have a seroprotective antibody level are likely to develop an anamnestic response in the context of an HBV infection. The results observed in these studies are in line with the results observed when children and adolescents were primed with three doses of a monovalent hepatitis B vaccine. More specifically, it is consistent with the literature that suggest a low frequency of breakthrough cases and long-term persistence and immune memory induced against hepatitis B by Engerix-B, extending up to at least 20 years after primary vaccination. (Van Damme P and Van Herck K. A review of the long-term protection after hepatitis vaccination. Medicine and Infectious Disease 2007; 5:79–8. Red Book. Hepatitis B vaccines: WHO position paper – July 2017).
Injection site pruritus and pain in extremity were reported at higher frequencies than presented in the SmPC of Engerix B Junior.
As infants were primed with Infanrix and not Engerix is this study, and as the booster dose of Engerix in adolescents is not recommended in the SmPC, it is agreed that the safety and immunogenicity data of this study are not relevant to the Engerix PI.

103860/005 – HBV 104

- **Description**

Comparative study of the immunogenicity & safety of two dosing schedules of Engerix-B in neonates.

Study initiation and completion: from August 1989 to April 1991.

- **Methods**

  - Objective(s)

Immunogenicity: Comparison of the safety and the immunogenicity of 2 dosing schedules of Engerix-B between a standard 0,1, 6 months or an accelerated 0, 1, 2 months schedules in neonates.

  - Study design

A prospective, randomized, two-armed study.
Neonates were randomized to receive 10 µg of Engerix-B on either a 0, 1, 6 month schedule or a 0, 1, 2 month schedule.
Blood samples were obtained from each newborn at months 0 for HBV markers determination and at months 2, 3, 6, and 7 for anti-HBs Ab titers determination.

- Study population /Sample size

A total of 299 subjects were screened and received at least one dose of vaccine. Of these, 220 subjects had evaluable data for at least one timepoint and were eligible for the immunogenicity analysis.

- Treatments

Vaccine: Engerix-B.
Vaccine dose: 10 µg of HBsAg adsorbed on 0.25 mg aluminium as aluminium hydroxide in a volume of 0.5 mL.
Vaccination schedule: subjects were randomized to receive Engerix-B on either a 0, 1, 6 month schedule or a 0, 1, 2 month schedule.
Route of administration and site: intramuscularly in the anterolateral thigh.

- Outcomes/endpoints

Immunogenicity: Anti-HBs Ab concentration at months 2, 3, 6 and 7. Seroprotection rates at months 2, 3, 6 and 7.

Seroconversion (SC) and Seroprotection (SP) rates are defined as anti-HBs titers ≥1.0 mIU/Ml and ≥10.0 mIU/Ml respectively.

Safety : Occurrence of local and systemic adverse events following doses 1, 2 and 3.

- Statistical Methods

The comparison of seroprotection rates at each timetpoint was accomplished using the chi-square test. Analyses of the primary endpoints (months 3&6) were performed at the 0.05 level of significance. Prior to the study, it was determined that 100 evaluable neonates per group would provide an 80% power at a two-side type I error of 0.05 to detect a 15% difference in seroprotection rates at months 3 and 6 using a two-tailed chi-square test. GMT's were calculated by determining the log for each titer, then taking the anti-log of the mean of the logs.

➢ **Results**

- Recruitment/ Number analysed

A total of 299 subjects were screened and received the first dose of vaccine. Of these, 220 subjects were eligible to continue in the study.
A total of 220 subjects were included in the immunogenicity analysis.

- Baseline data

Demographic characteristics for all subjects enrolled (Table 16) and for subjects with evaluable immunogenicity data (Table 17).
The groups were similar with respect to gender, race and weight.

Table 16 Demographic characteristics for all subjects enrolled

	Schedule A - 0,1,6 (N = 146)		Schedule B - 0,1,2 (N = 153)		Total 299
	n	(%)	n	(%)	
Number of Males	80	(54.8)	78	(51.0)	158
Number of Females	66	(45.2)	75	(49.0)	141
Race					
White - Number	21	(14.4)	22	(14.4)	43
Black - Number	41	(28.1)	47	(30.7)	88
Hispanic - Number	38	(26.0)	37	(24.2)	75
Asian -Number	22	(15.1)	22	(14.4)	44
Other - Number	24	(16.4)	25	(16.3)	49
Weight (lbs)					
Mean ± S.D.	7.24 ± 1.00		7.24 ± .98		

Table 17 Demographic characteristics for all subjects with evaluable immunogenicity data

	Schedule A - 0,1,6 (N = 115)		Schedule B - 0,1,2 (N = 105)		Total 220
	n	(%)	n	(%)	
Number of males	65	(56.5)	54	(51.4)	119
Number of females	50	(43.5)	51	(48.6)	101
Race					
White - Number	19	(16.5)	17	(16.2)	36
Black - Number	34	(29.6)	35	(33.3)	69
Hispanic - Number	32	(27.8)	26	(24.8)	58
Asian -Number	13	(11.3)	10	(9.5)	23
Other - Number	17	(14.8)	17	(16.2)	34
Weight (lbs)					
Mean ± S.D.	7.27 ± 1.01		7.24 ± .89		

- Immunogenicity results

Administration of the second dose of Engerix-B at month 2 rather than month 6 resulted in a significantly greater percentage of neonates with protective Ab titers at month 3 (23%, p=0.00006, Table 18). This effect persisted and was still significantly different at month 6 (p=0.008, Table 18). By month 7, when all infants had received three doses of vaccine, there was no difference in the seroprotection rates between the groups (p=0.9, Table 18).

Table 18 Seroconversion (SC), seroprotection (SP) rates and Geometric mean anti-HBs titers (GMTs) for all evaluable subjects

	Schedule A - 0,1,6	Schedule B - 0,1,2	P Values
MONTH 2			
SC	90.6% (87/96)	89.6% (86/96)	
SP	54.2% (52/96)	54.2% (52/96)	1.0
GMT	14.2 (n=87)	15.9 (n=86)	
MONTH 3			
SC	93.4% (85/91)	100% (86/86)	
SP	71.4% (65/91)	94.2% (81/86)	0.00006 †
GMT	36.9 (n=85)	152.8 (n=86)	
MONTH 6			
SC	95.7% (89/93)	100% (72/72)	
SP	84.9% (79/93)	97.2% (70/72)	0.008 †
GMT	116.9 (n=89)	338.2 (n=72)	
MONTH 7			
SC	97.7% (85/87)	98.8% (79/80)	
SP	97.7% (85/87)	97.5% (78/80)	0.9
GMT	3392.1 (n=85)	480.3 (n=79)	

* (anti-HBs titer ≥ 1 mIU/mL)
** (anti-HBs titer ≥ 10 mIU/mL)
*** (In seroconverters)
† Significant

- Safety results

A total of 375 doses of Engerix B were administered at 0, 1 and 6 months for the standard schedule and a total of 388 doses were administered at 0, 1 and 2 months for the accelerated schedule. The incidence of AE's related or possibly related to Engerix B was 1.1% (4/375) for the standard schedule and 0.3% (1/388) for the accelerated schedule. None of these AE's were reported as serious. Two subjects experienced AE's in the standard schedule (the first one: malaise and fever, the second one: nodule formation at the site of injection after the 1st and the 2nd doses) and 1 subject in the accelerated schedule (malaise).
Table 19 and Table 20 summarize the adverse experiences according to the schedule.

Table 19 Summary of Adverse experiences, standard schedule

ADVERSE EXPERIENCE*	Number Of Subjects Receiving Dose 1 N = 146	Dose 2 N = 128	Dose 3 N = 101
	n (%)	n (%)	n (%)
Fever		1 (0.8)	
Malaise		1 (0.8)	
Nodule	1 (0.7)	1 (0.8)	

* 'Related' or 'Possibly Related' relationship to study vaccine.

Table 20 Summary of Adverse experiences, accelerated schedule

ADVERSE EXPERIENCE*	Number Of Subjects Receiving Dose 1 N = 153	Dose 2 N = 119	Dose 3 N = 116
	n (%)	n (%)	n (%)
Malaise		1 (0.8)	

* 'Related' or 'Possibly Related' relationship to study vaccine.

Assessors' comment:

HBV 104 is a descriptive study comparing the immunogenicity and safety of two schedules (0, 1, 6 months and 0, 1, 2 months) of Engerix-B (10 µg of HBsAg) in neonates. The study was performed in the 1990th i.e. prior to the marketing authorization in EU. No clear objective was described and study documentation is very limited. A high proportion of the vaccinated subjects (24%) were excluded from the immunogenicity analysis, resulting in 220 subjects with evaluable data for at least one timepoint and eligible for the immunogenicity analysis.
The schedules assessed in the study are those described in the Engerix Junior SmPC.
Overall, the immunogenicity data are nconsistent with the data presented in the SmPC.
A nodule formation at the site of injection was reported in the present study, which is not included in the table of undesirable effects in the SmPC. 'Nodule formation' should be discussed by the MAH in the next PSUR.

103860/013 – HBV 079

- **Description**

A comparative study of two different doses of Smith Kline-RIT rec-DNA hepatitis B vaccine (10 and 20 µg).

Study initiation and completion: from January 1987 to June 1990.

- **Methods**

  - Objective(s)

Immunogenicity: (i) To determine the immunogenicity of the vaccine in a high risk population. (ii) To determine the optimal dose of vaccine which will produce a satisfactory antibody response.

Safety: To evaluate the incidence and type of reactions to the vaccine.

- Study design

A prospective, randomized, two-armed, blinded study.
All the children were vaccinated with Engerix-B (with 10 or 20 µg vaccine dose) at months 0, 1, 6. Blood samples were obtained from each children at day-7 and months 0, 1, 3, 6, 7 and 12 for HBV markers and SGPT determination.

- Study population and sample size

Chinese children of hepatitis B carrier mothers, negative for HBsAg, anti-HBs and anti-HBc Ab, ages: 1½ to 11 years.
Number of subjects: 180. Of these 180 children, one hundred and twenty-four of the participants were initially seronegative.

- Treatments

Vaccine: Engerix-B.
Vaccination dose: Group 1: 10 µg HBsAg, Group 2: 20 µg HBsAg.
Vaccination schedule: 0, 1, and 6 months.
Vaccination route and site: Intramuscular, deltoid.

- Outcomes/endpoints

Immunogenicity: Seroconversion and seroprotection rates, and GMTs determination calculated at months 1, 3, 6, 7 and 12; Distribution of anti-HBs Ab at screening, months 1, 3, 6, 7 and 12.

Safety: Occurrence of local and general adverse events following dose 1, 2 and 3 and comparison between groups (10 and 20 µg doses).

- Statistical Methods

Two-way analysis compared mean age between sex and group; Student's t test compared means between dose levels, seroconversion rates and GMT's between groups.

➢ **Results**

- Recruitment and numbers analysed.

Of 180 enrolled subjects, 126 were included in the reactogenicity study and 119 in the immunogenicity analysis. (See baseline data)

- Baseline data

The 3 tables (Tables 21, 22 and 23) below present the demographic characteristics of the total population, of subjects with evaluable reactogenicity or immunogenicity data.
The groups were similar with respect to gender and age.

Table 21 Demographic characteristics of the total population

Group	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D.
1	males	47	5.0	1	11	2.38
	females	40	5.3	1	11	2.40
	all	87	5.2	1	11	2.38
2	males	39	5.2	0	11	3.04
	females	54	4.4	0	11	3.01
	all	93	4.8	0	11	3.03
1 - 2	males	86	5.1	0	11	2.68
	females	94	4.8	0	11	2.79
	all	180	5.0	0	11	2.74

Notes : Individual subject data in Appendix Table I

N = total number of subjects
S.D. = standard deviation

There are 3 subjects with an unknown age in group 1 and 2 subjects in group 2

Statistics :

Student's t test, comparing means age between both groups, is not significant (p=0.31)

Chisquare test, comparing the ratio of males to females between groups, is not significant (p=0.11)

Table 22 Demographic characteristics of the subjects included in the reactogenicity

Group	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D.
1	males	36	5.2	1	11	2.30
	females	25	5.1	1	11	2.64
	all	61	5.1	1	11	2.42
2	males	29	5.0	0	11	3.06
	females	36	4.5	0	11	3.13
	all	65	4.7	0	11	3.08
1 - 2	males	65	5.1	0	11	2.64
	females	61	4.8	0	11	2.93
	all	126	4.9	0	11	2.78

Notes : Individual subject data in Appendix Table I

N = total number of subjects
S.D. = standard deviation

Statistics :

Student's t test, comparing means age between both groups, is not significant (p=0.39)

Chisquare test, comparing the ratio of males to females between groups, is not significant (p=0.11)

Table 23 Demographic characteristics of the subjects included in the analysis of immunogenicity

Group	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D.
1	males	34	5.1	1	11	2.36
	females	22	5.0	1	11	2.79
	all	56	5.1	1	11	2.51
2	males	28	5.1	0	11	3.06
	females	35	4.5	0	11	3.18
	all	63	4.8	0	11	3.11
1 - 2	males	62	5.1	0	11	2.67
	females	57	4.7	0	11	3.02
	all	119	4.9	0	11	2.84

Notes : Individual subject data in Appendix Table I

N = total number of subjects
S.D. = standard deviation

Statistics :

Student's t test, comparing means age between both groups, is not significant (p=0.55)

Chisquare test, comparing the ratio of males to females between groups, is not significant (p=0.08)

- Immunogenicity results

One month after the full vaccine course, all subjects had seroconverted and GMT's were 5559 (range: 51-156000) and 3847 (range: 17-105252) mIU/ml for groups 1 and 2 respectively (p=0.32). All vaccinees had attained the 10 mIU/ml protective antibody level by month 7. Of the subjects followed up to month 12 (47, group 1 and 49, group 2) all had protective antibody levels with GMT's of 1578 (range:11-124725) and 1017 (range:16-33990) mIU/ml, groups 1 and 2 respectively (p=0.22).
After 2 doses of vaccine, a trend for higher number of children with protective Ab level is however noted with the 20 µg dose (Table 24).

Table 24 Distribution of antibody titers following vaccination

Group	Timing	N	>=10	%	>=100	%	>=1000	%
1	PI(m1)	53	8	15.1	1	1.9	0	0.0
	PII(m3)	53	46	86.8	27	50.9	1	1.9
	PII(m6)	55	50	90.9	32	58.2	2	3.6
	PIII(m7)	51	51	100.0	49	96.1	41	80.4
	PIII(m12)	47	47	100.0	45	95.7	33	70.2
	PIII(m24)	35	33	94.3	31	88.6	17	48.6
2	PI(m1)	60	10	16.7	0	0.0	0	0.0
	PII(m3)	62	59	95.2	34	54.8	1	1.6
	PII(m6)	60	57	95.0	34	56.7	2	3.3
	PIII(m7)	56	56	100.0	53	94.6	43	76.8
	PIII(m12)	49	49	100.0	43	87.8	25	51.0
	PIII(m24)	36	35	97.2	26	72.2	13	36.1

Notes : Vacc.schedule : 0,1 and 6 months
----- Vacc.dose of lot : Group 1 : 10 mcg dose of lot 44SP10 and 45SP10
Group 2 : 20 mcg dose of lot ENG.101A4

N = number of subjects tested

Statistics

Chisquare test, comparing the seroprotection rates between groups, is:
not significant at month 1 (0.82)
Fisher's exact test is not significant at month 3 (p=0.18)
not significant at month 6 (p=0.48)
not significant at month 24 (p=0.61)

- Safety results

Both solicited and non-solicited symptoms were recorded. The vaccine was well tolerated as no serious adverse events were reported. Overall, of the 362 symptom sheets returned, 341 (94.0%) were symptom-free. The reported symptoms were fever, gastrointestinal symptoms, soreness, swelling, dizziness.

Assessors' comment:

HBV-079 is a descriptive study comparing the immunogenicity and safety of two different doses of Smith Kline-RIT rec-DNA hepatitis B vaccine (10 and 20 µg) administered according to a 0,1,6 months) schedule. The study was performed in children 1.5 to 11 years of age negative for HBsAg, anti-HBs and anti-HBc Ab, and whose mothers are Hep B carriers.

The study was performed in the 1990th, i.e. prior to the marketing authorization.

The study used early batches of the vaccine, and to which extend these batches are comparable to the currently licensed vaccine is unclear.

Study documentation is very limited and some inconsistencies are noted. A high proportion of the vaccinated subjects (34%) were excluded from the immunogenicity analysis, resulting in 126 evaluable subjects. The minimum age of the included children is not clear and is inconsistent with the study population (protocol versus table). Detailed immunogenicity results described in

the study report differ from those described in the summary of both the study report and the synopsis. The assessor has considered the antibody GMT described in the clinical report.

Overall, the immunogenicity and AE data are consistent with the data presented in the SmPC. The study shows high seroconversion rates and GMTs levels for both dose levels. After the full vaccine course, all subjects had seroconverted. This seroprotection rate of 100% at month 7 in children form 1 ½ to 18 years of age, is agreement with the seroprotection rate of ≥96% at month 7 with a 0, 1, 6 months schedule described under the section 5.1, healthy subjects, of the SmPC of Engerix Junior and Engerix B.

In those children 1.5 to 11 years of age, after the 2-doses schedule (at Month 3), a trend for higher frequency of children with protective Ab level is however noted with the 20 µg dose compared to the 10 µg dose (95.2% vs. 86.8%). The seroprotection rate obtained at Month 3 with the 10 µg dose is consistent with the data presented in the SmPC.

The seroprotection rate obtained in this study at Month 3 following two doses of 20 µg (at 0 and 1 month) is higher than that obtained following three doses of 10 µg dose (at 0, 1 and 2 month) (95.2% in this study vs. 89% as described in the SmPC for children up to 15 years for the rapid 0, 1, 2 month schedule).

These data suggest that a more rapid protection could be obtained with only two doses of the 20 µg in an at risk population as compared to three doses of 10 µg. It is understood that the schedule licensed at present is based on consideration of both the efficacy and the safety of the administered doses in the different age groups and target populations, and that optimal use of the available antigen is important. The MAH should therefore discuss whether the 0,1,6 months schedule with 20 µg could be relevant when rapid protection is needed. Overall, the MAH should discuss whether the data from this study are consistent with the statements in the 4.2. section of the SmPC of Engerix Junior, including with respect to using differently the 10 and the 20 µg dose levels across age categories (<10, 10-15, 16+ years of age) in this at risk population.

The data from study HBV-079 should be reflected in the section 5.1. of the SmPC of Engerix Junior. The data should also be reflected in the SmPC in 4.9 Overdose with cross-reference to 5.1.

103860/018 – HBV 153

- **Description**

Immunogenicity and protective efficacy of SK Biologicals rec-DNA hepatitis B vaccine (10 µg doses) in newborns of HBsAg positive or negative mothers.

Study conducted in Italy, 1990.

- **Methods**

  - Objective(s)

Immunogenicity: The determination of the immunogenicity of the vaccine in healthy newborns, and its protective efficacy during one year, following a vaccination course using 10 µg doses of surface antigen.

Safety: The evaluation of the incidence and type of eventual reactions to the vaccine administration.

- Study design

Prospective study.
All the newborns were vaccinated with Engerix-B at months 0, 1, 2, 12.
Blood samples were obtained from each newborn at months 0, 1, 2, 3, 12 and 13 for HBV markers and SGPT determination.

- Study population /Sample size

30 newborns were enrolled, born from HBsAg positive or negative mothers. 18 healthy newborns completed the vaccination course (0, 1, 2, 12 months) and the follow-up schedule. They all were negative for HBsAg, anti-HBs and anti-HBc with normal SGPT levels. Doses of HB-immunoglobulins (HBIg) were administered by intramuscular route to newborns of HBsAg positive mothers (28 subjects).

- Treatments

Vaccine: Engerix-B.
Vaccine dose: 10 µg HBsAg.
Vaccination schedule: months 0, 1, 2, 12.
Route of administration and site: intramuscular, anterolateral thigh.

- Outcomes/endpoints

Immunogenicity: Anti-HBs Ab titers determination during vaccination course and comparison between children who did or didn't received HBIg at birth. Seroprotection rates determination during vaccination course.
Safety: Occurrence of local and systemic reaction at each dose (scored symptoms).

- Statistical Methods

Not described.

➢ **Results**

- Recruitment and number analysed.

On the 30 enrolled newborns, only 18 completed the study. 17 newborns received HBIg at birth.

- Baseline data

Demographic characteristics are detailed in the Table 25 below.

Table 25 Characteristics of the population

Record	PROVENIENCE	CODEX	SEX	BIRTH	IG	HBSAGO	ANTIHBSO	ANTIHBCO
2	M	01PR	M	18.05.88	19.05.88	-	175	+
3	M	02MMG	F	29.05.88	30.05.88	-	0.01	+
4	M	03DAA	M	04.06.88	06.06.88	-	0.01	+
5	M	04AF	F	10.06.88	11.06.88	-	0.01	-
6	M	05GG	M	14.06.88	15.06.88	-	0.01	-
7	M	06DGS	M	20.06.88	21.06.88	-	0.01	+
8	M	07PE	M	30.06.88	01.07.88	-	0.01	+
9	M	08VR	F	29.06.88	30.06.88	-	0.01	+
10	M	09FM	M	02.07.88	03.07.88	-	0.01	+
11	M	10GM	M	06.07.88	07.07.88	-	0.01	+
13	M	12LR	F	11.07.88	12.07.88	-	0.01	-
14	M	13APL	M	27.07.88	28.07.88		0.01	
15	M	14FMP	F	09.08.88	10.08.88	-	0.01	+
16	M	15CI	F	18.08.88	18.08.88	-	0.01	+
18	M	16FL	M	25.08.88	25.08.88	-	0.01	+
20	M	17RR	M	07.09.88	08.09.88	-	25	+
	M	18FC	F	01.10.88	NON	-		
	M	11DC	M	04.07.88	NON	-	0.01	-
22	M	19NI	F	18.10.88	19.10.88	-	2100	+
23	M	20PV	F	18.10.88	19.10.88	-	0.01	+
24	M	21MDV	F	20.10.88	21.10.88	-	0.01	-
25	M	22MM	F	21.10.88	21.10.88	-		
26	M	23AR	M	24.10.88	24.10.88	-	0.01	+
27	M	24BS	M	24.11.88	25.11.88	-	0.01	+
28	M	25VG	M	05.10.88	05.10.88			
29	M	26EA	F	05.10.88	06.10.88			
31	M	27CD	M	28.09.88	29.09.88			
34	M	28AV	F	28.09.88	29.09.88			
35	M	29DL	F	05.12.88	05.12.88			
37	M	30AC	M	14.12.88	15.12.88	-	0.01	+

- Immunogenicity results

93% of the 30 subjects were already seroprotected after the first dose of vaccine. All the 18 children with complete follow-up developed protective Ab titers. At month 12, 14/17 children who received HBIg at birth were seroprotected from HBV infection. After the booster dose, 100% were seroprotected. The only newborn who didn't receive HBIg at birth was seroprotected at month 13.
Table 26 summarizes the results of serological determination at several time and the Table 27 the percentages of seroprotected newborns after each vaccination.

Table 26 Anti-HBs GMT (expressed in mIU/ml) at several timepoints

Newborns who received Ig (28)		Newborns who did not receive Ig (2)	
MONTH 1		MONTH 1	
Anti-HBS GMT (26 data)	59.16	Anti-HBS Titre (1 datum)	158
MONTH 2		MONTH 2	
Anti-HBS GMT (25 data)	159.15	Anti-HBS Titre (1 datum)	10
MONTH 3		MONTH 3	
Anti-HBS GMT (23 data)	67.86	Anti-HBS Mean Titre (2 data)	76.95
MONTH 12		MONTH 12	
Anti-HBS GMT (17 data)	133.66	Anti-HBS Titre (1 datum)	811
MONTH 13		MONTH 13	
Anti-HBS GMT (17 data)	3100.06	Anti-HBS Titre (1 datum)	71159

Table 27 Percentages of seroprotected newborns after the vaccinations

	Newborns receiving Ig at birth	Newborns not receiving Ig at birth
MONTH 1	96% (27/28)	100% (1/1)
MONTH 2	100% (27/27)	100% (1/1)
MONTH 3	100% (23/23)	100% (2/2)
MONTH 12	82% (14/17)	100% (1/1)
MONTH 13	100% (17/17)	100% (1/1)

- Safety results

None of the children experienced any local or systemic adverse reaction to the vaccine.

Assessors' comment:

HBV-153 is a descriptive study assessing the immunogenicity of SK Biologicals rec-DNA hepatitis B vaccine (10 µg doses) administered according to 0, 1, 2, 12 schedule in newborns of HBsAg positive or negative mothers.

The sample size is very limited (30 enrolled newborns, 18 who completed the study). The study was performed in the 1990th. Study documentation is very limited.

The study shows immunogenicity and seroprotection, whether in presence of HBIg coadministration at birth or not (only 1 neonate who did not received HBIg had a complete follow-up).

The schedule and dose level assessed in the study are those described in the Engerix Junior SmPC. Overall, the immunogenicity and AE data are consistent with the data presented in the SmPC.

103860/021 – HBV 177

- **Description**

Immunogenicity and protective efficacy of Smith Kline -RIT's rec-DNA hepatitis b vaccine (10 µg) in newborns of HBsAg positive or negative mothers.

Study conducted in Italy, from March 1989 to July 1991.

- **Methods**

  - Objective(s)

Formation cohort HBsAg positive or negative pregnant women to:
(i) determine the immunogenicity of the vaccine in healthy newborns with 10 µg dose.
(ii) evaluate the incidence and type of reactions to the vaccine.
(iii) evaluate the protective efficacy during one year.

  - Study design

Prospective study.
All the newborns were vaccinated with Engerix-B at months 0, 1, 6. Blood samples were obtained from each newborn at day -7 to -3, months 1, 6, 7 and 12 for HBV markers and SGPT determination.
At month 0, blood sample of the mother was collected for HBV markers determination.
HBIg wat administered at month 0 by im route if newborns HBsAg positive mothers.

  - Study population and sample size

30 newborns of HBsAg positive or negative mothers, with a weight of 2,000 grams or more at birth and having a 5 minutes Apgar score of 7 or higher. They had to be negative for HBsAg, anti-HBs and anti-HBc antibodies and with a normal serum SGPT level and be physically in good condition. They had to be without clinical signs of acute disease and with no significant and persisting hematologic, hepatic (normal SGPT), renal, cardiac or respiratory diseases as established at the moment of entry into the study.

Administration of HB Immunoglobuline by the intramuscular route was made only in newborns of HBsAg positive mothers.

- Treatments

Vaccine : SK-RIT 0.5 ml (Engerix-B) containing 10 µg HBsAg adsorbed in Al(OH)3.
Vaccination schedule: 0, 1, 6 months.
Administration route and site: intramuscular, anterolateral thigh.
Follow-up: 1 year.

- Outcomes/endpoints

Immunogenicity: determination of anti-HBsAg, anti-HBc and anti-HBs Ab titers (mIU/ml) with RIA technique.
Safety: Occurrence (recording and scoring) of general and local clinical signs and symptoms at dose 1, 2 and 3 (during 3 days post-vaccination). Evaluation of the scoring by the investigators 48h after each vaccination.

- Statistical Methods

Not described

➢ **Results**

- Recruitment and number analysed

17 vaccinated newborns who didn't received HBIg at birth, 10 completed the 12 months follow up (2 the 13 months follow-up).
11 vaccinated newborns who did received HBIg at birth, 8 completed the 12 month follow-up.

- Baseline data

No data available.

- Immunogenicity results

At month 7, 84.6% of recipients without HBIg and 100% of recipients with HBIg had anti-HBs Ab titers >10 mIU/ml. GMT titers were higher for recipients with HBIg.
At month 12, 80% of recipients without HBIg and 100% of recipient with HBIg had anti-HBs Ab titers >10 mIU/ml. Overall, GMT titers declined form month 7 to month 12.
Results are summarized in the Tables below.

Table 28 Seroprotection (SP) rate and Geometric mean anti-HBs titers (GMTs) for neonates who didn't received HBIg at birth

Tempo	Tot. Sogg. >10 mIU/ml	MGT (media log+/−DS)	mIU/ml 10–100	100–1000	>1000
1	8/17 (47.1%)	110.1 (2.0+/− 0.2)	4 (50%)	4 (50%)	–
6	10/17 (58.8%)	44.1 (1.6+/− 0.5)	9 (90%)	1 (10%)	–
7	11/13 (84.6%)	564.0 (2.7+/− 0.9)	2 (18.2%)	4 (36.4%)	5 (45.4%)
12	8/10 (80%)	203.5 (2.3+/− 0.7)	2 (25%)	5 (62.5%)	1 (12.5%)
13	2/2 (100%)	851.9 (2.9+/− 1.7)	–	1 (50%)	1 (50%)

Table 29 Seroprotection (SP) rate and Geometric mean anti-HBs titers (GMTs) for neonates who received HBIg at birth

Tempo	Tot. Sogg. >10 mIU/ml	MGT (media log+/−DS)	mIU/ml 10–100	100–1000	>1000
1	11/11 (100%)	122.4 (2.1+/− 0.1)	3 (27.3%)	8 (72.7%)	–
6	9/10 (90%)	48.9 (1.7+/− 0.4)	7 (77.8%)	2 (22.2%)	–
7	7/7 (100%)	1310.6 (3.1+/− 0.6)	1 (14.3%)	1 (14.3%)	5 (71.4%)
12	8/8 (100%)	282.8 (2.4+/− 0.7)	2 (25%)	4 (50%)	2 (25%)

- Safety results

Not data available.

Assessors' comment:

HBV-177 is a descriptive study assessing the immunogenicity Smith Kline -RIT's rec-DNA hepatitis b vaccine (10 µg) administered according to 0, 1, 6 months schedule in newborns of HBsAg positive or negative mothers.

The sample size is very limited (28 evaluable newborns). The study was performed in the 1990th. Study documentation is very limited. Safety results are not available.

The study shows immunogenicity and seroprotection, whether in presence of HBIg coadministration at birth or not. However, those who received HBIg at birth had higher GMT than those who did not received HBIg and the proportion of seroprotected children was also higher one month post dose 3.

The schedule and dose level assessed in the study are those described in the Engerix Junior SmPC. Overall, the immunogenicity data are in line with the data presented in the SmPC.

103860/023 – HBV 155

- **Description**

Immunogenicity and protective efficacy of Smith Kline -RIT's rec-DNA hepatitis b vaccine (10 µg) in newborns of HBsAg positive mothers.

Study conducted in Italy from October 1988 to April 1991.

- **Methods**

  - Objective(s)

Formation cohort HBsAg positive or negative pregnant women to:
(i) To determine the immunogenicity of the vaccine in healthy newborns with dose 10 µg.
(ii) To evaluate the incidence and type of reactions to the vaccine.
(iii) To evaluate the protective efficacy during one year.

  - Study design

Prospective study.
All the newborns were vaccinated with Engerix-B at months 0, 1, 2 and 12 (booster dose). Blood samples were obtained from each newborn at day -7 to -3, months 1, 2, 3, 12 and 13 for HBV markers and SGPT determination. Administration of HB Immunoglobulin by the im route was made in newborns.

  - Study population and sample size

30 newborns of HBsAg positive mothers, with a weight of 2,000 grams or more at birth and having a 5 minutes Apgar score of 7 or higher. They had to be negative for HBsAg, anti-HBs and anti-HBc antibodies and with a normal serum SGPT level and be physically in good condition. They had to be without clinical signs of acute disease and will have no significant and persisting hematologic, hepatic (normal SGPT) , renal, cardiac or respiratory diseases as established at the moment of entry into the study.
Administration of HB Immunoglobulin by the intramuscular route was made in newborns.

  - Treatments

Vaccine: SK-KIT 0.5 ml (Engerix-B) containing 10 µg HBsAg adsorbed in Al(OH)3.
Vaccination schedule: 0, 1, 2 months, with booster dose at 12 month.
Administration route and site route: intramuscular, anterolateral thigh.

- Outcomes/endpoints

Immunogenicity: Determination of anti-HBsAg, anti-HBc and anti-HBs Ab titers (mIU/ml) with RIA technique.
Safety: Occurrence (recording and scoring) of general and local clinical signs and symptoms at dose 1, 2 and 3 and at the booster dose (during 3 days post-vaccination). Evaluation of the scoring by the investigators 48h after each vaccination.

- Statistical Methods

Not described.

➢ **Results** see 103860/034 – HBV 154 as results were pooled for analysis

Assessor's comment:
See HBV-154.

103860/034 – HBV 154

➢ **Description**

Immunogenicity and protective efficacy of Smith Kline -RIT's rec-DNA hepatitis b vaccine (10 µg) in newborns of HBsAg positive or negative mothers.

Study conducted in Italy from August 1988 to December 1990.

➢ **Methods**

- Objective(s)

Formation cohort HBsAg positive or negative pregnant women to:
(i) To determine the immunogenicity of the vaccine in healthy newborns with dose 10 µg.
(ii) To evaluate the incidence and type of reactions to the vaccine.
(iii) To evaluate the protective efficacy during one year.

- Study design

Prospective study.
All the newborns were vaccinated with Engerix-B at months 0, 1, 2 and 12 (booster dose). Blood samples were obtained from each newborn at day -7 to -3, months 1, 2, 3, 12 and 13 for HBV markers and SGPT determination. Administration of HBIg im route if newborns HBsAg positive mothers.

- Study population and sample size

30 newborns of HBsAg positive or negative mothers, with a weight of 2,000 grams or more at birth and having a 5 minutes Apgar score of 7 or higher. They had to be negative for HBsAg, anti-HBs and anti-HBc antibodies and with a normal serum SGPT level and be physically in good condition. They had to be without clinical signs of acute disease and will have no significant and persisting hematologic, hepatic (normal SGPT) , renal, cardiac or respiratory diseases as established a t the moment of entry into the study.

Administration of HB Immunoglobulin by the intramuscular route was made only in newborns of HBsAg positive mothers.

- Treatments

Vaccine: SK-KIT 0.5 ml (Engerix-B) containing 10 µg HBsAg adsorbed in Al(OH)3.
Vaccination schedule: 0, 1, 2 months, with booster dose at 12 month.
Administration route and site route: intramuscular, anterolateral thigh.

- Outcomes/endpoints

Immunogenicity: Determination of anti-HBsAg, anti-HBc and anti-HBs Ab titers (mIU/ml) with RIA technique.
Safety: Occurrence (recording and scoring) of general and local clinical signs and symptoms at dose 1, 2 and 3 and at the booster dose (during 3 days post-vaccination). Evaluation of the scoring by the investigators 48h after each vaccination.

- Statistical Methods

Not described.

➢ **Results** Results of 103860/034 – HBV 155 were pooled with those of the present study

- Recruitment/ Number analysed

30 newborns per study were to be included. Finally, a total of 84 newborns were recruited:
- 56 newborns from mothers HBsAg positive who did receive HBIg.
- 8 newborns from mothers without HBsAg but with close contact (family cocoon) with subject HBsAg positive and therefore who did receive HBIg.
- 20 newborns from mothers without HBsAg.

- Baseline data

Of the 84 newborns, 51% were males and 56% were born from HBsAg positive mothers.

- Immunogenicity results

Table 30 describes anti-HBs Ab titers in term of seroprotection at the different timepoints during vaccination according if children did or didn't receive HBIg at birth. At month 13, all children were seroprotected.

Table 30 Seroprotection rates at several timepoints

NEONATI CON HBIG SOMMINISTRATE ALLA NASCITA		NEONATI SENZA HBIG SOMMINISTRATE ALLA NASCITA	
MESE 1		MESE 1	
Sieroprotetti:	63/64 (98%)	Sieroprotetti:	6/20 (30%)
MESE 2		MESE 2	
Sieroprotetti:	61/62 (98%)	Sieroprotetti:	11/16 (69%)
MESE 3		MESE 3	
Sieroprotetti:	53/54 (98%)	Sieroprotetti:	17/18 (94%)
MESE 6		MESE 6	
Sieroprotetti:	17/17 (100%)	Sieroprotetti:	10/11 (91%)
MESE 12		MESE 12	
Sieroprotetti:	15/17 (88%)	Sieroprotetti:	3/3 (100%)
MESE 13		MESE 13	
Sieroprotetti:	8/8 (100%)	Sieroprotetti:	3/3 (100%)

- Safety results

No local or systemic adverse symptoms were reported.

Assessors' comment:
HBV-155 and HBV-154 are descriptive studies assessing the immunogenicity of SK Biologicals rec-DNA hepatitis B vaccine (10 µg) administered according to a 0, 1, 2, +12 month (booster) schedule in newborns of HBsAg positive mothers (HBV-155) or both positive and negative mothers (HBV-154). Administration of HB Immunoglobulin by the IM route was made in part of the newborns.
The sample size is very limited. Thirty subjects per study were to be enrolled. However, the total number of subjects (n=84) presented in the pooled analyses does not match with the number for both studies (n=60). This protocol deviation is not reported and not justified in the study report.
For both studies (pooled analysis), 56 newborns from HBsAg+ mothers who received HBIg, 8 newborns from HBsAg- mothers but with close contact (family cocoon) with HBsAg+ subject and therefore who did received HBIg, and 20 newborns from HBsAg- mothers were enrolled.
The studies were performed in the 1990th. Study documentation is very limited. Results reported in the synopsis in English partially differ from those reported in the study report mainly written in Italian. The assessor has considered the results from the study report (Italian's part), which is common for both studies.
At month 13, all children were seroprotected. The studies show immunogenicity and seroprotection, whether in presence of HBIg coadministration at birth or not.
No AE was described. This should be explained by the MAH because safety was a pre-specified endpoint.
The schedule and dose level assessed in the study are those described in the Engerix Junior SmPC. Overall, the immunogenicity and AE data are not consistent with the data presented in the SmPC.

103860/035 – HBV 156

- **Description**

Immunogenicity and protective efficacy of Smith Kline -RIT's rec-DNA hepatitis b vaccine (10 µg) in seronegative siblings vaccinated with a 10 µg dose.

Study conducted in Italy from October 1988 to April 1991.

- **Methods**

  - Objective(s)

(i) To determine the immunogenicity of the vaccine in healthy siblings.
(ii) To evaluate the incidence and type of reactions to the vaccine.
(iii) To evaluate the protective efficacy during one year in comparison with the historical control group.

  - Study design

Prospective study.
All the HBsAg negative infants and children were vaccinated with Engerix-B at months 0, 1, 6. A booster dose was administrated at month 12 if necessary (anti-HBs Ab ≤ 10mIU/ml). If the subject was HBsAg positive, he will serve as a historical control.
Blood samples were obtained from each children at months 0, 1, 2, 6, 8, 12 and 13 (if booster injection) for HBV markers and SGPT determination.

  - Study population and sample size

15 siblings (age between 3 months to 12 years old) of a historical cohort of newborns classified according to their HBsAg positive status.
They had to be negative for HBsAg, anti-HBs and anti-HBc antibodies and with a normal serum SGPT level and be physically in good conditions. Subjects should not have received immunosuppressive therapy for the past year.
They had to be without clinical signs of acute disease and with no significant and persisting hematologic, hepatic (normal SGPT), renal, cardiac or respiratory diseases as established at the moment of entry into the study.

  - Treatments

Vaccine: SK-RIT, vial of 0.5 ml containing 10 µg HBsAg adsorbed in Al(OH)3.
Vaccination schedule: 0, 1, 6 month, with booster dose at 12 month.
Administration route and site route: intramuscular, deltoid region.

  - Outcomes/endpoints

Immunogenicity: Determination of anti-HBsAg, anti-HBc and anti-HBs Ab titers (mIU/ml) with RIA technique.
Safety: Occurrence (recording and scoring) of general and local clinical signs and symptoms at dose 1, 2 and 3 (during 3 days post-vaccination). Evaluation of the scoring by the investigators 48h after each vaccination.

- Statistical Methods

Not described.

➢ Results

- Recruitment and number analysed

Children among 15 siblings were to be recruited. Of these children (age between 3 months to 12 years old), 26 were actually enrolled and vaccinated and 24 were follow-up until month 12. Only 4/26 received a booster dose.
Numbers of enrolled and/or included subjects are inconsistent (vary across the tables, i.e. 26, 27, 34, 36).

- Baseline data

Not data available.

- Immunogenicity results

Percentage of children with anti-HBs Ab titers > 10 mIU/ml increased with the number of vaccine doses administered. At month 12, 6 months post dose 3, 87% had anti-HBs Ab titers > 10 mIU/ml. Only 4 subjects had to receive the vaccine booster dose at month 12, and 1 month later, 3 of them mount anti-HBs Ab titers > 10 mIU/ml (Table 31).

Table 31 Seroprotection rates and anti-HBs GMTs for the subjects enrolled in the study

Tempo	Tot. Sogg. >10 mIU/ml	MGT (media log+/-DS)	mIU/ml 10–100	100–1000	>1000
1	5/26 (19.2%)	33.6 (1.5+/-0.4)	4 (80%)	1 (20%)	–
2	18/27 (66.7%)	51.7 (1.7+/- 0.5)	13 (72.2%)	5 (27.8%)	–
6	22/28 (78.6%)	246.0 (2.4+/- 0.4)	2 (9.1%)	18 (81.8%)	2 (9.1%)
7	18/19 (94.7%)	2507.5 (3.4+/- 0.7)	1 (5.5%)	3 (16.7%)	14 (77.8%)
12	21/24 (87.5%)	1623.7 (3.2+/ 0.6)	1 (4.8%)	7 (33.3%)	13 (61.9%)
13	3/4 (75%)	80.1 (1.9+/-0.4)	2 (66.7%)	1 (33.3%)	–

- Safety results

Not data available.

Assessors' comment:
HBV-156 is a descriptive study assessing the immunogenicity of Engerix-B at months 0, 1, 6 in HBsAg negative children between 3 months to 12 years old. A booster dose was administered at month 12 if necessary (anti-HBs Ab ≤10mIU/ml).
The sample size is very limited (15 siblings). The study was performed in the 1990th. Study documentation is very limited and safety results are not available. Number of inclusion are

inconsistent through the text. The assessor assessed the results from the investigator; additional results are given but it is unclear to what they correspond. It is also not clear what are the historical controls and results are not discussed.
The schedule and dose level assessed in the study are those described in the Engerix Junior SmPC.
Overall, the immunogenicity data are in line with the data presented in the SmPC.

103860/065 – HV 405

- **Description**

Comparative Study of the Immunogenicity & Safety of Two Doses of Engerix-B Administered to Healthy Infants at 2, 4 and 6 Months of Age.

Study performed from November 1990 to November 1992.

- **Methods**

  - Objective(s)

Immunogenicity: Comparison of immunogenicity induced by two doses (5 and 10 µg) of Engerix-B when administered to infants at 2, 4, and 6 months of age.
Safety: Comparison of safety induced by two doses (5 and 10 µg) of Engerix-B when administered to infants at 2. 4. And 6 months of age.

  - Study design

The study was a prospective, two-armed, randomized comparison of the immunogenicity and safety of two doses of Engerix-B in healthy infants.
Vaccine was administrated to each infants at 2, 4 and 6 months of age.
Blood samples were obtained from each infants at 2 months of age for HBV markers determination and at 4, 6 and 8 months of age for anti-HBs Ab titers determination.

  - Study population /Sample size

A total of 190 infants at 3 facilities were screened and vaccinated with the first dose of a three-dose schedule. Ninety-four (94) infants received 5 µg of Engerix-B (Group A) and 96 received 10 µg of Engerix-B (Group B).
Infants were excluded from the study if he/she: had a positive serum test for HBsAg, anti-HBs or anti-HBc Ab, was expected to receive immunosuppressive therapy, was born to mothers at risk for human immunodeficiency virus infection, was expected to receive blood/blood products while enrolled in the study, had significant and persistent hematologic, hepatic, renal, cardiac or respiratory disease, or was concurrently participating in another vaccine clinical trial, had received a non-FDA approved drug within 30 days prior to this study.

  - Treatments

Vaccine: Engerix-B containing 10 µg of HBsAg in a volume of 0.5 mL or half that formulation, i.e., 5 µg of HBsAg in a volume of 0.25 mL.
Vaccine schedule 2, 4 and 6 months of age
Administration route and site : intramuscular, anterolateral thigh.

- Outcomes/endpoints

Immunogenicity: Primary endpoint: 8 month GMT (anti-HBs Ab).
Determination of anti-HBsAg, anti-HBc and anti-HBs Ab titers (mIU/ml) with RIA technique.
The seroconversion (SC) and seroprotection (SP) rates were defined as anti-HBs Ab titers ≥1 mIU/mL and ≥10 IU/mL, respectively.
Safety: Occurrence (recording and scoring) of general and local clinical signs and symptoms at dose 1, 2 and 3 (until 1 month post dose 3). Description and grading of the adverse events by the investigators.

- Statistical Methods

AE were compared using the chi-square test. Statistical analyses of differences in seroconversion and seroprotection rates between the study groups were performed using the chi-square test. Comparisons of differences between anti-HBs Ab titers were performed using the unpaired student's t-test. Analyses of the primary endpoint (8 month GMT) was performed at the 0.05 level of significance. Analyses for other comparisons used the 0.01 level of significance to correct for multiple tests. GMTs were calculated by determining the log for each titer, then taking the anti-log of the mean of the logs.

➢ Results

- Recruitment and number analysed

A total of 190 infants at 3 facilities were screened and vaccinated with the first dose of a three-dose schedule. Ninety-four (94) infants received 5 µg of Engerix-B (Group A) and 96 received 10 µg of Engerix-B (Group B). Of these, 153 infants were eligible to continue in the study and immunogenicity data were analysed for them.
The reasons for the exclusion of 37 infants are described in the table 32.

Table 32 Summary of infants excluded from immunogenicity analysis

Reason for Exclusion	Group A 5 µg	Group B 10 µg	Total
No Post-Vaccination Titers Available	11	16	27
Anti-HBc Positive at Study Entry	1	1	2
Anti-HBs and Anti-HBc Positive at Study Entry	2	1	3
Anti-HBs Positive at Study Entry	3	2	5
Total Number Excluded	17	20	37

- Baseline data

The two groups were comparable with regard to gender, race, age and weight.
Demographic characteristics are summarized in Table 33 for the all enrolled infants and in Table 34 for the infants with evaluable immunogenicity data.

Table 33 Infant distribution and demography for all infants enrolled

	Group A (N=94)		Group B (N=96)		Total 190
	n	(%)	n	(%)	
Number of males	51	(54.3)	52	(54.2)	103
Number of females	43	(45.7)	44	(45.8)	87
Race (number)					
Black	64	(68.1)	65	(67.7)	129
White	9	(9.6)	11	(11.5)	20
Asian	11	(11.7)	8	(8.3)	19
Other	10	(10.6)	12	(12.5)	22
Age (days)					
Mean ± S.D.	60.63±12.51		61.53±11.51		
Weight (lbs)					
Mean ± S.D.	11.07± 2.11		11.21± 2.18		

Table 34 Infant distribution and demography for all infants with evaluable immunogenicity data

	Group A (N=77)		Group B (N=76)		Total 153
	n	(%)	n	(%)	
Number of males	41	(53.2)	40	(52.6)	81
Number of females	36	(46.8)	36	(47.4)	72
Race (number)					
Black	48	(62.3)	48	(63.2)	96
White	9	(11.7)	9	(11.8)	18
Asian	11	(14.3)	8	(10.5)	19
Other	9	(11.7)	11	(14.5)	20
Age (days)					
Mean ± S.D.	59.97±11.84		60.18±11.46		
Weight (lbs)					
Mean ± S.D.	11.03± 1.88		11.10± 2.22		

- Immungenicity results

Both doses proved to be highly immunogenic, producing high SC and SP rates and GMTs two months (month 8) following the three-dose schedule. Although 10 µg induced a greater GMT (1641 mIU/mL) compared with 5 µg (880 mIU/mL) at this time, most importantly, the SP rates were identical, 98.5% for 10 µg and 5 µg, respectively.
Table 35 summarized the SC and SP rates, GMTs for both groups of vaccinated infants at several time.

Table 35 Seroconversion (SC) rates, Seroprotection (SP) rates and Geometric Mean anti-HBs Titers (GMTs) in infants vaccinated at 2, 4 and 6 months of age.

	Group A 5 µg	Group B 10 µg	P value
4 MONTHS OF AGE			
SC	51.4% (38/74)	77.6% (59/76)	<0.001 +
SP	18.9% (14/74)	35.5% (27/76)	0.022
GMT	8.09 (n=74)	10.43 (n=76)	0.40
6 MONTHS OF AGE			
SC	95.8% (68/71)	100% (69/69)	0.084
SP	88.7% (63/71)	100% (69/69)	0.004 +
GMT	110.63 (n=71)	228.02 (n=69)	0.004 +
8 MONTHS OF AGE			
SC	100% (68/68)	100% (66/66)	
SP	98.5% (67/68)	98.5% (65/66)	
GMT	880.23 (n=68)	1641.16 (n=66)	0.013 +

* (anti-HBs titer ≥ 1 mIU/mL) ** (anti-HBs titer ≥ 10 mIU/mL) *** (In seroconverters)

+ = significant

- Safety results

Both doses of Engerix-B were generally well tolerated and no serious AEs related or possibly related to Engerix-B were reported. In fact, only a few AEs related or possibly related to Engerix-B were reported by the parents of the infants.
Adverse experience are detailed in the Tables 36 and 37 below.

Table 36 Summary of Adverse experiences for infants in group A (5 µg)

ADVERSE EXPERIENCE	Dose 1 (%) N=94	Dose 2 (%) N=78	Dose 3 (%) N=70	Total (%) N=242 (Total Doses)
Injection Site Reaction	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)
Malaise	2 (2.1)	0 (0.0)	0 (0.0)	2 (0.8)
Rash	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)

* For AEs related or possibly related to the vaccine.

Table 37 Summary of Adverse experiences for infants in group B (10 µg)

ADVERSE EXPERIENCE	Dose 1 (%) N=96	Dose 2 (%) N=77	Dose 3 (%) N=69	Total (%) N=242 (Total Doses)
Agitation	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.4)
Edema	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
Emotional Lability	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
Fever	4 (4.2)	1 (1.3)	1 (1.4)	6 (2.5)
Malaise	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
Rhinitis	0 (0.0)	0 (0.0)	2 (2.9)	2 (0.8)

* For AEs related or possibly related to the vaccine.

Assessor's comment:
HV-405 is a descriptive study comparing the immunogenicity and safety induced by two dose levels (5 and 10 µg) of Engerix-B when administered to infants at 2, 4, and 6 months of age.
Of 190 vaccinated subjects, 153 were included in the immunogenicity analysis.
Both dose levels were immunogenic, and high level of seroprotection were obtained, although titres were higher for the 10 µg level.
Overall, the immunogenicity and AE data are consistent with the data presented in the SmPC.
The schedule assessed in this study is not reflected in the SmPC, and there is no plan to include it. The rapid schedule (0, 1, 2 months) recommended in the Engerix B SmPC allows faster protection. The assessed schedule (0, 2, 4 months) presents no advantage as compared to the registered rapid schedule.
A presentation containing 5 µg of HBsAg has never been available or registered.
Overall it is agreed that no update in the PI is needed.

103860/093 – HBV 217

- **Description**

A comparative, Single-Blind, Randomised Study of the Immunogenicity and Safety of Engerix-B administered at two different dose levels.

Study performed from January 1991 to December 1993.

- **Methods**

  - Objective(s)

To compare the immunogenicity and safety of two dosages of Engerix-B (10 µg and 20 µg) in adolescents.

  - Study design

2 Groups. Enrollment in 3 Parts.
Group 1:
Part 1: Engerix-B 10 µg. (Subject no. 1 to 200)
Part 2: Engerix-B 10 µg. (Subject no. 201 to 240)
Part 3: Engerix-B 10 µg. (Subject no. 241 to 340)
Group 2:
Part 1: Engerix-B 20 µg. (Subject no.1 to 200)
Part 2: Engerix-B 20 µg. (Subject no. 201 to 240)

Part 3: Engerix-B 20 µg. (Subject no. 241 to 340)

Blood samples drawn at month 0, 1, 2, 3, 12 and 13 were tested for anti-HBs at SmithKline Biologicals' Laboratory. Additionally, blood samples drawn at month 0 were tested for HBsAg and anti-HBc in the Investigator's laboratory.

- Study population /Sample size

Number of subjects:
Planned: 340.
Enrolled: 309.

Population group: Healthy adolescents between the ages of 12 and 18 years.

- Treatments

Vaccine: Engerix-B(10 µg) Engerix-B (20 µg) containing Hepatitis B (recombinant HBsAg): 10 µg 20 µg and aluminium salts: 0.25 mg 0.5 mg in a volume of 0.5 ml (10µg) or 1 ml (20 µg).
Vaccination schedule (months): 0, 1, 2,and 12.
Administration route and site: Intramuscular, deltoid.

- Outcomes/endpoints

Immunogenicity: Determination of GMTs, seropositivity (≥1mIU/ml; S+) and seroprotection (≥10mIU/ml; SP) rates by RIA for anti-HBs antibodies at month 0, 1, 2, 3, 12 and 13.
Safety: Occurrence of adverse avents suring the study period of 13 months.

- Statistical Methods

Intention To Treat analysis (total population) was performed which included all subjects for whom data were available**.** The GMT rate for anti-HBs antibodies was calculated using the logtransformation of the titres >1mlU/ml and taking the anti-log of the mean of these transformed values.

➢ **Results**

- Recruitment and number analysed

Number of subjects:
Planned: 340.
Enrolled: 309.
Completed: 217.
Dropped out: 92.

Population group: Healthy adolescents between the ages of 12 and 18 years.

- Baseline data

No data available.

- Immunogenicity results

At one month following the full vaccine course (month 13):

All subjects except two (one in each group) were seropositive and had seroprotective levels for anti-HBs antibodies:
(i) Seropositivity rate: 98.9% for group 1 and 99% for group 2.
(ii) Seroprotection rate: 98.9% for group 1 and 99% for group 2.
(iii) GMT antibody titres: 9263 for group 1 and 14606 for group 2.

After 2 doses of vaccine, a trend for higher number of children with protective Ab level is however noted with the 20 µg dose.

Table 38 Geometric mean titers (GMT) of anti-HBs antibody, seropositivity and seroprotection rates

Group	Timing	N	S+	%	L.L.	U.L.	SP	%	L.L.	U.L.	GMT	L.L.	U.L.	Min	Max
1	PRE	115	6	5.2	1.9	11.0	3	2.6	0.5	7.4	24.1	1.0	587.7	1	3257
1	PI(M1)	107	35	32.7	24.0	42.5	10	9.3	4.6	16.5	7.0	3.5	14.0	1.2	20601
1	PII(M2)	101	80	79.2	70.0	86.6	51	50.5	40.4	60.6	19.4	13.6	27.8	1.5	6400
1	PIII(M3)	94	91	96.8	91.0	99.3	81	86.2	77.5	92.4	152.1	103.2	224.3	2	6200
1	PIII(M12)	95	92	96.8	91.0	99.3	89	93.7	86.8	97.6	130.5	97.6	174.5	1.4	6267
1	PIV(M13)	95	94	98.9	94.3	100.0	94	98.9	94.3	100.0	9262.8	6378.2	13451.9	40	415515
2	PRE	118	9	7.6	3.5	14.0	5	4.2	1.4	9.6	11.4	3.6	36.0	1.5	150
2	PI(M1)	109	52	47.7	38.1	57.5	24	22.0	14.6	31.0	9.9	6.2	15.9	1.1	7300
2	PII(M2)	106	100	94.3	88.1	97.9	78	73.6	64.1	81.7	33.2	23.6	46.5	1.5	14500
2	PIII(M3)	101	98	97.0	91.6	99.4	96	95.0	88.8	98.4	330.9	233.7	468.6	3.5	29300
2	PIII(M12)	104	103	99.0	94.8	100.0	98	94.2	87.9	97.9	188.8	140.1	254.5	1	10112
2	PIV(M13)	97	96	99.0	94.4	100.0	96	99.0	94.4	100.0	14605.9	10443.7	20426.7	119	536894

Group 1: HBV 10 mcg Group 2: HBV 20 mcg
GMTs calculated on subjects with titers greater than cut-off

- Safety results

No serious adverse experiences were reported during the study period.

Assessors' comment:

HBV-217 is a descriptive study comparing the immunogenicity and safety of two dose levels of Engerix-B (10 µg and 20 µg) administered according to a 0, 1, 2 +12 months schedule in adolescents 12 to 18 years. Such schedule (rapid schedule) is described in the Engerix Junior SmPC (10 µg) and in the Engérix SmPC (20 µg) respectively for individuals up to 15 years old and 16 years old and over.

Of 309 enrolled subjects, 217 completed the study.

Overall, the immunogenicity and safety data for both doses are in line with the data presented in the SmPC. Seroprotection rate was approximately 99% in both groups at Month 13.

However, there was a trend toward a higher proportion of seroprotected children after dose 1, 2 and 3 when using the 20 µg compared to the 10 µg dose level (respectively, at Month 1: 22.0% vs. 9.3%, at Month 2: 73.6% vs. 50.5%, at Month 3: 95.0% vs. 86.2%).

The seroprotection rates obtained in this study at Month 1, 3 and 13 with the 20 µg dose level are also higher than those described in the SmPC in children up to 15 years old for the same schedule with the 10 µg dose level (22.0%, 95.0%, 99.0% in this study vs. 15%, 89%, 95.8% as described in the SmPC for the rapid 0, 1, 2 + 12 month schedule).

These data suggest that a more rapid protection could be obtained with 20 µg as compared to 10 µg. The MAH should discuss how the data from this study are in contradiction with the statements in the 4.2. section of the SmPC of Engerix Junior, including with respect to using differently the 10 and the 20 µg dose levels across age categories (<10, 10-15, 16+ years of age). It should also be discussed whether additional relevant schedules using the 20 µg dose levels could be considered for the SmPC for at risk populations.

The data from study HBV-217 should be reflected in the section 5.1. of the SmPC of Engerix Junior.

103860/090 – HBV 243

- **Description**

Open, randomized study to evaluate the immunogenicity of Engerix-B when administered according to a vaccination schedule of 0, 1 and 12 months to healthy adolescents at two different doses (10 µg vs 20 µg).

Study performed from October 1992 to February 1994.

- **Methods**

  - Objective(s)

Comparison of the immunogenicity of two different dose levels of Engerix-B (10 µg vs 20 µg) administered to healthy young adolescents according to an extended schedule (0, 1, 12-months). A third group of adolescents received a 20 µg dose according to a 0, 1, 6-month schedule as a control.

  - Study design

Open, randomized, comparative study with three groups. Adolescents were allocated into one of three groups to receive intramuscularly either 10 µg or 20 µg of Engerix-B hepatitis B vaccine according to a 0, 1, 12-month schedule (groups 1 and 2) or 20 µg of the same vaccine according to a 0, 1, 6-month schedule (group 3).

  - Study population and sample size

Number of subjects:
Enrolled: 359
Reactogenicity analysis: 359
Immunogenicity analysis: 351
Population group: healthy adolescents, 12-15 years old

- Treatments

Vaccine dose: Engerix®-B hepatitis B vaccine group 1: one dose (0.5 ml) contains 10 µg hepatitis B surface antigen; groups 2 and 3: one dose (1.0 ml) contains 20 µg hepatitis B surface antigen.
Vaccination schedule: groups 1 and 2: 0, 1, 12-months group 3: 0, 1, 6-months.
Route of administration and site: intramuscular, deltoid region.

- Outcomes/endpoints

Immunogenicity: serum conversion rates and geometric mean anti-HBs antibody titers assessed in blood samples taken one month after the second dose, just before the third dose and one month after the third dose.
Safety: Occurrence of unsolicited symptoms reported during the study period.

- Statistical Methods

Statistical comparisons were performed between groups 1 and 2. Group 3 was used as a descriptive control and therefore no statistical comparisons were made between groups 1 and 3 or groups 2 and 3. GMTs were compared at months 2, 12 and 13 using Student's t test and seroprotection rates were compared at the same time points using Fisher's exact test**.**

➢ Results

- Recruitment and numbers analysed

Figure 1 summarizes the number of subjects enrolled, excluded and eligible for final inclusion.

	Group 1	Group 2	Group 3
Total population enrolled	137	142	80
↓			
Excluded from immunogenicity analysis due to:			
- "Subject initially HBsAg positive" (code 222)	-	1	-
-"Subject who followed an irregular vaccination schedule (code 520)	-	3	4
↓			
Volunteers eligible for inclusion in the immunogenicity analysis	137	138	76

Figure 1 Number of subjects

- Baseline data

Table 39 summarized the demographic characteristics of the total population enrolled.
The groups were similar with respect to gender and age.

Table 39 Demographic characteristics

Group	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D.
1	males	52	13.0	12	14	0.75
	females	85	13.1	12	14	0.68
	all	137	13.1	12	14	0.70
2	males	50	13.0	12	14	0.81
	females	92	13.0	12	14	0.73
	all	142	13.0	12	14	0.75
3	males	31	13.0	12	14	0.75
	females	49	13.1	12	15	0.83
	all	80	13.0	12	15	0.80
All	males	133	13.0	12	14	0.77
	females	226	13.0	12	15	0.73
	all	359	13.0	12	15	0.74

Notes : Individual subject data in Appendix Table IA
N = total number of subjects
S.D. = standard deviation
Ratio of males:females - no significant difference between groups, Chi-square test p=0.84
mean ages between groups: no significant difference, two-way ANOVA p=0.75
mean ages between sexes: p=0.44 two-way ANOVA
interaction of sex and age between groups: not significant, p=0.97 two-way ANOVA

- Immunogenicity results

Statistical comparison of GMTs in groups 1 and 2 one month after the second dose showed no statistically significant difference.
Approximately one month after the second vaccine dose was administered, 75.2% of the adolescents who received the 10 µg doses (group 1) had protective anti-HBs titers compared with 88.8% of those receiving the 20 µg doses in group 2 (significant difference, p=0.004). At month 12, prior to booster vaccination, the GMT of group 2 (20 µg dose) was significantly higher than that of group 1 (10 µg dose). Statistical difference was demonstrated by Student's t test, Bonferroni method applied, p=0.0006). At month 12 prior to the third dose of vaccine, there was no significant difference (p=0.822) in the seroprotection rates in groups 1 and 2 (91.3% and 92.3%, respectively). In the control group 3, 100.0% of the subjects were seroprotected at this time. Approximately one month after the booster vaccine dose, GMTs increased (from month 12 to month 13) by 260-fold in group 1 and by 194-fold in group 2. At this time there was no significant difference between these two groups (p=0.29) in the comparison of GMTs. One month after the booster vaccination, seroprotection rates had increased to 97.7% in both group 1 and group 2.
Table 40 summarized the seropositivity rates and GM anti-HBs Ab titers and Table 41 the distribution of anti-HBs Ab titers at several timepoints.

Table 40 Seropositivity (S+) rates (%) and Geometric mean anti-HBs antibody titers (GMT)

Group	Timing	N	S+	%	GMT	CL 95% lower	CL 95% upper	Min titer	Max titer
1	Pre	137	0	0					
	PII(m2)	133	125	94.0	42	31	56	1	2600
	PII(m12)	126	120	95.2	98	77	125	2	3600
	PIII(m13)	131	129	98.5	25519	17685	36826	2	1332138
2	Pre	138	0	0					
	PII(m2)	134	129	96.3	66	50	86	1	2800
	PII(m12)	130	125	96.2	178	141	225	2	2200
	PIII(m13)	132	131	99.2	34619	22527	53204	5	1190051
3	Pre	76	0	0					
	PII(m2)	76	74	97.4	58	41	82	2	3700
	PIII(m12)	70	70	100	323	233	447	11	6056
	PIII(m13)	65	65	100	14124	9137	21834	137	540293

Notes : Individual subject data in Appendix Table III

Group 1: 0,1,12 months, 10 µg Group 2: 0,1,12 months, 20 µg Group 3: 0,1,6 months, 20 µg

Pre=prevaccination blood sample PII(m2),etc. = post-vaccination II blood sample at month 2, etc.

N = number of volunteers tested S+ = number of volunteers seropositive (titer ≥1 mIU/ml) at a given blood sampling

CL 95% : lower, upper = lower and upper 95% confidence limits

GMTs between groups 1 and 2: no significant difference at month 2: p=0.028, i=3; α=0.012 and month 13: p=0.29, significant difference at month 12 p=0.0006, i=1, α=0.0083 Student's t test, Bonferroni method applied

Table 41 Distribution of anti-HBs antibody titers

Group	Timing	N	≥ 10* mIU/ml		≥100 mIU/ml		≥1000 mIU/ml	
			n	%	n	%	n	%
1	Pre	137	0	0.0	0	0.0	0	0.0
	PII(m2)	133	100	75.2	33	24.8	6	4.5
	PII(m12)	126	115	91.3	66	52.4	4	3.2
	PIII(m13)	131	128	97.7	126	96.2	122	93.1
2	Pre	138	0	0.0	0	0.0	0	0.0
	PII(m2)	134	119	88.8	47	35.1	5	3.7
	PII(m12)	130	120	92.3	89	68.5	8	6.2
	PIII(m13)	132	129	97.7	124	93.9	118	89.4
3	Pre	76	0	0.0	0	0.0	0	0.0
	PII(m2)	76	65	85.5	24	31.6	2	2.6
	PII(m6)	70	70	100.0	59	84.3	11	15.7
	PIII(m7)	65	65	100.0	65	100.0	60	92.3

Notes: see Table 2A

Group 1: 0, 1, 12 months, 10µg Group 2: 0, 1, 12 months, 20µg Group 3: 0, 1, 6 months, 20µg

*≥10mIU/ml=protective level of anti-HBs antibody titers

Seroprotection rates between groups 1 and 2: significant difference at month 2, p=0.004,i=2,α=0.01 no significant difference at month 12: p=0.822 or 13 : p>0.99 Bonferroni method applied

- Safety results

Of the 1072 total doses of vaccine administered in this study, 85 doses were followed by a report of at least one unsolicited symptom.

One hundred twenty-nine unsolicited symptoms (33, 50 and 46 in groups 1, 2 and 3, respectively) were reported by 78 volunteers (22, 31 and 25 in groups 1, 2 and 3, respectively).

The vast majority of the symptoms were reported as mild. The 5 symptoms reported as severe (2 in group 1 and 3 in group 2) were unrelated to vaccination.
Table 42 summarized the unsolicited symptoms related to vaccination.

Table 42 Relationship of unsolicited symptoms to vaccination

Symptom	Relationship	Group 1		Group 2		Group 3		Total	
		n	%	n	%	n	%	n	%
General	Possibly related	1	3.4	3	6.5	6	17.6	10	9.2
	Probably unrelated	0	0.0	0	0.0	3	8.8	3	2.7
	Related	2	7.0	1	2.2	9	26.5	12	11.0
	Unrelated	26	90.0	42	91.3	16	47.1	84	77.1
	All	29		46		34		109	
Local	Related	4	100.0	4	100.0	12	100.0	20	100.0
	All	4		4		12		20	
Total	Possibly related	1	3.0	3	6.0	6	13.0	10	7.7
	Probably unrelated	0	0.0	0	0.0	3	6.5	3	2.3
	Related	6	18.2	5	10.0	21	45.6	32	24.8
	Unrelated	26	79.0	42	84.0	16	34.8	84	65.1
	All	33		50		46		129	

Notes: n = total number of symptoms in a given category

Five serious adverse events were reported (nos. 118 and 214 in group 1, nos. 135 and 178 in group 2 and no. 277 in group 3). All 5 of these volunteers were hospitalized for an event which was unrelated to vaccination.

Assessors' comment:

HBV-243 is a descriptive study assessing the immunogenicity of Engerix-B when administered according to a vaccination schedule of 0, 1 and 12 months to adolescents 12 to 15 years at two different dose levels (10 µg vs 20 µg). A third group of adolescents received a 20 µg dose according to a 0, 1, 6-month schedule as a control.

Of 359 enrolled subjects, 351 were included in the immunogenicity analysis.

The proportion of subjects who had protective anti-HBs titers one month after the second vaccine dose was higher with the 20 µg dose level (88.8% and 85.5% for group 2 and 3) as compared to the 10 µg dose level (75.2% for Group 1).

GMT at Month 12 was higher with the 20 µg dose level as compared to the 10 µg dose level. However, at month 12, there was no significant difference (p=0.822) in the seroprotection rates between groups 1 and 2 (91.3% and 92.3%, respectively).

One month after the booster vaccine dose, there was no significant difference between these two groups in the comparison of GMTs. At that time, seroprotection rates had increased to 97.7% in both group 1 and group 2.

The schedule assessed in the study are different for groups 1 and 2 than those described in the Engerix Junior SmPC. There is no plan to include it.

Overall, the immunogenicity and safety data for both doses are consistent with the data presented in the SmPC. However, after 2 doses of vaccine, a trend for a higher frequency of children with protective Ab level is noted with the 20 µg dose compared to the 10 µg dose.

The seroprotection rates obtained in this study after 2 doses of 20 µg (88.8% and 85.5%) are similar to those described in the SmPC for three doses of 10 µg (0, 1, 2 months) (89%) in children up to 15 years old.

These data suggest that a more rapid protection could be obtained with 20 µg as compared to 10 µg. The MAH should discuss whether additional schedules based on the 20 µg dose level could be relevant when rapid protection is needed, such as in at risk populations. The data from study HBV-243 should be reflected in the section 5.1 of the SmPC of Engerix Junior.

3. Discussion on clinical aspects

Note: If relevant any relevant Pharmacovigilance information related to the active substance should be mentioned and discussed in this section.

Data from 14 studies have been reviewed.
These studies aimed at assessing immunogenicity and safety of the vaccine in children and adolescents (from birth to 18 years old). The studies are descriptive, and most have a limited sample size (all studies have an overall sample size <300 except HBV-243 [n=351], and 6 studies enrolled <50 subjects in the relevant groups). Several of the studies (HBV -079, -104, -153, -154, -155, -156, -177) have very limited documentation. Some reports were in Italian with only a summary or only a partial report in English. There are inconsistencies in the data presented for several of the studies (such as for HBV-079, -154, -155, -156).
For some studies, safety data are not available, and for a few studies, immunogenicity data are not relevant to the Engerix SmPC.
Three different dose levels have been used in the studies (5, 10, 20 µg HBsAg). The 10 µg HBsAg dose level corresponds to Engerix B Junior, which is indicated up to 15 years of age, while the 20 µg dose level corresponds to Engerix which is indicated from 16 years of age. For most of the studies, schedules and dose levels studied are those reflected in the SmPC of Engerix Junior. Nevertheless, one study explored 5 µg HBsAg and three studies explored 20 µg HBsAg.
Several of the studies used early batches of the vaccine, and to which extent these batches are comparable to the currently licensed vaccine is unclear.
Overall, immunogenicity data are consistent with the data already presented in the SmPC. However, the assessment shows that the data with respect to the persistence of protection and the comparison of dose levels need to be updated in the SmPC.
No safety issue was raised by these studies.

- **Several of the studies used early batches of the vaccine. The MAH should clarify to which extent these batches are comparable to the currently licensed vaccine.**

a. Immunogenicity

Five studies described the **immune response induced by different dose levels and schedules in children and adolescents**.
The HBV-405 study did not follow a schedule recommended in the Engerix B/Engerix B Kinder (Junior) SmPCs and immunogenicity data from this study are therefore not relevant. HBV-156 is a small study that described the immunogenicity and safety of the 10 µg dose of Engerix B Junior with the 0, 1 and 6 month schedule in children.
HBV-243 compared two dose levels (10 and 20 µg HBsAg) but also under a vaccination schedule not recommended in the SmPC. A control group was included and received the 20 µg

vaccine dose with the recommended 0, 1 and 6 month schedule. This study generated relevant data with respect to the response following two vaccine doses at different dose levels. Both HBV-217 and HBV-079 included a comparison of the 10 and 20 µg dose levels with either a 0, 1, 2 and 12 or a 0, 1, 6 months schedule. The last 3 studies enrolled children from 1.5 to 18 years old. The 10 µg dose level and the schedules are those recommended under the section 4.2 of the SmPC of Engerix B Junior indicated up to 15 years of age. The higher (20 µg) dose level assessed in the studies corresponds to the dose recommended for Engerix indicated from 16 years of age.
The dose levels of 10 µg and 20 µg induced high and similar seroprotection rates 1 month after the completion of the vaccination schedule. The results are in agreement with the data reported in the SmPC (seroprotection rate of ≥96% at Month 7 and 95.8% at Month 13 respectively with a 0, 1, 6 months and a 0, 1, 2 12 months schedule described under the section 5.1, healthy subjects).
Nevertheless, in HBV-079 (children 1.5 to 11 years old), -217 (children 12 to 18 years old) and -243 (children 12 to 15 years old), a trend for an higher seroprotection rate after two doses of 20 µg compared to two doses of 10 µg was noted. HBV-079 suggest that seroprotection rate at Month 3 following two doses of 20 µg (at 0 and 1 month) is higher than that obtained following three doses of 10 µg dose (at 0, 1 and 2 month).
These data suggest that protection is more rapid with the 20 µg dose level in children 1.5 to 18 years old. A more rapid protection may even be obtained with only two doses of the 20 µg as compared to three doses of 10 µg.
The MAH is requested to discuss these data in the context of existing data on dose levels across age groups. In addition, the data related to the 20 µg vs the 10 µg dose levels should be described in the SmPC (section 5.1). This request concerns relevant data from these studies but also from the main studies who have guided this choice.

- **The MAH is invited to comment on the data showing that a more rapid seroprotection is obtained in children 1.5 to 18 years old after two doses of 20 µg compared to two or three doses of 10 µg of Engérix. This should be discussed in the context of pre-existing data, safety aspects that contribute to the benefit risk of such schedule in the concerned population, and in light of optimal use of antigen. Implications for the different recommendations on posology across age categories should be considered. The MAH should also discuss whether additional schedules based on the 20 µg dose level could be considered when rapid protection is needed, such as for at risk populations.**
- **Data related to the 20 µg vs the 10 µg dose levels, including the data from study HBV-079, HBV- 217 and HBV-243 should be described in the SmPC of Engérix Junior (section 5.1). Cross reference to these data should be made where appropriate, e.g. in 4.2. Posology and 4.9 Overdose.**

Six studies assessed the **vaccine immunogenicity under different dose levels and schedules in neonates** born from HBsAg -negative or -positive mothers. Infants enrolled in the two relevant groups of the Malaria-057 study received only one dose of Engerix-B Junior below 7 days. Coadministration data from this study (Engerix and RTS,S/AS01E vs. Engerix) are not relevant to the European context. The 5 remaining studies evaluated the 10 µg dose of Engerix B Junior with the 0, 1 and 6 month (HBV-104 and HBV-177) or 0, 1, 2, 12 month (HBV-153, HBV-154, HBV-155) schedules. HBV-104 also evaluated the 0, 1, 2 month schedule but without the 12-month boost.

HBV-153, -154, -155, -177 studies showed, one month after the complete vaccination schedule (0, 1 and 6 or 0, 1, 2 and 12), 98-100% seroprotection rate induced by the vaccine in neonates born from HBsAg-positive mothers with the simultaneous administration of HBIg. These results are in line with the data presented in the SmPC (section 5.1) and the statements in 4.2.

Three **booster** studies were submitted (HBV-319, DTPa-HBV-IPV-114 and DTPa-HBV-IPV-115). Overall, they enrolled subjects from 12 to 16 years of age who received a priming vaccination either with Engerix B Junior or Infanrix hexa. An anamnestic response was demonstrated in all studies. These data are consistent with the literature that suggests long-term persistence and immune memory induced by vaccines against hepatitis B, extending up to at least 20 years after primary vaccination and with a low frequency of breakthrough cases (Van Damme P and Van Herck K. A review of the long-term protection after hepatitis vaccination. Medicine and Infectious Disease 2007; 5:79–8. Red Book. Hepatitis B vaccines: WHO position paper – July 2017). The data are in line with the statement under the section 4.2 of the Engerix B Junior SmPC '*The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established'*. However, the immunogenicity results of study HBV-319, which are relevant to infants primed with Engerix B are not described under the section 5.1 of the Engerix B Junior SmPC.

- **Section 5.1 has to be updated with all data relevant to the persistence of protection. In particular, data from study HBV-319 must be included, as this study enrolled children older (15-16 years of age) than the study presented in the SmPC.**
- **In addition the statement 'The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established (Lancet 2000) should be updated to include additional and more recent relevant reports.**
- **The MAH is requested, in the next PSUR, to summarise the literature on long term persistence of protection, and need for booster, and discuss any strategy planned to further assess this important question.**

b. Safety

Studies HBV -079, -104, -153, -154, -155, -217, -243, -319, -405, DTPa-HBV-IPV-114, DTPa-HBV-IPV-115 and Malaria-057 reported safety data. Overall, there was no safety issue revealed by these studies. Most of the adverse reactions are reported under the section 4.8 of the SmPC of Engerix B Junior and Engerix B. Nodule formation described in the study HBV-104 and the low haemoglobin values grade 4 (n=1) and 3 (n=3) recorded in the Malaria-057 study are not mentioned in the summary table under section 4.8 of the Engerix B Junior SmPC.

- **The MAH is invited to discuss the 'low haemoglobin' and 'nodule formation' in the next PSUR.**
- **The MAH is invited to consider when it could be appropriate to update section 4.8. in terms of numbers of studies and of subjects included in the safety database and the frequency of adverse reactions.**

No clinically significant trend toward a higher frequency of AE was noted with the 20 vs. the 10 µg dose level, which is consistent with the statement in section 4.9. of the SmPC.

c. General comment on the SmPC.

- **In addition, the MAH is recommended to align the SmPC on EMA guidance. Relevant sections, including section 5.1. should be updated with relevant data, such as main immunogenicity and efficacy data, data on the different dose levels, and data on the persistence of protection.**

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH is requested to address the RSI (see section VI). In addition, a Type II variation is recommended to update relevant sections of the SmPC.

- **Recommendation**

The MAH is requested to address the request for supplementary information. In addition, a Type II variation is recommended.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

1. Several of the 14 studies used early batches of the vaccine. The MAH should clarify to which extent these batches are comparable to the currently licensed vaccine.

2. Studies comparing the 20 µg vs the 10 µg dose levels:
   (i) The MAH is invited to comment on the data showing that a more rapid seroprotection is obtained in children 1.5 to 18 years old after two doses of 20 µg compared to two or three doses of 10 µg of Engérix. This should be discussed in the context of pre-existing data, safety aspects that contribute to the benefit risk of such schedule in the concerned population, and in light of optimal use of antigen. Implications for the different recommendations on posology across age categories should be considered. The MAH should also discuss whether additional schedules based on the 20 µg dose level could be considered when rapid protection is needed, such as for at risk populations.
   (ii) Data related to the 20 µg vs the 10 µg dose levels, including the data from study HBV-079, HBV- 217 and HBV-243 should be described in the SmPC of Engérix Junior (section 5.1). Cross reference to these data should be made where appropriate, e.g. in 4.2. Posology and 4.9 Overdose.

3. Persistence of protection:
   (iii) Section 5.1 has to be updated with all data relevant to the persistence of protection. In particular, data from study HBV-319 must be included, as this study enrolled children older (15-16 years of age) than the study now presented in the SmPC.
   (iv) In addition the statement 'The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established (Lancet 2000) should be updated to include additional and more recent relevant reports.
   (v) The MAH is requested, in the next PSUR, to summarise the literature on long term persistence of protection, and need for booster, and discuss any strategy planned to further assess this important question.

4. The MAH is invited to discuss the 'low haemoglobin' and 'nodule formation' in the next PSUR.

5. The MAH is invited to consider when it could be appropriate to update section 4.8. in terms of numbers of studies and of subjects included in the safety database and the frequency of adverse reactions.

6. The MAH is recommended to align the SmPC on EMA guidance. Relevant sections, including section 5.1. should be updated with relevant data, such as main immunogenicity and efficacy data, data on the different dose levels, and data on the persistence of protection.
7. The MAH is requested to provide an updated list of EC countries where Engerix B is authorised (+ MA number)

VII. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1 : Several of the 14 studies used early batches of the vaccine. The MAH should clarify to which extent these batches are comparable to the currently licensed vaccine

Company's Answer:

The Engerix-B vaccine has been produced since 1986. There have been no changes in the vaccine with regards to the manufacturing processes of the antigen and the final product, the formulation, the composition, the strengths and the presentations since the vaccine was originally developed except for:
- The removal of the thiomersal in the drug product formulation in 2000
- The removal of the use of thiomersal in the manufacturing process of the active ingredient in 2006.

These two changes have been submitted and approved by all competent health authorities and have been demonstrated to have no impact on the quality, efficacy or safety of the vaccine. Thus, the Engerix-B vaccine batches before and after the removal of the thimerosal are considered to be equivalent. Moreover, adherence to Good Manufacturing Practices rules, process validation, process monitoring, trend analyses and annual product reviews ensure the long-term consistency of the vaccine lots. Therefore, lots used in early clinical studies can be considered as comparable to lots currently produced.

Assessors' comment:

All the studies were conducted after 1986. The Agency agrees with the MAH that the lots used in early clinical studies can be considered as comparable to lots currently produced.

Conclusion:

Point solved

Question 2 : Studies comparing the 20 µg vs the 10 µg dose levels:

(vi) The MAH is invited to comment on the data showing that a more rapid seroprotection is obtained in children 1.5 to 18 years old after two doses of 20 µg compared to two or three doses of 10 µg of Engérix. This should be discussed in the context of pre-existing data, safety aspects that contribute to the benefit risk of such schedule in the concerned population, and in light of optimal use of antigen. Implications for the different recommendations on posology across age categories should be considered. The MAH should also discuss whether additional schedules based on the 20 µg dose level could be considered when rapid protection is needed, such as for at risk populations.

(vii) Data related to the 20 µg vs the 10 µg dose levels, including the data from study HBV-079, HBV- 217 and HBV-243 should be described in the SmPC of Engérix Junior

(section 5.1). Cross reference to these data should be made where appropriate, e.g. in 4.2. Posology and 4.9 Overdose.

Company's Answer:

HBV-079: a study in children at risk (born to hepatitis B carrier mothers):

The Company acknowledged the comment on the increased percentage of protection observed after the 20 µg formulation compared to the 10 µg in these young children at risk, one month after 2 doses. However, the company emphasized that:

1) The study concluded that the 10 µg formulation works equally well as the 20 µg formulation provided that the primary vaccination schedule is completed,

2) The study was not powered to show statistically significant differences between the two formulations, and thus, to draw conclusions,

3) Since the conduction of the study, evidence has highlighted the role of anamnestic response in conferring protection against disease even in the absence of antibody concentrations above seroprotective levels especially in hyperendemic regions [Tsega, 1998].

Per current guidelines, children born to hepatitis B carrier mothers should be administered a birth dose of hepatitis B vaccine within 24 hours, with or without hepatitis B immunoglobulin. This practice is implemented with a coverage of 36% globally, as reported by WHO [WHO, 2008]. Also in line with current literature on effectiveness, emphasis is placed on the need to improve the coverage of the birth dose and less on the need to alter the dosage level. Finally, in regions with high endemicity and low coverage, (high) cost of vaccination is often a pertinent factor that accounts for low coverage. Therefore, the company believes that the current dosage and schedule recommended for children born to hepatitis carrier mothers offers optimal use of the antigen in terms of both protection and safety.

Studies HBV-217 and HBV-243:

Studies HBV-217 and HBV-243 were conducted in healthy adolescents comparing 3 doses of 20 µg versus 10 µg following 0, 1, 2 and 12 months (Study HBV-217) and 0, 1 and 12 months (Study HBV-243) schedules. Regarding the impact of dose formulation and schedule on seroprotection, the Comapny emphasized the following points:

1) Similar to HBV-079, these studies show that at the end of complete vaccination, both formulations conferred high and similar seroprotection rates.

2) Although both studies show a trend for higher seroprotection in the 20 µg arm, after dose 2 and after doses 1, 2 and 3, in studies HBV-243 and HBV-217, respectively, it should be noted that these studies were not powered for such comparisons.

3) Seroprotection rate observed in study HBV-243, after 2 doses in the 20 µg arm (2 months after the first dose) is similar to that specified in the SmPC after three doses of the 10 µg formulation (3 months after the first dose, following a 0, 1, 2, 12 month schedule). However, based on the efficacy/effectiveness data available [Van den Ende, 2017], the Company maintains that the accelerated schedule (0, 1, 2 months) with 10 µg confers rapid and high rate

of protection within 2 to 3 months after the first dose with the minimum amount of antigen in the paediatric population.

4) The advantage of a higher dosage in the paediatric population has not been established because the difference in dosage does not lead to a difference in the seroprotection rate or GMTs attained at the end of the vaccination course and consequently, on the long-term duration of protection.

5) Engerix-B Adult 3-dose schedule is recommended in individuals as of 16 years of age. In adolescents aged 11–15 years the current recommendation also allows Engerix-B Adult to be given in a 2-dose schedule (0 and 6 months) in situations where there is a low risk of hepatitis B infection and when compliance to the complete vaccination course can be assured.

6) The use of the 20 µg formulation at an accelerated schedule (0, 1, 2 months or 0, 1 months) would still require a booster dose at Month 12 to ensure long-term protection, potentially increasing the risk of non-compliance.

7) Since the WHO recommendation of routine hepatitis B vaccination in 1991, efforts have been made to maximize the vaccine coverage and as of 2015, more than 185 countries have included Hepatitis B vaccination (using monovalent or combination vaccines) in their national immunization programmes with a global coverage of the third dose estimated to be 83% [WHO, 2017]. After the introduction of hepatitis B vaccination in countries where hepatitis B was considered highly endemic, a significant reduction in the incidence of hepatitis B infection, HBsAg prevalence and in the long-term burden (e.g. reduction of hepatocellular carcinoma) have been reported. Efficacy and effectiveness data show high and sustained seroprotection in infants through adolescents after completion of the approved Engerix-B posology [Zanetti, 2008; Chien, 2006; Gilca, 2013]. Given the wealth of data describing the global impact of vaccination in children and in adults, the Company currently does not foresee a significant gap that needs to be addressed by a change in the paediatric vaccination posology.

Conclusion:

Despite the limitations of studies HBV-079, -217 and -243 in terms of number of subjects and/or statistical power, the Company considers data from these studies to be in line with data currently described in the SmPC and therefore, does not propose to update Section 5.1 of the SmPC. In addition, the Company mentions that these studies were all completed more than 25 years ago and the original datasets are not available for further analysis. In the absence of a critical gap in medical need, the Company believes that the currently approved vaccination schedule confers a high rate of sustained protection in the paediatric population after completion of the vaccination series, including in children at risk (born to carrier mothers). Therefore, the company does not propose changes to the relevant SmPC sections in terms of dosage or schedule in the paediatric population.

Assessors' comment:

It is acknowledged that HBV-079 is a study with limited sample size and conducted in the 1990's. The population is a high risk population and the age range is large (1 to 11 years of age). Inconsistencies were noted in the data (see first assessment). Findings should be interpreted with caution.

HBV-217 and HBV-243 studies included healthy adolescents. Sample size of both studies was larger. The studies were however not powered to show statistically significant differences between the two formulations.
It is understood that datasets of the three studies are not available for new analysis.

Although GMT and SPR were comparable between dose and schedule after the complete vaccination, all three studies suggested an advantage of the 20 µg over the 10 µg dose level; SPR tend to be higher after the second vaccine dose with the dose of 20 µg compared to the dose of 10 µg. This was true within each study but also when comparing to the SPR presented in the SmPC (as already mentioned in the first assessment). Although the studies were not powered to show statistically significant differences between the two formulations, findings of the three studies bring to consider a 20 µg dose level schedule vaccination.

In the absence of a birth dose, a vaccination of children at risk (born to hepatitis B carrier mothers) with a regimen that confers a more rapid immune response could still be advantageous. This is particularly true for countries where HBV is endemic.

Although their number would probably be very limited in Europe, where Hepatitis B vaccination is recommended, adolescents at short-term risk of Hepatitis B infection could also benefit from a vaccination with the dose level of 20 µg/ml.

Nevertheless, for the below reasons, it is acknowledged that changes to the SmPC sections in terms of dosage or schedule is not warranted:

- The seroprotection rate at the end of the primary vaccination course (0, 1, 6 months schedule) is similar with the 20 µg formulation and with the 10 µg formulation.

- An accelerated schedule is already available in the SmPC for the children and adolescents who need a more rapid protection. This schedule induces high seroprotection levels at 3 months.

- The vaccination of the adolescents with the dose of 20 µg/ml compared to the vaccination with the classical dose of 10 µg/ml might increase the risk of non-compliance to the third or to the booster doses if misinterpreted, i.e. perception that two vaccine 20 µg-doses are sufficient for optimal protection.

- Safety data for the 20 µg formulation are scarce in children and adolescents.

- The vaccination against Hepatitis B virus infection, with the current posology, is widely accepted and the use of vaccine has considerably reduced the incidence of new chronic Hepatitis B virus infections. The addition of a posology might mislead on the benefit of the current strategy.

In addition, in view of the different considerations above, it is also agreed that an update of the SmPC with the data of the three studies is not warranted.

Conclusion:
Point solved

Question 3: Persistence of protection

(iii) Section 5.1 has to be updated with all data relevant to the persistence of protection. In particular, data from study HBV-319 must be included, as this study enrolled children older (15-16 years of age) than the study now presented in the SmPC.

Company's Answer:

Based on additional evidence from study HBV-319 pertaining to persistence of protection and anamnestic response to a challenge dose, the Company will consider updating Section 5.1 of the SmPC through a Type II variation.

Assessors' comment:

The Agency acknowledges that the MAH will update Section 5.1 of the SmPC through a Type II variation.

Conclusion:

Point solved

(iv) In addition the statement 'The need for a booster dose in healthy individuals who have received a full primary vaccination course has not been established (Lancet 2000) should be updated to include additional and more recent relevant reports.

Company's Answer:

The Company acknowledged the assessor's comment that more recent reports do support the SmPC booster statement.

Long-term protection has been most commonly measured for hepatitis B vaccines including Engerix-B by determining the anamnestic response after administration of a challenge dose and via sero-epidemiological studies [Van den Ende, 2017]. More recent literature on this topic was presented [Behre 2012, Gilca 2013, Van Der Meeren 2016, Poovorawan 2011, Leuridan 2011].

These studies are in line with WHO position paper on Hepatitis B [WHO, 2017]. In summary, the currently available scientific evidence on long-term persistence of antibodies/seroprotection and immune memory does not establish the need for a booster dose following completion of the recommended vaccination schedule.

The Company consequently recommends maintaining the current SmPC wording. In addition, the Company also recommends deleting the 'Lancet 2000' reference from the SmPC and not including additional references, as these can easily be retrieved by health care professionals from other sources.

Assessors' comment:

The current evidences do not support the need of a boost in immunocompetent subjects having completed the complete Hepatitis B primary vaccination. The proposal of the MAH, that is maintaining the current SmPC wording and deleting the 'Lancet 2000' reference from the SmPC is endorsed.

Conclusion:

Point solved

(v)The MAH is requested, in the next PSUR, to summarise the literature on long term persistence of protection, and need for booster, and discuss any strategy planned to further assess this important question.

Company's Answer:

Information regarding long-term persistence of protection and the need for a booster dose is presented in the latest Engerix-B PBRER (data lock point 29 February 2016 to 28 February 2018). The Company briefly summarized the information regarding long-term persistence (Section 11 – Literature, Van Der Meeren 2016) and immune memory (Section 17.1.2 – Efficacy and Effectiveness) that can be found in the PBRER. This will be further addressed as appropriate in the next PBRER.
In conclusion, the current clinical and epidemiologic data available, do not support the need for booster doses in healthy individuals who have completed a full primary course of vaccination. However, GSK will continue to monitor scientific evidence as it becomes available with regards to long-term persistence and the need for booster doses.

Assessors' comment:

Information regarding long-term persistence of protection and the need for a booster dose was presented in the latest Engerix-B PBRER and briefly summarized in the present document. Relevant information will be further addressed in the next PBRER.
The Agency agrees with the MAH on the fact that the currently available clinical and epidemiologic data do not support the need for booster doses in healthy individuals who have completed a full primary course of vaccination.
The Agency acknowledges that the MAH will monitor scientific evidence as it becomes available with regards to long-term persistence and the need for booster doses.

Conclusion:

Point solved

Question 4 – Safety: The MAH is invited to discuss the 'low haemoglobin' and 'nodule formation' in the next PSUR.

Company's Answer:

Low haemoglobin

In the Malaria 057 study, 1 subject in the control group (received Engerix-B at birth and routine vaccines) and 3 subjects in an investigational group (received Engerix-B at birth, routine vaccines as well as malaria study vaccine) were reported to have haemoglobin values graded 4 and 3 respectively at day 7 post-vaccination (out of 120 that received Engerix-B at birth and out of 479 total vaccinated subjects). As per investigator, these were not considered clinically significant in the absence of relevant signs and symptoms and therefore, were not reported as AEs/SAEs.

The company presented a safety analysis of low haemoglobin; The GSK Worldwide Safety database was searched on 05 December 2018 using the following criteria:

- Data lock point: Cumulative since launch through 05 December 2018
- Suspect vaccine: Engerix-B
- Case report type: Clinical Trials, Spontaneous, Post-marketing Surveillance (PMS)
- MedDRA preferred term(s): Haemoglobin decreased
- Age: From birth up to and including 15 years of age (paediatric population)

The company described each cases found either in Clinical Trial (n=1), spontaneous case (n=7), or post-marketing surveillance (n=0).

In total, there was 1 clinical trial and 1 spontaneous case of haemoglobin decreased involving neonates who have received a birth dose of Engerix-B. Both cases occurred in the context of an underlying disease and/or concomitant medications. There were 6 other spontaneous cases in infants and older children who were found to have haemoglobin decreased, all of which were also associated with underlying disease or concomitant illness. The spontaneous and post-marketing surveillance cases of low haemoglobin correspond to a cumulative reporting frequency of 0.001 cases per 100,000 doses of Engerix-B Paediatric distributed. Based on this information, there is no indication of a causal association between low haemoglobin and the administration of Engerix-B in the paediatric population.

Injection Site Nodule

The GSK Worldwide Safety database was searched on 05 December 2018 using the following criteria:

- Data lock point: Cumulative since launch through 05 December 2018
- Suspect vaccine: Engerix-B
- Case report type: Clinical Trials, Spontaneous, Post-marketing Surveillance (PMS)
- MedDRA preferred term(s): Injection site nodule
- Age: From birth up to and including 15 years of age (paediatric population)

The company described cases found either in Clinical Trial (n=1, HBV-104 trial included in the WS procedure), spontaneous case (n=21), or post-marketing surveillance (n=1).
Age range from newborn to 15 years. Seven were infants. From these, 7 cases (1 from CT and 6 spontaneous cases) involved infants of which 2 case was resolved, 4 cases were ongoing (at the time of the reporting) and 1 case had an unknown outcome. In 4 cases, there were co-administered vaccine and it was not evident which vaccine resulted in injection site nodule formation. In 5 cases, injection site nodule formation was associated with either dose 2 or dose 3 only. In 3 cases, injection site nodule formation was linked to other conditions. From the 15 spontaneous cases involving children 1 year of age or above, 2 cases where the injection site nodule was clearly attributed to another vaccine. Of the remaining 13 cases, 5 were resolved at the time of reporting, 2 were resolved with sequelae/improved, 4 were unresolved and 2 had unknown outcome. The injection site nodule was observed after the first dose of vaccine in 2 cases, after the second dose in 2 cases, after the third dose in 6 cases and unknown in 3 cases. In 3 cases, there were co-administered vaccines involved for which it was not evident which vaccine resulted in injection site nodule formation while in 10 cases, there were no concomitant vaccinations mentioned. The nodules of the last case (post-marketing surveillance) were diagnosed as vaccination granulomas and attributed to the aluminium-containing vaccines namely DTP-Polio and hepatitis B.

In conclusion, in infants and children up to 15 years of age, the injection site nodules were most frequently reported after the third dose of Engerix-B and a third were co-administered with other vaccines and it was not evident which vaccine resulted in injection site nodule formation. More than half of the cases were resolved/resolved with sequelae/improved at the time of reporting. The frequency of Injection site nodule cases from Spontaneous and PMS sources is 0.003 per 100,000 doses distributed. Based on this information, there were no safety issues identified.

Conclusion
An analysis of low haemoglobin and injection site nodule formation involving neonates who have received a birth/first dose of Engerix-B was presented and placed in a cumulative context. The analysis did not suggest any new safety concerns. Considering the number of reports received, the company does not propose to update the SmPC. Nevertheless, this analysis will be presented in the upcoming Engerix-B PBRER.

Assessors' comment:

Low haemoglobin

In addition to the four cases in the Malraia-057 trial, eight cases of low haemoglobin were found in the GSK Worldwide Safety database (cumulative since launch through 05 December 2018). One case was found in a Clinical Trial and 7 cases were spontaneously reported. Two involved neonates, 2 involved infants, 4 involved children aged 1 year or more. All were also associated with underlying disease or concomitant illness. Although the probability that low haemoglobin was related to Engerix-B cannot be excluded, no causal relationship was established.
The spontaneous and post-marketing surveillance cases of low haemoglobin correspond to a cumulative reporting frequency of 0.001 cases per 100,000 doses of Engerix-B Paediatric distributed.

Injection Site Nodule

A total of 23 cases of injection site nodules (including the one of HBV-104 study) were found in the GSK Worldwide Safety database (cumulative since launch through 05 December 2018). The injection site nodules were most frequently reported after the third dose of Engerix-B. A third were co-administered with other vaccines and it was not evident which vaccine resulted in injection site nodule formation. The spontaneous and post-marketing surveillance cases of injection site nodule formation correspond to a cumulative reporting frequency of 0.003 per 100,000 doses distributed.

Based on this information, there is no indication of a causal association between low haemoglobin and the administration of Engerix-B in the paediatric population. No safety issue related to injection site nodule formation was identified. The Agency acknowledges that this analysis will be presented in the upcoming Engerix-B PBRER. It is endorsed that there is no need to update the SmPC at the moment.

Conclusion:

Point solved

Question 5. The MAH is invited to consider when it could be appropriate to update section 4.8. in terms of numbers of studies and of subjects included in the safety database and the frequency of adverse reactions.

Company's Answer:

The safety profile presented in the current SmPC is based on an analysis of pooled safety data (done in 2006) from key clinical trials completed after 1996, where Engerix-B was administered according to the recommended primary immunisation schedules. Studies reported before 1996 were excluded for the following reasons: (1) the study database was not available and/or data collection did not reflect current adverse event (AE) reporting i.e. coding was based on a modified World Health Organisation Adverse Reaction Terminology (i.e. WHOART) instead of Medical Dictionary for Regulatory Activities (MedDRA), and (2) mapping to MedDRA was operated through preferred term (PT) rather than initial verbatim.
The majority of the paediatric studies submitted as part of the current Article 45/46 were completed before 1996 (10 studies) while those completed after the last pooling (4 studies) were long-term persistence/ booster-challenge and co-administration studies and do not meet criteria

for inclusion in a pooled analysis which only includes studies on primary vaccination schedule without co-administration. However, the safety data from these studies are still consistent with the table of adverse reactions and their frequency as listed in the current SmPC.
Therefore, the Company considers that an update of Section 4.8 in terms of numbers of studies, number of subjects and the frequency of adverse reactions is currently not warranted. At present, there are no ongoing/planned clinical trials in the Engerix-B clinical development plan. However, the Company will continue to assess adverse event frequencies compared to the SmPC at the completion of any clinical trial using Engerix-B (e.g., as comparator, control or co-administration), and will evaluate the need for additional safety pooling and subsequent update of Section 4.8 as appropriate.

Assessors' comment:

The MAH considers that an update of Section 4.8 of the SmPC is currently not warranted. The justification put forward (differences in methodology before/after 1996, difference of administration schedule, consistency of the data) by the MAH is acceptable. The Agency acknowledges that the MAH will continue to assess AE frequencies at the completion of any clinical trial using Engerix B and will update the Section 4.8 if needed.

Conclusion:

Point solved

Question 6: The MAH is recommended to align the SmPC on EMA guidance. Relevant sections, including section 5.1. should be updated with relevant data, such as main immunogenicity and efficacy data, data on the different dose levels, and data on the persistence of protection.

Company's Answer:

The Company will consider the request from the reviewer to update the Section 5.1 of the SmPC with the results from Study HBV-319 through a Type II variation.
With regards to the 'Lancet 2000' reference included in the SmPC booster statement, the Company agrees that more recent reports are indeed available on that matter.
Scientific evidence currently available on long term protection and immune memory do not support the need for a booster dose after completion of the recommended vaccination schedule. For more details, please refer to the response to question 3. Consequently, the Company recommends maintaining the current SmPC wording. However, the Company proposes to delete the 'Lancet 2000' reference from the SmPC and not include additional reference as these can be easily retrieved by health care professionals from other sources.

Please refer to response to question 2 regarding addition of the results from studies providing data on different dose levels (Studies HBV-079, HBV- 217 and HBV-243) in Section 5.1. The Company considers data from these studies to be in line with data currently described in the SmPC and therefore, does not propose to update the Section 5.1. Additionally, given the data describing the global impact of Hepatitis B vaccination in children and in adults, the Company currently does not see a critical medical gap that needs to be addressed by a change in the paediatric vaccination posology.

Finally, as explained in response to question 5, the safety profile presented in the current SmPC is based on an analysis of pooled safety data (done in 2006) from key clinical trials completed

after 1996, where Engerix-B was administered according to the then-recommended primary immunization schedules. The majority of the paediatric studies submitted as part of the current Article 45/46 were completed before 1996 while those completed after the last pooling do not meet criteria for inclusion in a pooled analysis.
Therefore, the Company considers that an update of Section 4.8 is currently not warranted. However, the Company will continue to monitor any scientific evidence as it becomes available to identify any information which could be relevant to the prescriber and to other Health-care professionals.

Assessors' comment:

The Agency acknowledges that the MAH will update Section 5.1 of the SmPC with the results from study HBV-319 through a Type II variation. The MAH would take this opportunity to update the SmPC as recommended in the EC guideline on SmPC, Sept 2009.
Currently, the main studies supporting the posology (healthy subjects ≤ 15 yoa) are not optimally reflected. In addition, the data presented in the SmPC do not seem fully consistent with the data in the literature. The number and main characteristics of the subjects included in the main studies could be better reflected in section 5.1. The MAH is invited to consider if this proposed general non-mandatory update might be beneficial to the SmPC.

Point solved (Q3 (iii))

Booster dose: Maintenance of the current SmPC wording and deleting the 'Lancet 2000' reference from the SmPC is endorsed.

Point solved (Q3 (iv))

The MAH considers data from the studies HBV-079, HBV- 217 and HBV-243 to be in line with data currently described in the SmPC and therefore, does not propose to update the Section 5.1.

Based on the different considerations discussed in Q2, it is accepted that the data of the three studies do not have to be presented in the SmPC.

Point solved (Q2)

The Company considers that an update of Section 4.8 of the SmPC is currently not warranted. The justification put forward by the Company is acceptable. The Agency acknowledges that the Company will continue to assess AE frequencies at the completion of any clinical trial using Enegrix B and to monitor scientific evidences becomes available. The MAH will identify any information which could be relevant to the prescriber and to other Health-care professionals and will update the Section 4.8 if needed.

Point solved (Q5)

Conclusion:

Points solved

Question 7: The MAH is requested to provide an updated list of EC countries where Engerix B is authorised (+ MA number).

Company's answer:

The Company presented the list of EU countries where Engerix-B is registered via Mutual Recognition Procedure (*Table 43*) and the list where Engerix-B is nationally registered (*Table 44*).

Table 43. List of EU countries where Engerix-B Paediatric is registered via mutual recognition procedure

Country	MRP/DCP no.	National MA number	First approval date
Austria	BE/H/0009/002	2-00145	3/05/1995
Belgium	BE/H/0009/002	BE252716, BE252725	28/06/1989
Denmark	BE/H/0009/002	31823, 31824	30/05/1988
Finland	BE/H/0009/002	10122	7/12/1989
France	BE/H/0009/002	NL19960	12/10/1994
Germany	BE/H/0009/002	593a/93	30/05/1995
Greece	BE/H/0009/002	1963202	26/05/1995
Iceland	BE/H/0009/002	870250	1/01/1990
Ireland	BE/H/0009/002	PA 1077/023/001	26/06/1998
Italy	BE/H/0009/002	026653055, 026653067, 026653093, 026653105, 026653117, 026653129, 026653131	17/01/1991
Luxembourg	BE/H/0009/002	2005058745	12/10/1994
Netherlands	BE/H/0009/002	RVG 24290	19/12/2000
Norway	BE/H/0009/002	01-4702	27/04/2001
Portugal	BE/H/0009/002	2294080, 3737483, 3737582, 3737681,	23/06/1989

Country	MRP/DCP no.	National MA number	First approval date
		3737889, 3737988, 3738085, 3738184, 3738283, 3738382, 4779583, 8671933, 8671941, 8671958	
Spain	BE/H/0009/002	58.866, 60.652	14/06/1990
Sweden	BE/H/0009/002	21911	21/05/1996
United Kingdom	BE/H/0009/002	PL 10592/0165, PL 10592/0166	25/08/1987

Table 44. List of EU countries where Engerix-B Paediatric is nationally registered

Country	National MA number	First approval date
Bulgaria	20000246	7/07/1988
Croatia	UP/I-530-09/13-02/24, UP/I-530-09/13-02/25	19/12/1994
Cyprus	12940	4/09/1990
Czechia	59/170/87-A/C	30/11/1987
Estonia	125296	10/01/1996
Hungary	OGYI-T-8259/01, OGYI-T-8260/01	10/03/1994
Latvia	02-0216, 97-0007	5/03/1997
Lithuania	LT/1/96/2154/001-004	29/03/1996
Malta	MA 172/00503, MA172/00501	31/10/2006
Poland	R/0564	29/11/1988
Romania	6545/2014/01-17	31/01/1991
Slovakia	59/0170/87-C/S	18/02/1988
Slovenia	H/97/00551/003	28/04/1997

Assessors' comment:

The Agency acknowledges the lists of EU countries where Engerix-B is registered either by Mutual Recognition or national procedures.

In 2000, a harmonization of the SmPC was adopted (CPMP/1493/01).

The MAH will update the section 5.1 of the SmPC with data of the HBV-319. The MAH is invited to take the opportunity to verify that the SmPCs are still harmonized across countries and to harmonize them if applicable.

Conclusion:

Point solved

VIII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH complied with the Article 46 requirement regarding the submission of paediatric data. The MAH will update Section 5.1 of the SmPC with the results from study HBV-319 through a Type II variation. The 'Lancet 2000' reference will be deleted from section 4.2, booster dose. The MAH would take this opportunity to update the SmPC as recommended in the EC guideline on SmPC, Sept 2009. The MAH is invited to consider if the SmPC might benefit from an update better reflecting the main studies supporting the posology (healthy subjects ≤ 15 years) and to harmonize the SmPCs across EC countries, if applicable.

- **Recommendation**

Type II variation to be submitted within 3 months after publication of the public AR.