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Procedure Management and Committees Support Division

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

HBVAXPRO

hepatitis b vaccine (rdna)

Procedure no: EMEA/H/C/000373/P46/058

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

On 31 July 2015, the MAH submitted final clinical study report (CSR) of a paediatric study for HBVAXPRO, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of post-authorisation measures (i.e. FUM 089, FUM 100, FUM 100.1) originating from HEXAVAC.

- In FUM 089 (assessment of HXV01C study): assessment led to conclusions that the MAH should make efforts to measure boostability at the 10-year checkpoint after priming, as especially in this age the risk of Hepatitis B infection increases
- In FUM 100, the MAH commits to address this recommendation with a new immunogenicity study (HXV02C)
- In FUM 100.1, the MAH provided the HXV02C concept sheet, which has been endorsed by the CHMP.

Since the Marketing Authorization of HEXAVAC was withdrawn on 28 June 2012, the FUM 100 of HEXAVAC has been transferred on the HBVAXPRO licence.

In order to fulfil the Commitment as well as the article 46 regulation, the MAH provides the final CSR of the HXV02C study.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Clinical aspects

2.1.1. Clinical study

HXV02C
An open-label, controlled, multi-centre study of the immunogenicity and safety of a challenge dose of HBVAXPRO®5 µg to explore the anamnestic immune response in healthy children vaccinated 10 years ago with a primary series (3 doses) of either HEXAVAC® or INFANRIX®-HEXA

The study was conducted between 22 January 2014 and 18 December 2014 in 8 centers in Italy.

Objectives

Primary objectives were to describe the percentage of subjects with an anti-HBs concentration >=10 mIU/mL, one month after a challenge dose of HBVAXPRO® 5 µg given at least 10 years later, in subjects vaccinated with 3 doses of HEXAVAC® as infants or 3 doses of INFANRIX®-HEXA as infants.

Secondary objectives were to describe in subjects vaccinated with HEXAVAC® or INFANRIX®-HEXA as infants and challenged with a dose of HBVAXPRO® 5 µg given at least 10 years later, (1) the level of anti-HBs antibody before and one month after a challenge dose of HBVAXPRO® 5 µg, (2) the level of anti-HBs antibody before and one month after a challenge dose of HBVAXPRO® 5 µg, by subsets of subjects defined according to the pre-challenge anti-HBs concentration (<10 mIU/mL and >=10 mIU/mL), (3) the safety profile of HBVAXPRO® 5µg.

The primary and secondary objectives were descriptive, thus no formal statistical hypothesis was tested.

Study design

This study was an open-label, controlled, multicentre study in two cohorts defined on vaccination history, a 3-doses primary series of either HEXAVAC® or INFANRIX®-HEXA given at about 3, 5 and 11 months of life during routine practice.

A maximum of 750 healthy preadolescents (12 to 13 years of age) were planned to be enrolled in the study (approximately 375 in each cohort). The recruitment in each cohort was stopped, when it was ascertained that 112 subjects were vaccinated in each subset of subjects defined as anti-HBs concentration <10 mIU/mL and >=10 mIU/mL at inclusion. For this purpose, the number of subjects with an anti-HBs concentration <10 mIU/mL and >=10 mIU/mL at inclusion were monitored during the recruitment period.

At the time of enrolment, subjects had to meet all inclusion criteria and none of the exclusion criteria. The Informed Consent Form was signed by the parent(s) or legal representative and investigator and a signed Assent form was signed by the child before the first study procedure.

Collection of medical history and vaccination history (hexavalent primary vaccination documented by trade name and dates of vaccination) and physical examination were conducted at Day 0 for all subjects.

A baseline number was assigned to each subject.

Blood Sampling had to be drawn from all subjects at the following time intervals:

- Blood Sample 1 (BL01) prior to the challenge dose administration, at the time of Visit 1.
- Blood Sample 2 (BL02) between Day 21 and Day 35 following to the challenge dose administration, at the time of Visit 2.

HBVAXPRO® 5µg was administered by intra muscular route in the deltoid region.

Timeframe for the vaccinations and blood samples is summarized in Table 9.1

Table 9.1. **Study Schedule of immunogenicity and safety measurements**

	Visit 1 Day 0	**Visit 2** Month 1 (Day 21 to Day 35)
Cohort **(vaccination history)**	**Challenge dose at least 10 years after the third dose of the primary series**	
HEXAVAC®	HBVAXPRO® 5 µg	
INFANRIX®-HEXA		
Immunogenicity assessment	Blood sample 1 (BL01: pre-challenge dose)	Blood sample 2 (BL02: post-challenge dose)
Safety assessment	Record of safety	

Immunogenicity assays were performed after Visit 1 and Visit 2 by laboratory staff who were blinded for the vaccines (HEXAVAC® or INFANRIX®-HEXA).

The following serology tests were performed:
- Anti-HBs was measured before the HBVAXPRO® 5µg challenge dose (BL01) and at 21 days to 35 days following the HBVAXPRO® 5µg challenge dose (BL02) by MEIA –AxSYM® AUSAB.

- Hepatitis B core antibody (Anti-HBc) was measured at 21 days to 35 days following the HBVAXPRO® 5µg challenge dose (BL02) by MEIA – AxSYM® CORE.

- In serum found with anti-HBc positive, Hepatitis B surface antigen (HBsAg) and HBV Deoxyribonucleic Acid (DNA) were additionally tested by MEIA – AxSYM® HBsAg (V2) and Real-Time polymerase chain reaction (PCR) – Cobas TaqMan® HBV, respectively.

All subjects were kept under medical surveillance for at least 20 minutes post-vaccination to collect all immediate adverse events. For safety follow-up, the subjects' parents or legal representatives received a Diary Card (DC) at Visit 1 and were informed on how to complete it from Visit 1 to Visit 2 following the challenge dose of HBVAXPRO® 5µg. On the DC, the subjects'parents or legal representatives recorded the subjects' body temperature, the injection site and systemic reactions and unsolicited adverse events as described in Protocol.

All serious adverse events and non-serious adverse events assessed as related to the study vaccine which persisted at the time of the last visit of the concerned subjects were to be followed up by the investigators until their complete disappearance (resolution) or stabilization.

The maximum duration of the follow-up for a subject was 35 days post-challenge dose.

After receipt of the subject's serology results concerning the post-challenge sample (BL02) by the investigator, children with an anti-HBs concentration <10 mIU/mL and with anti-HBc test negative were handled in accordance with the local standard practice of vaccination (ref. Piano Nazionale Prevenzione Vaccinale 2012-2014, Ministero della Salute) and under the participating investigator's responsibility.

Study population

The main criteria for inclusion included healthy child of either gender, vaccinated with 3 doses of HEXAVAC® or 3 doses of INFANRIX®-HEXA as infant (documented vaccination history), the third dose of HEXAVAC® or INFANRIX®-HEXA being administered at least 10 years prior to the challenge dose and no more than 3 doses of any Hepatitis B containing vaccine either alone or in any combination; no history of clinical diagnosis of infection due to Hepatitis B; no history or current close contact with known carriers of Hepatitis B virus; no known haematological, malignant or immunological disorder; no known sensitivity and/or allergy to any component of the study vaccine; no immunosuppressive condition or treatment or autoimmune disorder; no history of febrile illness in the past 3 days prior to the challenge dose; no high dose systemic corticosteroids (*i.e.* >=1 mg/day/kg prednisone equivalent administered orally or parenterally) given >=14 days in the 30 days prior to the challenge dose (inhaled, nasal or topical corticosteroids were not considered as systemic treatment); no receipt of inactivated vaccine in the past 14 days or live vaccine in the past 28 days; subject not pregnant; no participation to another clinical study during the present study period.

Treatments

During the course of the study, all children received 1 dose of HBVAXPRO® 5 µg at Visit 1 (Day 0), via intramuscular injection into the deltoid muscle.

Outcomes/endpoints

Primary endpoint

- the percentage of subjects with anti-HBs concentrations >=10 mIU/mL measured 1 month (21 to 35 days) after the challenge dose of HBVAXPRO® 5 µg

Secondary endpoints:

- The percentage of subjects with anti-HBs concentrations >=10 mIU/mL measured before the challenge dose,
- The geometric mean of anti-HBs concentrations (*i.e.* GMC) measured before and 1 month after the challenge dose,
- The geometric mean of individual anti-HBs concentration ratios (*i.e.* GMCR) from before to 1 month after the challenge dose.
- From Day 0 to Day 4, the percentage of subjects with solicited injection-site adverse reactions (erythema, swelling and pain) and the percentage of subjects with pyrexia defined as body temperature >=38.0°C,
- From Day 0 to Day 14, the percentage of subjects with unsolicited injection-site adverse reactions and the percentage of subjects with unsolicited systemic adverse events,
- From the challenge dose to the last visit, the percentage of subjects with serious adverse events.

Statistical Methods

The primary immunogenicity analysis was performed on a Per Protocol Set (PPS): the one-month post-challenge percentage of subjects with anti-HBs concentrations >=10 mIU/mL was calculated within each cohort (HEXAVAC® or INFANRIX®-HEXA), together with their two-sided 95% CI.

The same analysis as above was also performed on the Full Analysis Set (FAS) as a supportive analysis

A descriptive statistical analysis was also performed for secondary immunogenicity objectives:

- Within each cohort, the pre-challenge percentages of subjects with an anti-HBs >=10 mIU/mL were calculated together with their two-sided 95% CI
- Within each cohort and within each subset of subjects (i.e. pre-challenge anti-HBs <10 mIU/mL and >=10 mIU/mL):
    - The pre- and post-challenge GMC were calculated together with their two-sided 95% CI
    - The GMCR from pre- to post-challenge dose was calculated together with their two-sided 95% CI.
- Within each subset of subjects with a pre-challenge anti-HBs <10 mIU/mL, the one month post-challenge percentages of subjects with an anti-HBs >=10 mIU/mL were calculated together with their two-sided 95% CI

With a sample size of 100 evaluable subjects in each subset, the half width of the two-sided 95% confidence interval was not expected to exceed 8%.

Safety summaries were provided for each cohort and overall for the Safety Analysis Set in term of incidence, intensity, seriousness and causal relationship to HBVAXPRO® 5 µg for systemic adverse events. Systemic adverse events were analyzed according to the investigator's relationship evaluation (vaccine-related or -unrelated). Injection-site adverse reactions were considered to be related to study vaccine.

Results

Recruitment / Number analysed

A total of 751 subjects were enrolled: 409 were included in the HEXAVAC® cohort and 342 in the INFANRIX®-HEXA cohort (Table 10.1). All enrolled subjects received the challenge dose of HBVAXPRO® 5 µg.

In total, 749 subjects (99.7%) completed the study: 408 subjects (99.8%) of the HEXAVAC® cohort and 341 subjects (99.7%) of the INFANRIX®-HEXA cohort.

Table 10.1. Disposition of Subjects

	HEXAVAC® Cohort	INFANRIX®-HEXA cohort	All
	n (%)	n (%)	n (%)
Screened [(a)]			753
Screening failure			2
- Inclusion / exclusion criteria not met any longer			1
- Subject refused blood sample			1
Vaccinated [(b)]	409 (100)	342 (100)	751 (100)
Withdrawn after vaccination	1 (0.2)	1 (0.3)	2 (0.3)
- Lost to follow-up	0 (0)	1 (0.3)	1 (0.1)
- Other[(c)]	1 (0.2)	0 (0)	1 (0.1)
Completed	408 (99.8)	341 (99.7)	749 (99.7)

%: Percentages based on the number of vaccinated subjects
(a) Informed consent signed
(b) Subjects who received the challenge dose of HBVAXPRO® 5 µg
(c) Subject hospitalised in another town, not available to continue the study.

A total of 2 subjects (0.3 %) were withdrawn from the study after screening, but prior to vaccine administration. One subject did not meet the inclusion/exclusion criteria any longer (the subject received an inactivated vaccine in the 14 days prior to challenge dose) and one subject refused blood sampling.

Overall, 19 subjects (2.5%) presented at least one protocol deviation or other reason leading to the exclusion from the PPS: 13 subjects (3.2%) in the HEXAVAC® cohort and 6 subjects (1.8%) in the INFANRIX®-HEXA cohort (Table 10.3).

Table 10.3. Protocol Deviations - Vaccinated Set

	HEXAVAC® Cohort (N=409)	INFANRIX®-HEXA Cohort (N=342)	All (N=751)
	n (%)	n (%)	n (%)
Subjects with at least one protocol deviation or other condition leading to exclusion from the Per Protocol Set	13 (3.2)	6 (1.8)	19 (2.5)
Subjects with at least one protocol deviation leading to exclusion from the Per Protocol Set	7 (1.7)	2 (0.6)	9 (1.2)
Non-compliance with entry criteria	3 (0.7)	0 (0.0)	3 (0.4)
Child not vaccinated with 3 doses of HEXAVAC® or INFANRIX®-HEXA	*3 (0.7)*	*0 (0.0)*	*3 (0.4)*
Non-compliance with blood sample requirement	4 (1.0)	2 (0.6)	6 (0.8)
No post-challenge immunogenicity data	*1 (0.2)*	*1 (0.3)*	*2 (0.3)*
Post-vaccination blood sample (BL02) outside of day range (>35 days)	*3 (0.7)*	*1 (0.3)*	*4 (0.5)*
Non-authorized medication or non-study vaccine	0 (0.0)	1 (0.3)	1 (0.1)
Received immunosuppressive therapy or systemic corticosteroids after the challenge dose	*0 (0.0)*	*1 (0.3)*	*1 (0.1)*
Subjects with at least one other condition leading to exclusion from the Per Protocol Set	6 (1.5)	4 (1.2)	10 (1.3)
Suspected Hepatitis B infection before the first visit of the study	*6 (1.5)*	*4 (1.2)*	*10 (1.3)*

Baseline data

Demographic and other baseline characteristics were comparable in both groups.

Overall, the gender distribution was 44.1% of boys and 55.9% of girls, the mean (+/- SD) age when the challenge dose was administered was 11.9 (+/-0.5) years, mean weight was 44.8 (+/-11.0) kg, and mean height was 151 (+/-9) cm.

Overall, the median time interval between the last hexavalent vaccine dose and the challenge dose was 10.9 years (range 10.0; 12.3): 11.0 years (range 10.0;12.3) in the HEXAVAC® cohort and 10.8 years (10.0;12.2) in the INFANRIX®-HEXA cohort.

Efficacy results

Primary immunogenicity analysis

The Per Protocol Set (PPS) consisted of 732 subjects (97.5%): 396 subjects (96.8%) in the HEXAVAC® cohort and 336 subjects (98.2%) in the INFANRIX®-HEXA cohort.

One month after the challenge dose of HBVAXPRO® 5 µg, 83.6% of subjects in HEXAVAC® cohort and 96.4% in INFANRIX®-HEXA cohort had anti-HBs concentration >= 10 mIU/mL (Table 11.4, PPS, N=732).

Table 11.4. **Percentages of subjects with anti-HBs concentrations >=10 mIU/mL one month after the challenge dose of HBVAXPRO® 5 µg – Per Protocol Set**

		HEXAVAC® Cohort (N=396)	INFANRIX®-HEXA Cohort (N=336)
Post-challenge anti-HBs >=10 mIU/mL	n (%)	331 (83.6)	324 (96.4)
	[95% CI]	[79.6; 87.1]	[93.8; 98.1]
	Missing	0	0

Comparable results were observed on the Full Analysis Set.

Secondary immunogenicity analyses (in PPS)

Before the challenge dose, 23.9% [95%CI: 19.7, 28.4] of subjects in the HEXAVAC® cohort and 69.0% [95%CI: 63.8, 74.0] in the INFANRIX®-HEXA cohort had an anti-HBs concentration >=10 mIU/mL.

One month after the challenge dose the percentage of subjects with an anti-HBs >=10 mIU/mL, for the specific subset of subjects with a pre-challenge anti-HBs concentration <10 mIU/mL, was 78.7% [95%CI: 73.6, 83.2] in the HEXAVAC® cohort and 88.5% [95%CI: 80.7, 93.9] in the INFANRIX®-HEXA cohort.

Table 11.6 (PPS, N=732) summarized the GMC and GMCR by subsets of subjects defined according to their pre-challenge anti-HBs concentration (<10 mIU/mL and >=10 mIU/mL): the pre-challenge GMC, the post-challenge GMC and the post/pre-challenge GMCR of anti-HBs concentrations were higher in the INFANRIX®-HEXA cohort, compared to the HEXAVAC® cohort.

Table 11.6. **Summary of the anti-HBs concentrations (mIU/mL) before and one month after the challenge dose of HBVAXPRO® 5 µg – Per Protocol Set**

		HEXAVAC® cohort (N=396)			INFANRIX®-HEXA cohort (N=336)		
Anti-HBs concentration at baseline		**<10 mIU/mL**	**>=10 mIU/mL**	**ALL**	**<10 mIU/mL**	**>=10 mIU/mL**	**ALL**
Pre-challenge	n	300	94	394	104	232	336
	GMC	5.0	29.8	7.7	5.0	56.8	26.8
	[95% CI]	NA	[25.2; 35.2]	[7.0; 8.3]	NA	[49.0; 65.9]	[22.9; 31.4]
	Median	5.0	26.3	5.0	5.0	51.4	23.4
	Min; Max	5.0; 5.0	10.2; 344.5	5.0; 344.5	5.0; 5.0	10.0; 1943.0	5.0; 1943.0
	Missing	0	0	2	0	0	0
Post-challenge	n	300	94	396*	104	232	336
	GMC	91.1	2113.4	191.9	221.6	4691.6	1823.8
	[95% CI]	[72.5; 114.5]	[1608.2; 2777.5]	[152.8; 241.0]	[148.7; 330.3]	[3927.4; 5604.4]	[1449.0; 2295.5]
	Median	128.7	2537.0	268.6	267.2	4512.0	2669.0
	Min; Max	5.0; 32460.0	47.9; 40460.0	5.0; 40460.0	5.0; 12730.0	64.6; 176600.0	5.0; 176600.0
	Missing	0	0	0	0	0	0
Ratio post/pre-challenge anti-HBs concentrations	n	300	94	394	104	232	336
	GMCR	18.2	70.9	25.2	44.3	82.6	68.1
	[95% CI]	[14.5; 22.9]	[54.3; 92.6]	[20.8; 30.6]	[29.7; 66.1]	[70.5; 96.7]	[57.6; 80.5]
	Median	25.7	84.6	36.0	53.4	87.0	78.6
	Min; Max	1.0; 6492.0	1.8; 664.8	1.0; 6492.0	1.0; 2546.0	1.8; 1162.8	1.0; 2546.0
	Missing	0	0	2	0	0	0

* For two subjects (10010 and 10051) the pre-challenge blood samples were invalidated because of a suspected inversion of the first blood samples, the data were considered as missing, therefore for post-challenge data it was not possible to assign these 2 subjects to a subset defined as anti-HBs concentration at baseline (<10 mIU/mL ; >=10 mIU/mL) and then they were not included in the post-challenge GMC by subset although they were included in the post-challenge Total GMC measured in the 396 subjects.

The reverse cumulative distribution curves (RCDC) for pre and post-challenge time-points are provided in Figure 11.1 (HEXAVAC® cohort) and Figure 11.2 (INFANRIX®-HEXA cohort).

Figure 11.1. Reverse Cumulative Distribution Curve for pre and post-challenge anti-HBs concentration (mIU/mL): HEXAVAC® cohort - Per Protocol Set (N=396)

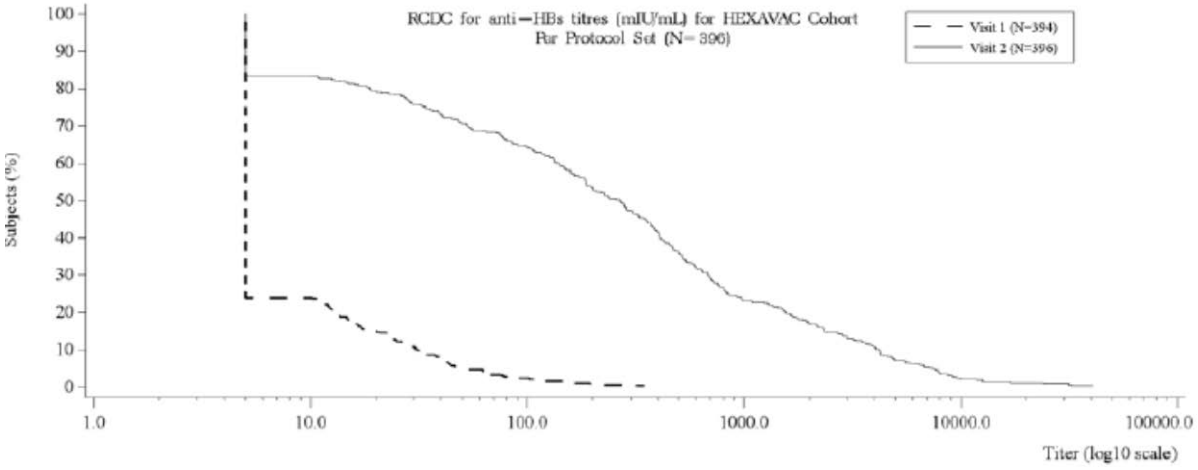
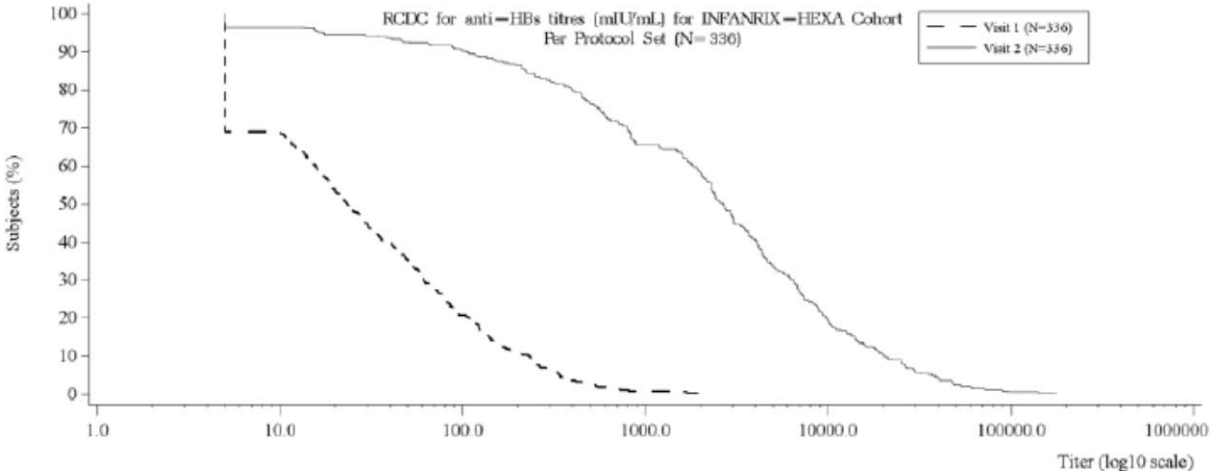


Figure 11.2. Reverse Cumulative Distribution Curve for pre and post-challenge anti-HBs concentration (mIU/mL): INFANRIX®-HEXA cohort - Per Protocol Set (N=336)



Comparable results were observed in the Full Analysis Set.

The weighted estimates of GMC and percentages of subjects with an anti-HBs >=10 mIU/mL one month after the challenge dose were also calculated (Table 11.8).

Table 11.8. **Weighted estimates of the GMC and percentages of subjects with an anti-HBs concentration >=10 mIU/mL one month after the challenge dose of HBVAXPRO® 5 µg – Per Protocol Set**

		HEXAVAC Cohort (N=396)	INFANRIX-HEXA Cohort (N=336)
Post-challenge anti-HBs concentration (mIU/mL)	n	394	336
	GMC*	438.8	1019.7
	[95% CI]*	[357.8; 538.1]	[831.7; 1250.1]
	Missing	2	0
One month post-challenge percentages of subjects with an anti-HBs concentration >=10 mIU/mL	%	89.3	94.2
	[95% CI]**	[84.9; 91.5]	[89.6; 96.6]
	Missing	2	0

The same weight is given to each subset of subjects defined as pre-challenge anti-HBs concentration <10 mIU/mL and >=10 mIU/mL

*: based on an ANOVA with cohort, baseline status (two levels: pre-challenge anti-HBs concentration <10 mIU/mL versus >=10 mIU/mL) and interaction between cohort and baseline status as independent variables.

**: calculated using the stratified Wilson method for unequal proportions.

When the same weight was given to each subset of subjects, defined as pre-challenge anti-HBs concentration <10 mIU/mL and >=10 mIU/mL, the post-challenge anti-HBs GMCs were also higher in the INFANRIX®-HEXA cohort, compared to the HEXAVAC® cohort.

The weighted percentage of subjects with an anti-HBs >=10 mIU/mL one month after the challenge dose was 89.3% in the HEXAVAC® cohort and 94.2% in the INFANRIX®-HEXA cohort.

Additional information on immunogenicity results

At Visit 2, all BL02 were tested for anti-HBc to detect any diagnosis of hepatitis B viral infection. If the serum was found anti-HBc positive, HBs antigen and HBV DNA were also tested.
Among 749 subjects who had a BL02 tested for anti-HBc, 10 subjects (1.3%) were positive one month after receiving the challenge dose of HBVAXPRO® 5µg: 6 subjects (1.5%) in HEXAVAC®

cohort and 4 subjects (1.2%) in INFANRIX®-HEXA cohort. All of them were found negative for HBsAg and for HBV DNA in the post-challenge blood sample.

This positive anti-HBc serology was confirmed for all 10 subjects by duplicate test performed as per manufacturing method.

Among these 10 subjects:
- 3 subjects had anti-HBs concentration > 10 mIU/mL before and after the challenge dose: 1 in the HEXAVAC® cohort (Subject 14500, 18,4 mIU/mL and 3395 mIU/mL respectively) and 2 in the INFANRIX®-HEXA cohort (subject 10212, 17.5 mIU/mL and 2194 mIU/mL and subject 10394, 92.6 mIU/mL and 25720 mIU/mL respectively).
- 5 subjects had anti-HBs <10 mIU/mL before the challenge dose and >= 10 mIU/mL after the challenge dose at BL02: 3 in HEXAVAC® cohort (Subject 10982, 864.4 mIU/mL ; Subject 12673, 11.6 mIU/mL ; Subject 14227, 203.2 mIU/mL) and 2 in INFANRIX®-HEXA cohort (subject 10078, 857.9 mIU/mL and Subject 10174, 2063 mIU/mL).
- 2 subjects in HEXAVAC® cohort had anti-HBs concentration < 10 mIU/mL before and after the challenge dose.

Safety results

The overall safety of HBVAXPRO® 5 µg on the Safety Analysis Set is presented in Table 12.2.

Table 12.2. **Global Summary of Safety - Safety Analysis Set**

	HEXAVAC® Cohort (N=409) n(%) [95% CI]	**INFANRIX®-HEXA Cohort (N=341)** n(%) [95% CI]	**All (N=750)** n(%) [95% CI]
With no adverse event from Day 0 to Day 14	**228 (55.7)** [50.8; 60.6]	**176 (51.6)** [46.2; 57.0]	**404 (53.9)** [50.2; 57.5]
With one or more adverse events from Day 0 to Day 14	**181 (44.3)** [39.4; 49.2]	**165 (48.4)** [43.0; 53.8]	**346 (46.1)** [42.5; 49.8]
With one or more vaccine-related adverse reactions from Day 0 to Day 14	161 (39.4) [34.6; 44.3]	149 (43.7) [38.4; 49.1]	310 (41.3) [37.8; 45.0]
Injection-site adverse reactions from Day 0 to Day 14	**159 (38.9)** [34.1; 43.8]	**146 (42.8)** [37.5; 48.3]	**305 (40.7)** [37.1; 44.3]
Solicited injection-site adverse reactions from Day 0 to Day 4	159 (38.9) [34.1; 43.8]	145 (42.5) [37.2; 48.0]	304 (40.5) [37.0; 44.1]
Injection-site erythema from Day 0 to Day 4	7 (1.7) [0.7; 3.5]	11 (3.2) [1.6; 5.7]	18 (2.4) [1.4; 3.8]
Injection-site swelling from Day 0 to Day 4	6 (1.5) [0.5; 3.2]	20 (5.9) [3.6; 8.9]	26 (3.5) [2.3; 5.0]
Injection-site pain from Day 0 to Day 4	156 (38.1) [33.4; 43.0]	139 (40.8) [35.5; 46.2]	295 (39.3) [35.8; 42.9]
Other injection-site adverse reactions from Day 0 to Day 14	1 (0.2) [0; 1.4]	1 (0.3) [0; 1.6]	2 (0.3) [0; 1.0]
Systemic adverse events from Day 0 to Day 14	**43 (10.5)** [7.7; 13.9]	**45 (13.2)** [9.8; 17.3]	**88 (11.7)** [9.5; 14.3]
Pyrexia* from Day 0 to Day 4	1 (0.2) [0; 1.4]	5 (1.5) [0.5; 3.4]	6 (0.8) [0.3; 1.7]
Other systemic adverse events from Day 0 to Day 14	43 (10.5) [7.7; 13.9]	44 (12.9) [9.5; 16.9]	87 (11.6) [9.4; 14.1]

In total, 751 subjects received HBVAXPRO® 5 µg, 409 previously vaccinated with HEXAVAC® and 342 previously vaccinated with INFANRIX®-HEXA. However, one subject in the INFANRIX®-HEXA cohort was lost to follow-up shortly after the injection and no safety data was available. The Safety Analysis Set therefore consisted of 750 subjects.

Overall, 346 subjects (46.1%) reported at least one injection-site adverse reaction or one systemic adverse event from Day 0 to Day 14 after the challenge dose of HBVAXPRO® 5 µg: 181 subjects (44.3%) in the HEXAVAC® cohort and 165 subjects (48.4%) in the INFANRIX®-HEXA cohort.

From Day 0 to Day 14, 305 subjects (40.7%) reported at least one injection-site adverse reaction in both cohorts: 159 subjects (38.9%) in the HEXAVAC® cohort, and 146 subjects (42.8%) in the INFANRIX®-HEXA cohort. All of injection-site adverse reactions were solicited and occurred between Day 0 and Day 4, except for 2 subjects who reported unsolicited injection-site adverse reactions between Day 0 an Day 14: one subject in the HEXAVAC® cohort reported one injection-site bruising and one injection-site swelling and one subject in the INFANRIX®-HEXA cohort reported one injection-site swelling. Most of the injection-site adverse reactions were pain at injection site (39.3%) and the other solicited injection-site adverse reactions were erythema and swelling reported by 2.4% and 3.5% of total subjects respectively. In the HEXAVAC® cohort, the subjects presented fewer solicited injection-site adverse reactions (total: 38.9%, erythema: 1.7%, swelling 1.5% and pain 38.1%) compared to the subjects in the INFANRIX®-HEXA cohort (total: 42.5%, erythema: 3.2%, swelling: 5.9%, pain: 40.8% subjects). Most injection-site adverse reactions were of mild intensity or with a size <2.5 cm. Five subjects (0.7% of the overall population) presented injection-site reactions of severe intensity (injection-site pain, injection-site bruising and injection-site swelling).

Between Day 0 and Day 14, 88 subjects (11.7%) reported at least one systemic adverse event in both cohorts: 43 subjects (10.5%) in the HEXAVAC® cohort, and 45 subjects (13.2%) in the INFANRIX®-HEXA cohort. In all subjects, the only solicited systemic adverse event from D0 to D4 was pyrexia (i.e. body temperature >=38°C) reported by 6 subjects (0.8%) in both cohorts: one subject (0.2%) in the HEXAVAC® cohort (not vaccine-related) and 5 subjects (1.5%) in the INFANRIX®-HEXA cohort (vaccine-related for 2 subjects [0.6%]). Most of systemic adverse events (11.6%) were unsolicited and reported by 43 subjects (10.5%) in the HEXAVAC® cohort and by 44 subjects (12.9%) in the INFANRIX®-HEXA cohort. Unsolicited systemic adverse events were headache (3.6%), oral pharyngeal pain (1.6%), nasopharyngitis (0.9%) and vomiting (0.7%). Between Day 0 and Day 14, vaccine-related systemic adverse events were reported by 1.9% of subjects after HBVAXPRO® (1.5% in the HEXAVAC cohort and 2.3% in the INFANRIX®-HEXA cohort).

Three systemic adverse events started after Day 14 in the HEXAVAC® cohort, none of which were vaccine-related.

From Day 0 to Visit 2, two subjects (0.3%) reported two serious adverse events: one (0.2%) in the HEXAVAC® cohort reported a Schwannoma of the left thigh and one (0.3%) in the INFANRIX®-HEXA cohort reported a multiple sclerosis. None of them were considered by the investigator to be related to HBVAXPRO® 5 µg.

None subject was withdrawn from the study due to an adverse event.

2.1.2. Discussion on clinical aspects

The main aim of Study HXV02C was to evaluate the immune response to a challenge dose of Hepatitis B vaccine at Year 10 checkpoint, in healthy children fully vaccinated with HEXAVAC® or INFANRIX®-HEXA during their infancy with a 3-dose primary series. The study design resembles previous HXV01C study, which was conducted in similar setting and methodology, except that it was designed to evaluate the immune response to a challenge dose of Hepatitis B vaccine at Year 5 checkpoint.

The 10-year persistence of antibody at protective levels of >= 10 mIU/mL was more prevalent in subjects of INFANRIX®-HEXA cohort (69.0%) than that in HEXAVAC® cohort (23.9%). Similarly, the pre-challenge GMCs were also lower in the HEXAVAC® cohort (7.7 mIU/ml) than in INFANRIX®-HEXA cohort (26.8 mIU/ml). These observations were consistent with previous studies and not unexpected.

Consistently, the booster effect observed at Year 10 checkpoint was also lower in subjects of the HEXAVAC® cohort compared to those in the INFANRIX®-HEXA cohort: the percentage of subjects mounting an secondary antibody response at anti-HBs concentration >=10 mIU/mL was 83.6% in the HEXAVAC® cohort and 96.4% in the INFANRIX®-HEXA cohort. This corresponds to 16.4% of subjects in HEXAVAC® cohort and 3.6% of subjects in INFANRIX®-HEXA cohort with no anamnestic immune response being detected, when measured one months after the challenge dose; the GMC were 191.9 mIU/ml in the HEXAVAC® cohort and 1823.8 mIU/ml in the INFANRIX®-HEXA cohort.

It is noteworthy that similar booster effects of HBVAXPRO 5 mg, both at seroprotection rate and at GMC were at checkpoint of Year 5, in healthy children fully vaccinated either with 3 doses of HEXAVAC® or 3 doses of INFANRIX®-HEXA as infants (Study HXV01C). Thus, results of Study HXV02C may suggest that a proportion of children fully vaccinated with HEXAVAC® as infants might start loss of immunological memory. In fact, and in support of this assumption, there was increased proportion (21.3%) of subjects in HEXAVAC® cohort with pre-challenge anti-HBs titer <10 mIU/mL did not respond to challenge dose given 10 years after primary series of vaccination, when compared to Year 5 checkpoint (13% in total for both HBVAXPRO booster and Engerix B booster). However, due to the unavailability of serology results in study subjects directly after completion of 3 doses primary series or the residual levels of anti-HBs at enrolment in HXV02C, direct comparison of booster response results should be exercised with caution.

In study HXV02C, benign breakthrough infections, characterized by isolated anti-HBc positivity without the development of HBsAg carriage, have occurred in 10 subjects (1.3%). Since these vaccines were born of HBsAg negative mothers, they very likely acquired infection after vaccination. It is noteworthy that 2 out of the 10 subjects (both from HEXAVAC® cohort) had undetectable anti-HBs before the challenge dose and did not respond to challenge dose (anti-HBs concentration <10mIU/mL one month after the challenge dose). The detection of anti-HBc alone in the absence of clinical diseases in such subjects may be the consequence of: 1) false positive test result; 2) occult infection with presence of HBV DNA below the detection limit of the current commercially available assays; 3) resolved natural infection with loss of anti-HBs. Although the long-term protection mechanism is largely unknown, this last point is in line with the assumption that is supported by a recent study (reference 1) in HBV endemic region that, the lack of a secondary response to a booster dose does not necessarily imply a lack of protection.

Furthermore, the fact of nearly even split in subjects with anti-HBc between HEXAVAC and INFANRIX-HEXA cohorts also argues against an increased risk for Hepatitis B infection for HEXAVAC subjects on the basis of anti-HBs levels.

No death or vaccine-related serious adverse event was reported during the study. No subject was withdrawn from the study due to an adverse event. Thus, the challenge dose of HBVAXPRO 5 µg was well-tolerated.

3. CHMP overall conclusion and recommendation

The immunological memory after priming either with HEXAVAC® or INFANRIX®-HEXA during infancy has been demonstrated for a period of 10 years in over 80% of children. Despite the absence of anamnestic immune response to a challenge dose was seen in a proportion of subjects, no evidence of clinical hepatitis B disease and no increased risk for chronic hepatitis B infection were observed in this study. Therefore, children who were fully vaccinated in infancy and did not respond to a challenge dose of HBVAXPRO 5 µg at Year 10 appear still to be protected from chronic hepatitis B infection.

The immunological data and other information support long-term protection offered by HEXAVAC® or INFANRIX®-HEXA during routine vaccination program. Open question remains whether and when the clinical breakthrough hepatitis B disease will occur in adolescents fully vaccinated as infants, but identification of this timeframe in low hepatitis B endemic regions appears challenging, and requires large surveillance studies.
The HEXAVAC® has been withdrawn from the Market in 2012. The results of this HXV02C study are useful to support the validity of HBVAXPRO product information, without requiring SPC update.

In conclusion, this PAM can be closed. No further regulatory action is required.

x Fulfilled.

Reference 1:

Bialek SR, Bower WA, Novak R, et al. Persistence of protection against hepatitis B virus infection among adolescents vaccinated with recombinant hepatitis B vaccine beginning at birth: a 15-year follow-up study. Pediatr Infect Dis J. 2008;27:881-885.