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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** A3L49 **Study Identifier:**
Proprietary Vaccine Name:	Euvax-B®	

Title of the Study: Persistence of Anti-Hep B Antibodies at 9 to 10 Years of Age in Subjects Having Received Hep B Vaccine at Birth and a DTaP-IPV-Hep B-PRP~T Hexavalent Vaccine at 2, 4 and 6 Months of Age, and Evaluation of Their Immune Memory Following a Challenge Re-vaccination with a Standalone Hep B Vaccine

Study centres: 4 clinical centers in Thailand

Publications: None at the time of report writing

Study period:	Date of First enrollment: 28 Feb 2016 Date of Last visit (contact): 14 June 2016
Development phase:	Phase III

Methodology / Trial Design:

Phase III, multi-center study in children previously vaccinated in study A3L12 with a 3-dose infant primary series of DTaP-IPV-HB-PRP~T hexavalent combined vaccine (Hexaxim® [Group 1]) or of DTaP-IPV-HB//PRP~T hexavalent combined vaccine (Infanrix® hexa [Group 2]) administered at 2, 4, and 6 months of age (MoA), both concomitantly with the heptavalent pneumococcal conjugate vaccine (PCV7; Prevenar®). As recommended by the Thai Standard Vaccination Schedule, all infants received hepatitis B (Hep B or HB when used in the name of the investigational vaccine) vaccination at birth.

Study A3L49 assessed the persistence of anti-Hep B antibody (Ab) at 9 to 10 years of age after the last priming dose in subjects who completed study A3L12. The study also evaluated their immune response against Hep B antigen one month after (re)vaccination (challenge vaccination) with a standalone (monovalent) Hep B vaccine (Euvax-B vaccine). In addition, all serious adverse events (SAEs) which occurred after Hep B vaccination were to be collected.

Some of the subjects enrolled in study A3L49 were also enrolled in a laboratory investigation (study A3L47) aiming at determining the levels of anti-Hep B Abs in sera collected during the scope of trial PNA19 which corresponded to sera taken 6 to 12 months post-third infant series vaccination. Therefore, some subjects enrolled in study A3L49 have been evaluated for anti-Hep B Abs at post-Dose 3 through study A3L12, 6 to 12 months post-Dose 3 through the A3L47 investigation, and 9-10 years post-Dose 3 through study A3L49.

In study A3L12, a total of 412 subjects were included and 393 completed the study (197 subjects in Group 1 and 196 subjects in Group 2). These 393 subjects, who received 3 injections of Hexaxim or Infanrix hexa vaccine at 2, 4, and 6 MoA during study A3L12, were invited to participate in study A3L49, 9 to 10 years after having completed study A3L12.

At Visit 1 (V01), all enrolled subjects from both A3L12 study vaccine groups received a single dose of the Euvax-B vaccine. The subjects provided 2 blood samples for immunogenicity assessment: one at baseline (pre-challenge vaccination, Day 0 [D0]) and one 28 days after (post-challenge vaccination D28).

For some subjects, the anti-Hep B Ab concentration did not reach a level above the 10 mIU/mL threshold

following the "challenge vaccination". These subjects will be proposed 2 additional standalone Hep B vaccine doses. This completed a full re-vaccination immunization regimen per international recommendations. These 2 additional doses were not provided to the Investigators by Sanofi Pasteur, and the immune status of the "non-responder" following completion of this full re-vaccination was not tested, as testing for immunity following revaccination is not recommended routinely.

Due to the well-established and good safety profile of the Euvax-B vaccine and as this trial was designed for exploration of the immune response following Hep B vaccination, only the SAEs that occurred in enrolled subjects were planned to be collected throughout the study, including SAEs due to study procedures.

Primary Objectives:

- To describe the persistence of anti-Hep B Ab at 9 to 10 years of age after last priming dose in subjects having received Hep B vaccine at birth and a hexavalent vaccine at 2, 4 and 6 MoA according to the vaccine received during study A3L12 (Hexaxim vaccine [Group 1] or Infanrix hexa vaccine [Group 2])
- To evaluate the immune response against Hep B one month after vaccination with a standalone monovalent Hep B vaccine (challenge [re]vaccination)

Primary Endpoints:

At baseline, before vaccination (D0, V01):

- Individual anti-Hep B Ab concentrations
- Individual anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL

One month after challenge vaccination (D28, V02):

- Individual anti-Hep B Ab concentrations
- Individual anti-Hep B Ab concentration ratios (one month post- / pre-challenge dose)
- Individual anti-Hep B Ab concentrations ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anamnestic response defined as a ≥ 4-fold increase in anti-Hep B Ab concentration from pre-challenge dose (V01) to post-challenge dose (V02) in subjects seroprotected (≥ 10 mIU/mL) prior to challenge dose, or a post-challenge dose anti-Hep B Ab concentration ≥ 10 mIU/mL in subjects not seroprotected prior to challenge dose (< 10 mIU/mL)

Secondary Objective:

To describe SAEs reported throughout the trial after administration of Hep B vaccine.

Secondary Endpoints:

Occurrence, nature (Medical Dictionary for Regulatory Activities referred term), time to onset, duration, outcome, seriousness and relationship to vaccination of any SAE reported from V01 through V02.

Observational objective:

Not applicable

Observational endpoint:

Not applicable

Sample size (Number of Subjects):

Planned sample size: as many subjects as possible were recruited from subjects who completed the 3-dose series in study A3L12. A minimum of 50 to 60 subjects per vaccine group were expected to allow the assessment of the objectives.

	Group 1 n (%)	**Group 2 n (%)**	**All Subjects n (%)**
Potentially enrolled (who completed study A3L12)	197	196	393
Actually enrolled subjects	71	79	150
Vaccinated with Euvax B	71 (100.0)	79 (100.0)	150 (100.0)
Not Vaccinated	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who completed the study	71 (100.0)	79 (100.0)	150 (100.0)
Early termination	0 (0.0)	0 (0.0)	0 (0.0)

n, number of subjects fulfilling the item listed

Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine; Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

The number and percentage of subjects who were included in the different populations used in the analyses are presented in the table below.

	Group 1 n (%)	**Group 2 n (%)**
Subject with data in CRF	71 (100.0)	79 (100.0)
With data in CRF but did not receive any vaccination	0 (0.0)	0 (0.0)
Full Analysis Set	71 (100.0)	79 (100.0)
Per-Protocol Analysis Set	69 (97.2)	77 (97.5)

n, number of subjects fulfilling the item listed

Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine; Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

Schedules of Vaccination and Specimen Collection:

Vaccination

All subjects received 1 dose of the Euvax-B vaccine at D0.

Blood sampling

All subjects provided a pre-vaccination blood sample (3 mL) at D0 and a post-vaccination sample at D28 (+ 7 days).

Collection of safety data

Information on SAEs was recorded from D0 through D28 (+ 7 days).

Duration of Participation in the Trial:

The duration of each subject's participation in the trial was 28-35 days.

Product Under Investigation:

Hep B vaccine Euvax-B manufactured by LG Life Sciences

Form/Dose/Route:

Liquid in vial (suspension for injection/ 0.5 mL/intramuscular

Batch number:

Commercial Lot: [redacted]

Control Product:

Not applicable

Inclusion Criteria:

A potential subject had to meet all of the following criteria to be considered for trial enrollment:

1) Informed consent form signed by subject's parent / legally acceptable representative
2) Assent form signed by subject
3) Subject and parent(s) / legally acceptable representatives able to attend the scheduled visits and to comply with all trial procedures
4) Receipt of primary vaccination with 3 doses of either Hexaxim or Infanrix hexa vaccine at the age of 2, 4, and 6 months in study A3L12, and Hep B vaccine at birth

Exclusion Criteria:

A potential subject meeting **any** of the following criteria was ineligible for trial enrollment:

1) Participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure in the 4 weeks preceding the inclusion in the trial
2) Incomplete primary immunization in study A3L12
3) Diagnostic of Hep B infection (clinical, serological, or virological confirmation) after completion of A3L12 study procedures
4) Subjects known to have received Hep B vaccine after completion of A3L12 study procedures
5) Receipt of any vaccine in the 4 weeks preceding the trial vaccination, except for Bacille Calmette Guerin vaccination (any administration of oral polio vaccine in the context of oral polio vaccine-national immunization days did not fall within the scope of this exclusion criterion)

6) Receipt of any blood, blood-derived products or immunosuppressant drugs at the latest 3 months before inclusion

7) Known or suspected diagnostic of congenital or acquired immunodeficiency since completion of A3L12 study procedures

8) Serious chronic illness occurring after receipt of the primary series (e.g., leukemia, lymphoma [T or B cells], Crohn's disease)

9) Known or suspected subject seropositivity against human immunodeficiency virus or hepatitis C since completion of A3L12 study procedures

10) Febrile (temperature ≥ 38.0°C) or acute, moderate or severe systemic illness on the day of inclusion

Criteria 1, 5, 6 and 10 were temporarily exclusion criteria. In case a subject met any of these criteria, a further appointment was scheduled to reassess the subject's eligibility.

Statistical methods

For all parameters, the 95% confidence intervals (CIs) were calculated:

- Using the exact binomial method (Clopper-Pearson method) for single proportions
- Using the normal approximation of the Log10 concentrations, followed by a back transformation for geometric mean concentrations (GMCs)

Primary analysis: immunogenicity

The analysis was descriptive according to the vaccine received during the primary series:

- Group 1: Hexaxim vaccine injected at primary series
- Group 2: Infanrix hexa vaccine injected at primary series

The following parameters were calculated:

- GMCs of anti-Hep B Ab (at baseline and one month after the challenge dose)
- Geometric mean of individual anti-Hep B Ab concentration ratio (GMCR)
- Percentage of subjects with anti-Hep B Ab concentration above pre-defined thresholds (at baseline and one month after the challenge dose)
- Anamnestic response rate, defined as the percentage of subjects with an anamnestic response

Reverse cumulative distribution curves (RCDCs) of anti-Hep B Ab concentration were prepared. Additionally, individual kinetic curves including post-(infant) primary immune results obtained in study A3L12 were plotted.

Secondary analysis: safety

The analysis of SAEs was planned to be descriptive according to the vaccine received during the primary series (Group 1 [Hexaxim vaccine] / Group 2 [Infanrix hexa vaccine]).

Results summary:

Study subjects

Out of the 393 subjects who completed study A3L12, 150 subjects participated to study A3L49. All these subjects were vaccinated with the Euvax-B vaccine at D0 (Visit 1): 71 subjects in Group 1 and 79 subjects in Group 2.

Out of the 150 subjects who participated to study A3L49, 147 subjects (98.0%) fulfilled all inclusion and exclusion criteria: 1 subject (1.4%) in Group 1 and 2 subjects (2.5%) in Group 2 did not receive the primary immunization per protocol as planned in study A3L12.

All subjects received 1 intramuscular injection (deltoid) of the Euvax-B vaccine. Adherence to the schedule was high; almost all subjects (149 subjects [99.3%]) had a blood sample taken during Visit 2 between 28 and 35 days after receiving the injection of the Euvax-B vaccine. For 1 subject (1.4%) in Group 1, the blood sample was taken more than 35 days (39 days) after receiving the injection of the Euvax-B vaccine.

All 150 subjects were present at Visits 1 and 2 and had a blood sample taken at each visit. All subjects completed the study and there was no early termination of the study.

All 150 subjects were included in the Full Analysis Set (FAS) (71 subjects [100%] in Group 1 and 79 subjects [100%] in Group 2).

A total of 146 subjects (97.3%) were included in the Per Protocol Analysis Set (PPAS) (69 subjects [97.2%] in Group 1 and 77 subjects [97.5%] in Group 2).

In Group 1, 53.5% of the subjects were male and 46.5% were female. In Group 2, 54.4% of the subjects were male and 45.6% were female. The Male/Female ratio was 1.15 and 1.19 in Groups 1 and 2, respectively.

The mean age of the subjects was 9.5 years in Group 1 and in Group 2.

Baseline demographics were similar for the PPAS and FAS.

A total of 4 subjects (2.7%) (1 subject [1.4%] in Group 1 and 3 subjects [3.8%] in Group 2) had a past and current significant medical history. For 1 subject (1.4%) in Group 1, the medical history condition was ongoing at inclusion (precocious puberty).

Immunogenicity

A summary of the pre- and post-dose seroprotection rates and the anamnesic response rates in the FAS is presented in Table S1, and the corresponding Ab concentrations are presented in Table S2.

Table S1. Summary of seroprotection and anamnestic response rates – Anti-Hep B Ab concentrations (mIU/mL) – Full Analysis Set

		Group 1 (N=71)			**Group 2 (N=79)**		
		n/M	**%**	**95% CI**	**n/M**	**%**	**95% CI**
Pre-Dose (V01)	≥10 mIU/mL	35/71	49.3	37.2; 61.4	34/79	43.0	31.9; 54.7
	≥100 mIU/mL	8/71	11.3	4.99; 21.0	5/79	6.3	2.09; 14.2
Post-dose (V02)	≥10 mIU/mL	66/71	93.0	84.3; 97.7	78/79	98.7	93.1; 100

	≥100 mIU/mL	63/71	88.7	79.0; 95.0	77/79	97.5	91.2; 99.7
Post-Dose response based on pre-Dose (V02/V01)	Anamnestic response*	66/71	93.0	84.3; 97.7	78/79	98.7	93.1; 100

* Anamnestic response is defined as a ≥ 4-fold increase in anti-Hep B Ab concentration from pre-challenge dose (V01) to post-challenge dose (V02) in subjects seroprotected (≥10 mIU/mL) prior to challenge dose OR an anti-Hep B Ab concentration ≥ 10 mIU/mL post-challenge dose in subjects not seroprotected prior to challenge dose (< 10 mIU/mL)

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine; Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

Table S2. Summary of geometric means of concentrations – Anti-Hep B Ab concentration (mIU/mL) – Full Analysis Set

		Group 1 (N=71)			Group 2 (N=79)		
		M	**GM**	**95% CI**	**M**	**GM**	**95% CI**
Anti-Hep B (mIU/mL)	Pre-Dose (V01)	71	13.0	8.67; 19.4	79	8.19	6.10; 11.0
	Post-Dose (V02)	71	3507	1795; 6854	79	4386	2882; 6675
	Post-Dose (V02)/Pre-Dose (V01)	71	271	167; 440	79	536	375; 765

M: number of subjects with available data for the relevant endpoint

Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine; Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

At baseline, as expected, only 49.3% of subjects primed with Hexaxim and 43.0% of subjects primed with Infanrix hexa were still presenting anti-Hep B surface antigen (HBsAg) Ab concentrations ≥ 10 mIU/mL (with GMCs respectively at 13.0 mIU/mL and 8.19 mIU/mL). One month after this challenge (re)vaccination, 93.0% of subjects primed with Hexaxim and 98.7% of subjects primed with Infanrix hexa were presenting anti-HBsAg Ab concentrations ≥ 10 mIU/mL (with GMCs respectively at 3507 mIU/mL and 4386 mIU/mL).

Among the 5 subjects who were Hexaxim-primed and who did not respond one month post-challenge (re)vaccination, 4 had also Ab concentrations < 10 mIU/mL before challenge (re)vaccination but had responded well one month after Hexaxim in study A3L12 (initial responder), and one had also Ab concentrations < 10 mIU/mL before challenge (re)vaccination and had not responded at all one month after Hexaxim in study A3L12 (true nonresponder).

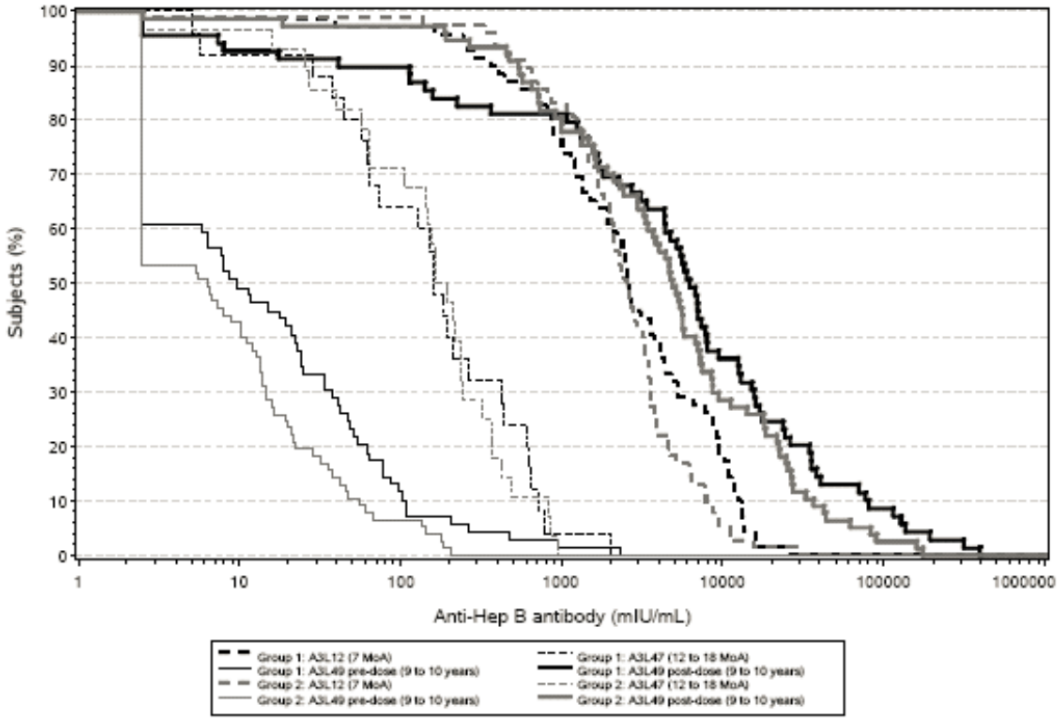
The subject who was Infanrix hexa-primed and who did not develop protection one month post-challenge (re)vaccination had also Ab concentrations < 10 mIU/mL before challenge (re)vaccination and had not

responded at all one month after Infanrix hexa in study A3L12 (true non-responder).

Results were similar in the PPAS.

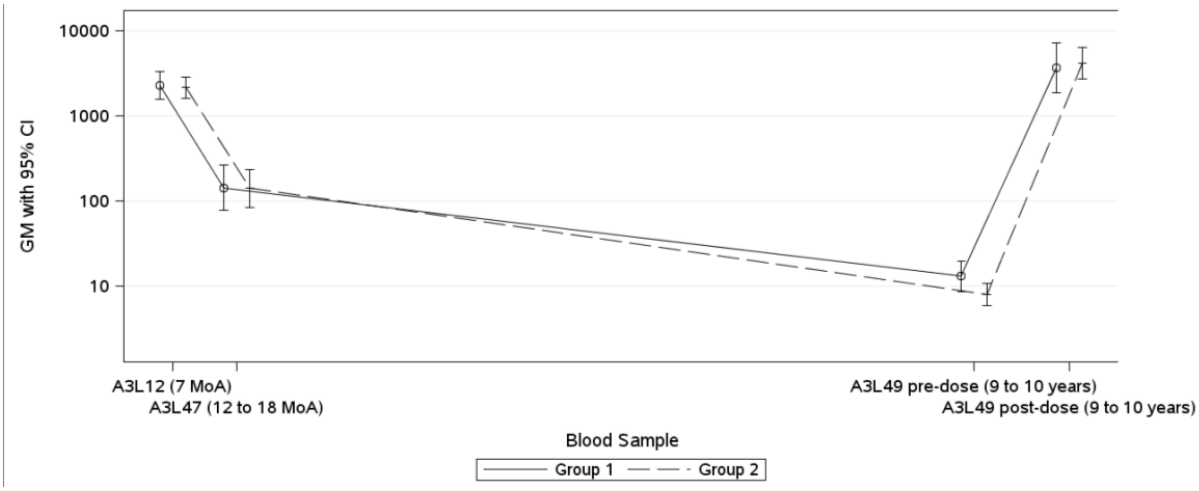
RCDCs on anti-Hep B Ab concentrations at one month post-primary vaccination (at 7 MoA in study A3L12), 6 to 12 months post-primary vaccination (at 12 to 18 MoA in A3L47 study), and 9 to 10 years later at pre- and post-Hep B re-vaccination (in study A3L49) are presented in Figure S1. The kinetic curves of mean anti-Hep B Ab concentrations are presented in Figure S2. The kinetic curves of individual anti-Hep B Ab concentration are presented in Figures S3 and S4 for Group 1 and Group 2 subjects, respectively.

Figure S1. RCDC on anti-Hep B antibody (mIU/mL) – Per-Protocol Analysis Set



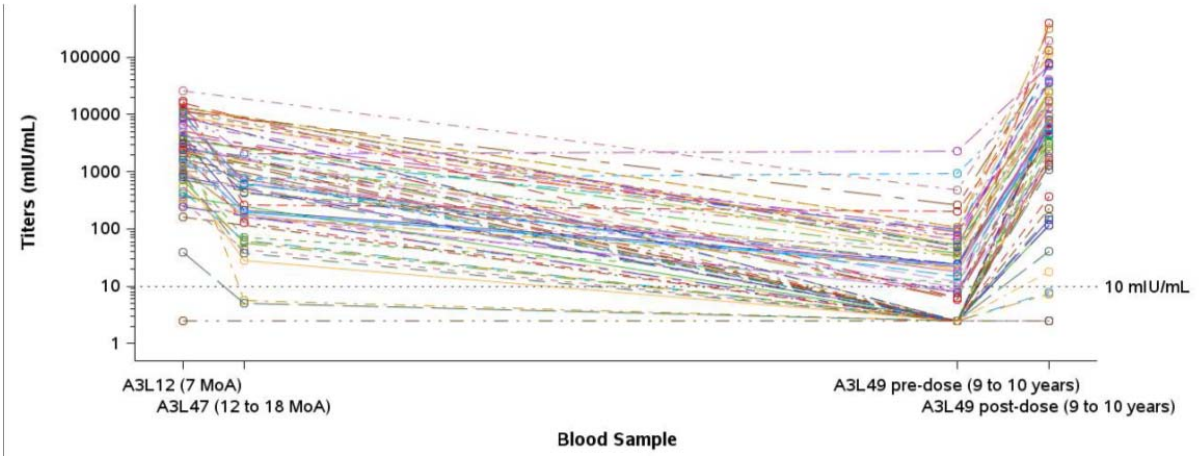
Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine
Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

Figure S2. Kinetic curves of anti-Hep B antibody (mIU/mL) at 4 timepoints by group – Per-Protocol Analysis Set



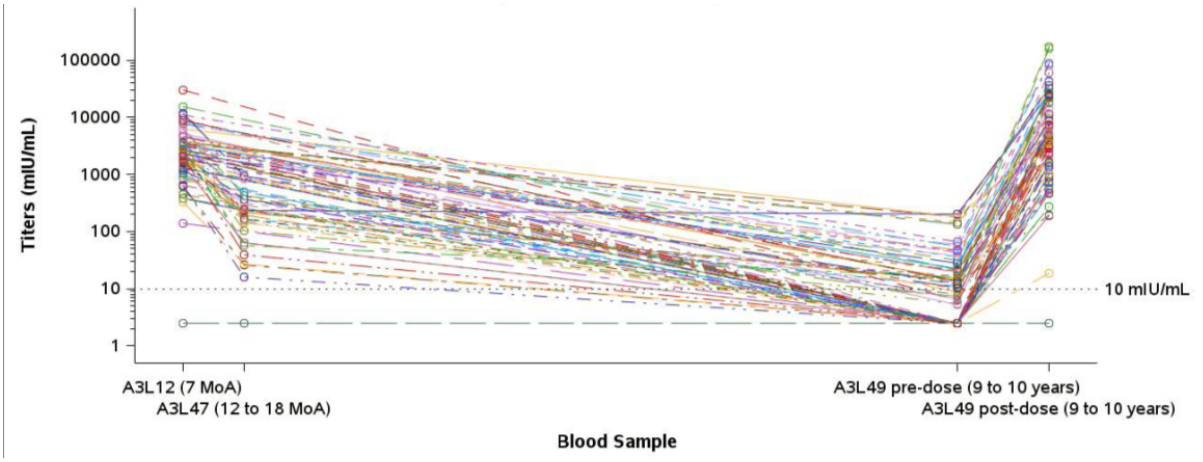
Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine
Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

Figure S3. Individual response curves of anti-Hep B antibody (mIU/mL) at 4 timepoints in Group 1 – Per-Protocol Analysis Set



Group 1: DTaP-IPV-HB-PRP~T (Hexaxim) + Prevenar vaccine

Figure S4. Individual response curves of anti-Hep B antibody (mIU/mL) at 4 timepoints in Group 2 – Per-Protocol Analysis Set



Group 2: DTaP-IPV-HB//PRP~T (Infanrix hexa) + Prevenar vaccine as received in study A3L12

Overall, the levels of anti-Hep B Abs decreased during the full period of follow-up after the primary infant vaccination series. Similar kinetic patterns were observed in subjects who received 3 injections of Hexaxim or Infanrix hexa vaccine at 2, 4, and 6 MoA during study A3L12.

Safety

There was no SAE reported during the entire study.

Conclusions:

This trial showed identical persistence of HBsAg Abs 9 years after completion of an infant series with two different hexavalent vaccines following Hep B vaccination at birth, and adequate anamnestic responses in the vast majority of subjects following a (re)vaccination with a standalone Hep B vaccine, evidencing good persistence of immune memory against HBsAg.

These data are similar to the observations made with similar vaccines used on cohorts followed for similar periods, and continue to support the claim of long-term persistence of clinical protection against Hep B virus infections afforded by all Hep B-containing vaccines.

Date of Report: 06 January 2017