EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

Assessment report under Article 46

Hexacima

International non-proprietary name: (diphtheria (d), tetanus (t), pertussis (acellular, component) (pa), hepatitis b (rdna) (hbv), poliomyelitis (inactivated) (ipv) and haemophilus influenzae type b (hib) conjugate vaccine (adsorbed))

Procedure no: EMEA-H-C-002702-P46-003

Note

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

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1. Introduction

On 9 December 2013, the MAH submitted the final Study report of paediatric study A3L27 for Hexacima, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Hexacima and that no consequential regulatory action is required.

2. Scientific discussion

Information on the development program

The MAH stated that A3L27 is a standalone study.

Clinical aspects

Note: All texts in italics represent the assessor's review of the data.

1. *Introduction*

Hexyon is indicated for active immunisation of infants and children from 6 weeks up to 2 years of age against disease caused by Tetanus, Diphtheria, Pertussis, Polio, Haemophilus influenza b, and Hepatitis B.

The MAH submitted a final report for:

A3L27

This report includes the data on immunogenicity and safety of the booster vaccination. The data from the primary vaccination course (A3L24) were part of the centralized procedure for marketing authorization and can be found in the EPAR.

2. *Clinical study*

A3L27

Evaluation of Antibody Persistence Following a Primary Series at 2, 4, and 6 Months on Trial A3L24 and Booster Effect of the DTaP-IPV-Hep B-PRP-T Combined Vaccine or Infanrix hexa® Concomitantly Administered with Prevenar® at 12 to 24 Months of Age in Healthy Latin American Infants

Description

Immunogenicity and safety of the booster dose during the second year of life concomitantly with a dose of Prevenar7. Infanrix hexa was used as the control vaccine and immunogenicity included pre-booster evaluation of antibody persistence.

Study design

The study was a PIII, randomized, active controlled, observer blind, multi-centre study as an extension of study A3L24.

3 Groups were used:

G1: Primary series ***Hexyon + Prevenar + Rotarix***, Booster **Hexyon + Prevenar**

G2: Primary series ***Hexyon + Prevenar + Rotarix***, Booster **Infanrix hexa + Prevenar**

G3: Primary series ***Infanrix hexa + Prevenar + Rotarix***, Booster **Hexyon + Prevenar**

Blood draws for immunogenicity was on D0 (pre-vaccination) and 30days post vaccination.

Immediate reactions were collected for the 30 minutes post vaccination, solicited AEs over the first 7 days, unsolicited over the first 30 days and SAEs during the complete study duration.

Inclusion and exclusion criteria are similar to the precursor study.

Of note: Due to national immunization recommendations an additional dose of MMRV and/or yellow fever vaccine was given optionally during the trial.

Table 1 Table of Study Procedures (source: Table 3.2, study report)

Visit (V)/Contact	V01	Phone calls*		V02	6-month follow-up
Trial Timeline (Days [D])	D0			D30	D180
Visit Interval (V [Days])		2- 3 days	8-10days	V01 + [30–44 days]	V01 + [180-210 days]
Age of Subject	12-24 months			13-25 months	18-30 months
Informed Consent Form signed	√				
Demography	√				
Medical history (subject and family) since primary series	√				
MMR, and V†, yellow fever and pneumococcal vaccination history‡	√			√	
Poliovirus vaccination history§	√				
Physical examination	√			√	
Inclusion & exclusion Criteria	√				
Blood Sampling (BL) (5 mL approx.)	√ (BL1)			√ (BL2)	
Booster vaccinations**	√				
Immediate surveillance (30 min)	√				
Collection of injection site reactions & systemic reactions/events				√	
Diary Card/Memory Aid (DC/MA): Provided Collected	DC			MA DC	
Concomitant medications	√			√	
Contraindications review	√				
6-Month follow-up status					√
Termination record				√	
SAE	*Any SAE to be reported up to 6 months after the booster dose (i.e. 6 months after V01).*				

* Two phone calls or home visits will be arranged between 2 to 3 days and 8 to 10 days after vaccine administration to ensure completion of the subject's DC. Parent(s)/guardian(s) are advised to call the site if any unusual medical event occurs.
† MMR,V: measles, mumps, rubella, varicella ‡ Since completion of A3L24 study § For subjects in Costa Rica
** Booster Vaccination: all subjects previously vaccinated at 2, 4 and 6 months of age with DTaP-IPV-Hep B-PRP-T or Infanrix hexa will receive one dose of DTaP-IPV-Hep B-PRP-T or Infanrix hexa, concomitantly with a booster dose of Prevenar (PCV7).

Reminder of content of study A3L24 (Excerpt from EPAR)

This study has been conducted in 1376 Latin American infants. It was a multicentre and multi-national randomized and observer blind trial. The trial had 4 arms with three arms being different lots of Hexyon and the fourth arm Infanrix hexa. All groups received Prevenar and Rotarix concomitantly with the hexavalent vaccines. The hexavalent vaccines and Prevenar were given at 2, 4 and 6 months of age, Rotarix at 2 and 4 months. Blood was drawn from all subjects prior to dose 1 and one month after the third dose of Hexyon or Infanrix hexa. In a subset of 242 infants (drawn equally from all groups, ~60 per group) there was an additional blood draw for anti-RV antibodies one month after the second Rotarix dose. Anti-pneumococcal antibodies were measured one month after the third dose also only in a subset of 481 infants, again equally selected from all groups (~120 per group); the antigens contained in the hexavalent vaccines were measured in all infants.

The subjects were followed-up for 6 months after the last vaccination.

Study subjects had to be healthy, term born infants with a birth weight of >2,5 kg. Informed consent had to be given by at least one parent or other legal representative. Not permitted were multiple trial participation, known hypersensitivities to vaccine substances, severe chronical illness (including neurological) or the need for blood products or systemic immune modulators as well as prior infection with one of the bacteria/viruses included in the vaccines.

The infants had already received one dose of BCG and HepB according to local immunization calendar.

Outcomes:

Overall, endpoints, conduct, and general outline of the study were adequate to demonstrate equivalence between the three lots of Hexyon and non-inferiority of the immune response to Hexyon versus Infanrix hexa. This is demonstrated for seroprotection and seroconversion levels as well as for GMT-thresholds of short- and long-term protection for all antigens of the hexavalent vaccines.

Seroconversion and GMTs against the different serotypes of Prevenar 7 are also very similar between the vaccination groups except for serotype 14 that shows a statistically though not clinically significantly lower value for the concomitant use with Hexyon versus Infanrix hexa.

Likewise, no clinically relevant differences were observed in Rotarix immunogenicity responses when co-administered with Hexyon or Infanrix hexa. GMTs and seroprotection rates in this study were similar to that known from approval studies where Rotarix had been administered without a concomitant vaccine.

There was no non-inferiority analysis made for concomitant use with the two hexavalent vaccines. Neither were the concomitant versus single use with both hexavalent vaccines part of this trial. Nevertheless, this study does not show any negative effect of the concomitant use of Hexyon with Prevenar and Rotarix for the immune response against any of the vaccines' antigens.

Assessor's comment

General study outline as well as inclusion and exclusion criteria are acceptable.

Objectives

Immunogenicity:

- To describe the antibody (Ab) persistence for all valences (except Prevenar [PCV7] and Rotarix), following a 3-dose primary series vaccination, of either DTaP-IPV-Hep B-PRP-T or Infanrix hexa at 2, 4 and 6 months of age
- To describe the immunogenicity of a booster dose of DTaP-IPV-Hep B-PRP-T or Infanrix hexa given at 12 to 24 months concomitantly with a booster dose of Prevenar (PCV7)
- To describe the immunogenicity of a booster dose of Prevenar (PCV7) given at 12 to 24 months in the same subset of subjects that participated in the Prevenar (PCV7) immunogenicity analysis in A3L24 study (maximum of 544 subjects)

Safety:

To describe the safety profile after a booster dose of DTaP-IPV-Hep B-PRP-T or Infanrix hexa given at 12 to 24 months of age concomitantly with a booster dose of Prevenar (PCV7)

Endpoints

Immunogenicity:

The following endpoints were used to assess the Ab persistence (for all valences) before the booster dose at day 0 (D0) (Visit 1 [V01]) of DTaP-IPV-Hep B-PRP-T vaccine or Infanrix hexa vaccine:

- Ab titers for each valence
- Ab titers above a pre-determined cut-off:
- Anti-D Ab titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
- Anti-T Ab titers ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Anti-Hep B Ab titers ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PRP Ab titers ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-PT and anti-FHA Ab ≥ lower limit of quantitation (LLOQ)

The following endpoints were used to assess the booster responses at D30 (V02):

- Ab titers for each valence (including Prevenar [PCV7] vaccine)
- Ab titers above a pre-determined cut-off:
- Anti-D Ab titers ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL
- Anti-T Ab titers ≥ 0.01 IU/mL, ≥ 0.1 IU/mL, and ≥ 1.0 IU/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Anti-Hep B Ab titers ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PRP Ab titers ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-pneumococcal serotype 4, 6B, 9V, 14, 18C, 19F, and 23F Ab titers ≥ 0.35 µg/mL (in a subset of subjects only, maximum of 544 subjects)
- Individual titer ratio for each valence (V02/V01), except for Prevenar (PCV7)
- Seroconversion for pertussis Ab (anti-pertussis toxoid [anti-PT] and anti- filamentous hemagglutinin [anti-FHA]) defined as:
- Anti-PT and anti-FHA ≥ 4-fold Ab titers increase from V01 to V02
- Booster response to pertussis antigens (PT and FHA) defined as:
- Subjects whose pre-vaccination Ab concentrations are less than the Lower Limit Of Quantitation (< LLOQ), will demonstrate the booster response if they have post-vaccination levels ≥ 4 x LLOQ
- Subjects whose pre-vaccination Ab concentrations are ≥ LLOQ but < 4 x LLOQ, will demonstrate the booster response if they have a 4-fold response (i.e. post-/pre-vaccination ≥ 4)
- Subjects whose pre-vaccination Ab concentrations are ≥ 4 x LLOQ, will demonstrate the booster response if they have a 2-fold response (i.e., post-/pre-vaccination ≥ 2)

Safety:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination for any unsolicited systemic AEs reported in the 30 minutes after each vaccination
- Occurrence, time to onset, number of days of occurrence, and severity for solicited (prelisted in the subject diary and case report form [eCRF]) injection site and systemic reactions occurring up to 7 days after each vaccination
- Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 30 days after each vaccination
- Occurrence of serious adverse events (SAEs) throughout the trial (including the 6-month follow up period)

Observational endpoints:

Effect of prophylactic antipyretics use

- Ab titers for each valence of DTaP-IPV-Hep B-PRP-T vaccine group only
- Ab titers above a cut-off (V02) for:
- Anti-D and anti-T Ab titers ≥ 0.01 IU/mL, ≥ 0.1 IU/mL and ≥ 1.0 IU/mL
- Anti-Hep B Ab titers ≥ 10 mIU/mL and ≥ 100 mIU/mL
- Anti-PRP Ab titers ≥ 0.15 µg/mL and ≥ 1.0 µg/mL
- Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)
- Seroconversion for pertussis Ab (anti-PT and anti-FHA) defined as:
- Anti-PT and anti-FHA ≥ 4-fold Ab titers increase from V01 to V02
- Booster response to pertussis (PT and FHA) as defined for the immunogenicity endpoints above

Effect of one additional standalone oral poliovirus vaccine

- The following endpoints will be used at D0 (V01) and D30 (V02):
- Ab titers for anti-poliovirus serotypes 1, 2 and 3
- Individual Ab titer ratio for anti-poliovirus 1, 2 and 3 (V02/V01)
- Ab titers above a cut-off for:
- Anti-poliovirus 1, 2 and 3 Ab titers ≥ 8 (1/dil)

Assessor's comment on objectives and endpoints

The use of accepted correlates of protection is appropriate.

The definitions of (S)AEs are according to ICH E2A and cover essential time-points. For convenience and comparability digital thermometers and flexible centimetre rulers were handed out along with the Diary cards, temperature measurements were to be made axillary. The safety observations were thus according to standard in vaccine studies conducted in the EU.

Statistical analysis

Descriptive statistics were produced:

- Safety data at each time point were summarized by vaccine groups.
- Immunogenicity endpoints were presented by vaccine groups including stratification on the age at inclusion. The following parameters were used:
    - For Ab persistence (pre-booster dose administration):
        - Geometric mean (GM) of Ab titers
        - Percentage of subjects with Ab titers above predefined thresholds
    - For booster response (post-booster administration)
        - GM of Ab titers
        - GM of individual Ab titers ratio post/pre-booster dose (GM of titers ratio calculated for all antigens, except for Prevenar [PCV7] antigens)
        - Percentage of subjects with titers above predefined thresholds
        - Seroconversion rate for PT and FHA antigens
        - Booster response rate for PT and FHA antigens

Subjects of Costa Rica who had participated at the National Campaign of Intensification against Polio with standalone oral poliovirus serotypes vaccine before inclusion in this trial were not included in the descriptive analysis of poliovirus 1, 2 and 3 antigens on the perprotocol analysis set for the main analysis.

Reverse cumulative curves for each antigen were presented.

The main safety and immunogenicity parameters were described with 95% confidence interval (CI).

No sample size calculation was done.

A total of 1376 subjects were enrolled in study A3L24. A maximum of 1376 subjects were to be included in study A3L27 and analyzed for safety and immunogenicity.

Assessor's comment

The statistical methods used for this trial's endpoints are in line with the other studies submitted for the initial opinion.

Assays

Assays used in this study are shown in Table 2 below. If applicable reference standards used are shown as well (WHO or CBER). All immunological measurements were made in the sponsor's global clinical immunological laboratory.

Table 2 Assays used in study A3L27 (source:XXX, study protocol)

Antibodies	Assay	Int. Reference standard
Anti-D	Toxin neutralization test	WHO int. standard for D-toxin
Anti-T	ELISA	WHO ref. stand. lot TE3
Anti-PT	ELISA	Ref. standard serum
Anti-FHA	ELISA	Ref. standard serum
Anti-Polio	Neutralization assay	-
Anti-HepB	VITROS ECi/ECiQ chemiluminescence detection	Comparison to calibrator used for WHO first int. ref. preparation for antibody to HBsAg (1977)
Anti-PRP	RIA	CBER ref. stand. Lot 1983
Anti-PnPS	ELISA	Ref. standard lot 89-SF

Assessor's comment

The assays and test reagents used are the same as for the primary vaccination study A3L24 in the same subjects.

Protocol Amendments and other major changes

There were 3 relevant changes made to the protocol and concerning the conduct of the trial:

- *MMRV and YF-vaccination were added as per local requirement in Costa Rica*
- *A fifth dose of PCV was added as per local requirement in Costa Rica*
- *The statistical analysis was planned to have 2 steps, in the end only one – the end-analysis - was performed.*

Results

Table 3 Analysis sets (source: study synopsis)

Primary vaccination	DTaP-IPV-Hep B-PRP-T		Infanrix hexa	All
Booster vaccination	DTaP-IPV-Hep B-PRP-T	Infanrix hexa	DTaP-IPV-Hep B-PRP-T	
	Group 1	Group 2	Group 3	Overall
	n	n	n	n
Planned to be included	516	516	344	1376
ITT (intent to treat analysis set)	416	415	275	1106
Subjects completing the trial from V01 (D0) to V02 (D30)	413	411	272	1096
Subjects discontinued before V02 (D30)	3	4	3	10
Subjects who completed 6-month follow-up	411	409	268	1088
PP (per protocol analysis set)	396	393	260	1049
SafAS (safety analysis set)	416	415	275	1106

Demography

Table 4 Demography (source: study synopsis)

Primary vaccination	DTaP-IPV-Hep B-PRP-T		Infanrix hexa	
Booster vaccination	DTaP-IPV-Hep B-PRP-T Group 1 (N=416)	Infanrix hexa Group 2 (N=415)	DTaP-IPV-Hep B-PRP-T Group 3 (N=275)	Overall (N=1106)
Sex				
Male: n (%)	213 (51.2)	229 (55.2)	147 (53.5)	589 (53.3)
Female: n (%)	203 (48.8)	186 (44.8)	128 (46.5)	517 (46.7)
Ethnic origin				
Black: n (%)	34 (8.2)	39 (9.4)	28 (10.2)	101 (9.1)
Hispanic: n (%)	382 (91.8)	376 (90.6)	247 (89.8)	1005 (90.9)
Age (Months) at V01				
Mean (SD)	17.6 (3.25)	17.6 (3.34)	17.8 (3.26)	17.7 (3.29)
Q1; Q3	14.8; 20.4	14.7; 20.5	14.9; 20.5	14.7; 20.5
Minimum; Maximum	12.3; 23.7	12.1; 23.6	12.2; 23.7	12.1; 23.7
Weight (kg) at V01				
Mean (SD)	10.8 (1.43)	10.8 (1.47)	10.8 (1.49)	10.8 (1.46)

The groups were comparable regarding sex, ethnic origin (~90% Hispanic and ~10% Black), age and weight **(Table 3).** *All subjects were accounted for; most subjects not present in the PP analysis had a dose outside the time interval. Overall compliance was high (94,8% in PP) and similar in all groups* **(Table 4)**.

Immunogenicity

Table 5 Correlates of protection and surrogates for protection used in the study

Antigen	Antibody titre as level of protection	Priority
Diphtheria	≥0,01 IU/mL (short-term) ≥0,1 IU/mL (long-term)	Established correlate
Tetanus	≥0,01 IU/mL (short-term) ≥0,1 IU/mL (long-term)	Established correlate
Polio 1,2,3	≥8 (1/dil)	Established correlate
PRP (Hib)	≥0,15 µg/mL (short-term) ≥1µg/mL (long-term)	Established correlate
Hepatitis B	≥10 IU/mL ≥100 IU/ml	Established correlate
PT, FHA (Pertussis)	≥2-4 fold titer increase depending on Ab-titer pre-booster[1]	Accepted surrogate

[1] See Endpoints for details.

Table 6 Post-primary Series, Antibody Persistence and Booster Response - PP Analysis Set (source: Table 5.1, study report)

Primary vaccination			DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination			DTaP-IPV-Hep B-PRP-T			Infanrix hexa			DTaP-IPV-Hep B-PRP-T		
			Group 1 (N=396)			Group 2 (N=393)			Group 3 (N=260)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-D (MIT-CV-IU/mL)	Primary Series – V06 (D140)	≥ 0.01 IU/mL	392/392	100.0	(99.1; 100.0)	391/391	100.0	(99.1; 100.0)	259/259	100.0	(98.6; 100.0)
		≥ 0.1 IU/mL	308/392	78.6	(74.2; 82.5)	290/391	74.2	(69.5; 78.4)	197/259	76.1	(70.4; 81.1)
	Pre-booster - V01 (D0)	≥ 0.01 IU/mL	382/390	97.9	(96.0; 99.1)	378/390	96.9	(94.7; 98.4)	246/257	95.7	(92.5; 97.8)
		≥ 0.1 IU/mL	156/390	40.0	(35.1; 45.1)	153/390	39.2	(34.4; 44.3)	70/257	27.2	(21.9; 33.1)
	Post-booster V02 (D30)	≥ 0.01 IU/mL	393/393	100.0	(99.1; 100.0)	387/387	100.0	(99.1; 100.0)	254/254	100.0	(98.6; 100.0)
		≥ 0.1 IU/mL	393/393	100.0	(99.1; 100.0)	386/387	99.7	(98.6; 100.0)	254/254	100.0	(98.6; 100.0)
		≥ 1.0 IU/mL	385/393	98.0	(96.0; 99.1)	371/387	95.9	(93.4; 97.6)	247/254	97.2	(94.4; 98.9)
Anti-T (ELISA - IU/mL)	Primary Series – V06 (D140)	≥ 0.01 IU/mL	392/392	100.0	(99.1; 100.0)	391/391	100.0	(99.1; 100.0)	258/258	100.0	(98.6; 100.0)
		≥ 0.1 IU/mL	392/392	100.0	(99.1; 100.0)	390/391	99.7	(98.6; 100.0)	258/258	100.0	(98.6; 100.0)
	Pre-booster - V01 (D0)	≥ 0.01 IU/mL	389/389	100.0	(99.1; 100.0)	386/387	99.7	(98.6; 100.0)	255/255	100.0	(98.6; 100.0)
		≥ 0.1 IU/mL	289/389	74.3	(69.6; 78.6)	286/387	73.9	(69.2; 78.2)	196/255	76.9	(71.2; 81.9)
	Post-booster - V02 (D30)	≥ 0.01 IU/mL	392/392	100.0	(99.1; 100.0)	385/385	100.0	(99.0; 100.0)	254/254	100.0	(98.6; 100.0)
		≥ 0.1 IU/mL	391/392	99.7	(98.6; 100.0)	385/385	100.0	(99.0; 100.0)	254/254	100.0	(98.6; 100.0)
		≥ 1.0 IU/mL	384/392	98.0	(96.0; 99.1)	372/385	96.6	(94.3; 98.2)	246/254	96.9	(93.9; 98.6)
Anti-PRP (RIA-µg/mL)	Primary Series – V06 (D140)	≥ 0.15 µg/mL	370/393	94.1	(91.3; 96.3)	375/392	95.7	(93.1; 97.5)	246/260	94.6	(91.1; 97.0)
		>=1 µg/mL	297/393	75.6	(71.0; 79.7)	305/392	77.8	(73.4; 81.8)	188/260	72.3	(66.4; 77.7)
	Pre-booster - V01 (D0)	≥ 0.15 µg/mL	290/395	73.4	(68.8; 77.7)	304/391	77.7	(73.3; 81.8)	197/258	76.4	(70.7; 81.4)
		>=1 µg/mL	110/395	27.8	(23.5; 32.6)	129/391	33.0	(28.3; 37.9)	73/258	28.3	(22.9; 34.2)
	Post-booster - V02 (D30)	≥ 0.15 µg/mL	395/396	99.7	(98.6; 100.0)	391/391	100.0	(99.1; 100.0)	258/258	100.0	(98.6; 100.0)
		>=1 µg/mL	391/396	98.7	(97.1; 99.6)	387/391	99.0	(97.4; 99.7)	258/258	100.0	(98.6; 100.0)

Primary vaccination			DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination			DTaP-IPV-Hep B-PRP-T			Infanrix hexa			DTaP-IPV-Hep B-PRP-T		
			Group 1 (N=396)			Group 2 (N=393)			Group 3 (N=260)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-PT (ELISA - EU/mL)	Primary Series – V06 (D140)	≥ 2 EU/mL	393/393	100.0	(99.1; 100.0)	391/391	100.0	(99.1; 100.0)	259/259	100.0	(98.6; 100.0)
	Pre-booster - V01 (D0)	≥ 2 EU/mL	344/385	89.4	(85.8; 92.2)	349/382	91.4	(88.1; 94.0)	225/257	87.5	(82.9; 91.3)
	Post-booster - V02 (D30)	≥ 2 EU/mL	391/391	100.0	(99.1; 100.0)	383/383	100.0	(99.0; 100.0)	254/254	100.0	(98.6; 100.0)
	Booster - V02/V01 (D30/D0)	4-fold increase	353/380	92.9	(89.8; 95.3)	351/374	93.9	(90.9; 96.1)	234/252	92.9	(88.9; 95.7)
		Booster response	375/380	98.7	(97.0; 99.6)	365/374	97.6	(95.5; 98.9)	245/252	97.2	(94.4; 98.9)
Anti- FHA (ELISA - EU/mL)	Primary Series – V06 (D140)	≥ 2 EU/mL	391/391	100.0	(99.1; 100.0)	390/390	100.0	(99.1; 100.0)	259/259	100.0	(98.6; 100.0)
	Pre-booster - V01 (D0)	≥ 2 EU/mL	389/389	100.0	(99.1; 100.0)	384/384	100.0	(99.0; 100.0)	253/255	99.2	(97.2; 99.9)
	Post-booster - V02 (D30)	≥ 2 EU/mL	390/390	100.0	(99.1; 100.0)	385/385	100.0	(99.0; 100.0)	254/254	100.0	(98.6; 100.0)
	Booster - V02/V01 (D30/D0)	4-fold increase	336/384	87.5	(83.8; 90.6)	334/376	88.8	(85.2; 91.8)	235/252	93.3	(89.4; 96.0)
		Booster response	370/384	96.4	(94.0; 98.0)	367/376	97.6	(95.5; 98.9)	249/252	98.8	(96.6; 99.8)

Primary vaccination			DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination			DTaP-IPV-Hep B-PRP-T			Infanrix hexa			DTaP-IPV-Hep B-PRP-T		
			Group 1 (N=396)			Group 2 (N=393)			Group 3 (N=260)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-Hep B (VITROS ECi - mIU/mL)	Primary Series – V06 (D140)	≥ 10 mIU/mL	391/393	99.5	(98.2; 99.9)	391/392	99.7	(98.6; 100.0)	260/260	100.0	(98.6; 100.0)
		≥ 100 mIU/mL	389/393	99.0	(97.4; 99.7)	387/392	98.7	(97.0; 99.6)	259/260	99.6	(97.9; 100.0)
	Pre-booster - V01 (D0)	≥ 10 mIU/mL	386/396	97.5	(95.4; 98.8)	382/391	97.7	(95.7; 98.9)	257/259	99.2	(97.2; 99.9)
		≥ 100 mIU/mL	327/396	82.6	(78.5; 86.2)	333/391	85.2	(81.2; 88.5)	213/259	82.2	(77.0; 86.7)
	Post-booster - V02 (D30)	≥ 10 mIU/mL	394/395	99.7	(98.6; 100.0)	391/393	99.5	(98.2; 99.9)	259/259	100.0	(98.6; 100.0)
		≥ 100 mIU/mL	386/395	97.7	(95.7; 99.0)	384/393	97.7	(95.7; 98.9)	257/259	99.2	(97.2; 99.9)
Anti-polio 1 (MIT-WT-1/dil)	Primary Series – V06 (D140)	≥ 8 (1/dil)	338/338	100.0	(98.9; 100.0)	329/329	100.0	(98.9; 100.0)	214/214	100.0	(98.3; 100.0)
	Pre-booster - V01 (D0)	≥ 8 (1/dil)	334/338	98.8	(97.0; 99.7)	320/326	98.2	(96.0; 99.3)	210/213	98.6	(95.9; 99.7)
	Post-booster - V02 (D30)	≥ 8 (1/dil)	339/339	100.0	(98.9; 100.0)	327/327	100.0	(98.9; 100.0)	212/212	100.0	(98.3; 100.0)
Anti-polio 2 (MIT-WT-1/dil)	Primary Series – V06 (D140)	≥ 8 (1/dil)	338/338	100.0	(98.9; 100.0)	327/327	100.0	(98.9; 100.0)	214/214	100.0	(98.3; 100.0)
	Pre-booster - V01 (D0)	≥ 8 (1/dil)	335/337	99.4	(97.9; 99.9)	328/328	100.0	(98.9; 100.0)	213/213	100.0	(98.3; 100.0)
	Post-booster - V02 (D30)	≥ 8 (1/dil)	340/340	100.0	(98.9; 100.0)	327/327	100.0	(98.9; 100.0)	212/212	100.0	(98.3; 100.0)
Anti-polio 3 (MIT-WT-1/dil)	Primary Series – V06 (D140)	≥ 8 (1/dil)	338/338	100.0	(98.9; 100.0)	328/328	100.0	(98.9; 100.0)	214/214	100.0	(98.3; 100.0)
	Pre-booster - V01 (D0)	≥ 8 (1/dil)	324/338	95.9	(93.1; 97.7)	309/326	94.8	(91.8; 96.9)	211/213	99.1	(96.6; 99.9)
	Post-booster - V02 (D30)	≥ 8 (1/dil)	340/340	100.0	(98.9; 100.0)	326/326	100.0	(98.9; 100.0)	212/212	100.0	(98.3; 100.0)

N: Number of subjects analyzed according to PP Analysis Set n: number of subjects M: number of subjects available for the endpoint
%: percentages and 95% CI are calculated according to the subjects available for the endpoint
Booster response to pertussis (PT and FHA) defined as:
Subjects whose pre-vaccination Ab concentrations are less than the Lower Limit of Quantitation (< LLOQ), will demonstrate the booster response if they have post-vaccination levels ≥ 4 x LLOQ

Subjects whose pre-vaccination Ab concentrations are ≥ LLOQ but < 4 x LLOQ, will demonstrate the booster response if they have a 4 –fold response (i.e., post-/pre-vaccination ≥ 4)

Subjects whose pre-vaccination Ab concentrations are ≥ 4 x LLOQ, will demonstrate the booster response if they have a 2-fold response (i.e., post-/pre-vaccination ≥ 2)

Table 7 Summary of Geometric Means of Titers for Study Vaccine - PP Analysis Set (source: Table 5.2, study protocol)

Primary vaccination		DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination		DTaP-IPV-Hep B-PRP-T Group 1 (N=396)			Infanrix hexa Group 2 (N=393)			DTaP-IPV-Hep B-PRP-T Group 3 (N=260)		
Component	Timepoint	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)
Anti-D (MIT-CV- IU/mL)	Primary series – V06 (D140)	392	0.265	(0.237; 0.295)	391	0.254	(0.227; 0.285)	259	0.251	(0.220; 0.286)
	Pre-booster - V01 (D0)	390	0.077	(0.069; 0.086)	390	0.074	(0.066; 0.083)	257	0.059	(0.051; 0.068)
	Post-booster - V02 (D30)	393	5.55	(5.07; 6.08)	387	4.40	(3.99; 4.86)	254	6.05	(5.41; 6.76)
Anti-T (ELISA - IU/mL)	Primary series – V06 (D140)	392	1.50	(1.39; 1.61)	391	1.54	(1.44; 1.65)	258	1.80	(1.68; 1.93)
	Pre-booster - V01 (D0)	389	0.208	(0.188; 0.231)	387	0.224	(0.200; 0.251)	255	0.201	(0.180; 0.225)
	Post-booster - V02 (D30)	392	5.72	(5.21; 6.27)	385	5.21	(4.78; 5.68)	254	7.52	(6.63; 8.52)
Anti-PT (ELISA - EU/mL)	Primary series – V06 (D140)	393	99.6	(94.0; 106)	391	102	(96.6; 108)	259	97.0	(90.1; 105)
	Pre-booster - V01 (D0)	385	7.43	(6.63; 8.32)	382	8.47	(7.52; 9.56)	257	7.41	(6.38; 8.61)
	Post-booster - V02 (D30)	391	154	(143; 166)	383	191	(178; 206)	254	140	(127; 153)
Anti-FHA (ELISA - EU/mL)	Primary series – V06 (D140)	391	179	(169; 190)	390	187	(176; 199)	259	120	(112; 129)
	Pre-booster - V01 (D0)	389	21.2	(18.9; 23.8)	384	23.4	(20.8; 26.3)	255	14.4	(12.5; 16.8)
	Post-booster - V02 (D30)	390	316	(293; 342)	385	418	(386; 454)	254	260	(231; 293)
Anti-Hep B (VITROS ECi - mIU/mL)	Primary series – V06 (D140)	393	3050	(2715; 3427)	392	3180	(2834; 3568)	260	2910	(2556; 3313)
	Pre-booster - V01 (D0)	396	386	(332; 449)	391	406	(349; 472)	259	336	(284; 397)
	Post-booster - V02 (D30)	395	8462	(7154; 10010)	393	11218	(9482; 13272)	259	9688	(7940; 11821)
Anti-PRP (RIA- µg/mL)	Primary series – V06 (D140)	393	3.19	(2.69; 3.78)	392	3.60	(3.05; 4.25)	260	2.13	(1.78; 2.54)
	Pre-booster - V01 (D0)	395	0.482	(0.406; 0.573)	391	0.556	(0.472; 0.656)	258	0.455	(0.375; 0.553)
	Post-booster - V02 (D30)	396	42.4	(37.0; 48.6)	391	41.5	(36.6; 47.0)	258	56.5	(48.4; 65.9)

Primary vaccination		DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination		DTaP-IPV-Hep B-PRP-T Group 1 (N=396)			Infanrix hexa Group 2 (N=393)			DTaP-IPV-Hep B-PRP-T Group 3 (N=260)		
Component	Timepoint	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)
Anti-polio 1 (MIT-WT-1/dil)	Primary series – V06 (D140)	338	656	(587; 734)	329	705	(625; 796)	214	1276	(1098; 1484)
	Pre-booster - V01 (D0)	338	132	(116; 150)	326	134	(116; 154)	213	224	(188; 267)
	Post-booster - V02 (D30)	339	2140	(1937; 2364)	327	2633	(2363; 2933)	212	2978	(2592; 3421)
Anti-polio 2 (MIT-WT-1/dil)	Primary series – V06 (D140)	338	1152	(1035; 1282)	327	1241	(1101; 1398)	214	1945	(1676; 2256)
	Pre-booster - V01 (D0)	337	251	(214; 294)	328	289	(245; 341)	213	380	(313; 461)
	Post-booster - V02 (D30)	340	4232	(3821; 4688)	327	4887	(4372; 5463)	212	6369	(5569; 7283)
Anti-polio 3 (MIT-WT-1/dil)	Primary series – V06 (D140)	338	1169	(1025; 1332)	328	1108	(979; 1255)	214	1948	(1647; 2304)
	Pre-booster - V01 (D0)	338	128	(109; 149)	326	126	(106; 150)	213	207	(173; 248)
	Post-booster - V02 (D30)	340	3569	(3164; 4027)	326	3322	(2939; 3755)	212	6015	(5244; 6898)

N: Number of subjects analyzed according to PP Analysis Set M: number of subjects available for the endpoint Subjects receiving one additional oral dose of polio were excluded from the PP for polio antigens only

Table 8 Summary of Descriptive Antibody Level Result for Prevenar Vaccine - PP Analysis Set (source: Table 5.3, study report)

Primary vaccination			DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination			DTaP-IPV-Hep B-PRP-T Group 1 (N=396)			Infanrix hexa Group 2 (N=393)			DTaP-IPV-Hep B-PRP-T Group 3 (N=260)		
Component (ELISA - µg/mL)	Timepoint	Criterion	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-pneumo 4	V02 (D30)	>=0.35 µg/mL	160/161	99.4	(96.6; 100.0)	146/147	99.3	(96.3; 100.0)	94/94	100.0	(96.2; 100.0)
Anti-pneumo 6B	V02 (D30)	>=0.35 µg/mL	155/160	96.9	(92.9; 99.0)	145/146	99.3	(96.2; 100.0)	93/94	98.9	(94.2; 100.0)
Anti-pneumo 9V	V02 (D30)	>=0.35 µg/mL	161/161	100.0	(97.7; 100.0)	147/147	100.0	(97.5; 100.0)	94/94	100.0	(96.2; 100.0)
Anti-pneumo 14	V02 (D30)	>=0.35 µg/mL	161/161	100.0	(97.7; 100.0)	147/147	100.0	(97.5; 100.0)	94/94	100.0	(96.2; 100.0)
Anti-pneumo 18C	V02 (D30)	>=0.35 µg/mL	160/161	99.4	(96.6; 100.0)	147/147	100.0	(97.5; 100.0)	94/94	100.0	(96.2; 100.0)
Anti-pneumo 19F	V02 (D30)	>=0.35 µg/mL	161/161	100.0	(97.7; 100.0)	144/147	98.0	(94.2; 99.6)	94/94	100.0	(96.2; 100.0)
Anti-pneumo 23F	V02 (D30)	>=0.35 µg/mL	158/158	100.0	(97.7; 100.0)	144/145	99.3	(96.2; 100.0)	93/93	100.0	(96.1; 100.0)

N: Number of subjects analyzed according to PP Analysis Set n: number of subjects M: number of subjects available for the endpoint

%: percentages and 95% CI are calculated according to the subjects available for the endpoint

Table 9 Summary of Geometric Means of Concentrations for Prevenar Vaccine – PP Analysis Set (source: Table 5.4, study report)

Primary vaccination		DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination		DTaP-IPV-Hep B-PRP-T Group 1 (N=396)			Infanrix hexa Group 2 (N=393)			DTaP-IPV-Hep B-PRP-T Group 3 (N=260)		
Component (ELISA - µg/mL)	Timepoint	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)
Anti-pneumo 4	V02 (D30)	161	2.79	(2.47; 3.15)	147	3.03	(2.64; 3.47)	94	3.58	(3.07; 4.17)
Anti-pneumo 6B	V02 (D30)	160	6.87	(5.68; 8.31)	146	8.98	(7.86; 10.3)	94	9.34	(7.76; 11.2)
Anti-pneumo 9V	V02 (D30)	161	2.51	(2.22; 2.85)	147	2.86	(2.57; 3.19)	94	2.92	(2.50; 3.42)
Anti-pneumo 14	V02 (D30)	161	11.6	(10.2; 13.2)	147	13.2	(11.5; 15.2)	94	12.3	(10.2; 14.7)
Anti-pneumo 18C	V02 (D30)	161	2.37	(2.10; 2.67)	147	2.63	(2.35; 2.95)	94	3.40	(2.92; 3.94)
Anti-pneumo 19F	V02 (D30)	161	3.01	(2.62; 3.47)	147	3.74	(3.19; 4.38)	94	3.72	(3.19; 4.32)
Anti-pneumo 23F	V02 (D30)	158	6.98	(6.14; 7.94)	145	7.20	(6.23; 8.33)	93	9.30	(7.79; 11.1)

N: Number of subjects analyzed according to PP Analysis Set M: number of subjects available for the endpoint

Table 10 GMTs and CIs of antipyretic use vs non-use for both Prime-booster combinations in PP analysis set (source: Table 9.67, study report)

	H+H†	I+H†	H+H†	I+H	H+H†	I+H
Component	No antipyretics		-6h to 12 h post booster		>12h post booster	
Anti-D	5,49 (4,94;6,11)	5.66 (4.87;6.58)	5.43 (4.33;6.81)	6.86 (5.48;8.58)	5.99 (4.50;7.98)	6.32 (4.89;8.17)
Anti-T	5,56 (4,97;6,23)	7.56 (6.53;8.76)	5.18 (4.20;6.40)	7.63 (5.65;10.3)	7.64 (5.80;10.1)	7.00 (4.66;10.5)
Anti- PT	154 (142;168)	145 (129; 163)	165 (139; 195)	128 (104; 158)	142 (114; 177)	146 (114; 187)
Anti-FHA	326 (298;358)	280 (243;323)	276 (232; 329)	232 (179; 300)	324 (248;423)	225 (152;334)
Anti-PRP	42,2 (35,7;49,8)	52.7 (43.3;64.2)	32.3 (22.5;46.5)	67.1 (49.4;91.2)	61.2 (45.6;82.2)	58.8 (37.5;92.2)
Anti-Hep B	9389 (7743;11386)	10189 (7820;13275)	5138 (3191;8273)	7686 (4983;11854)	10544 (6747;16480)	12642 (8358;19122)
Anti-polio 1	2124 (1889; 2388)	3257 (2731;3885)	1978 (1543;2536)	2914 (2181;3892)	2409 (1771;3275)	2048 (1352; 3103)
Anti-polio 2	4346 (3843;4914)	6589 (5630; 7713)	3892 (2961;5116)	6149 (4546; 8318)	4313 (3312;5617)	5312 (3453;8171)
Anti-polio 3	9389 (7743;11386)	5793 (4832;6944)	5138 (3191;8273)	7357 (5704;9488)	10544 (6747;16480)	4412 (2852;6826)

† **H+H**=Hexyon priming and booster; **I+H**= Infanrix hexa priming, Hexyon booster

Table 11 Effect of Stand Alone Oral Polio Vaccine on Anti –polio 1, 2 and 3 (MIT-WT-1/dil)-Subjects of Center 200-Summary of GMT-Per Protocol Analysis Set (source: Table 9.73 study report)

		Overall Subjects without OPV Standalone (N=231)			Overall Subjects with OPV Standalone (N=159)		
Component	Timepoint	M	Geometric mean	(95% CI)	M	Geometric mean	(95% CI)
Anti-polio 1 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	219	171	(142; 206)	152	480	(393; 587)
	Post-booster - V02 (D30)	223	2238	(1972; 2539)	150	2487	(2144; 2884)
Anti-polio 2 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	221	358	(293; 436)	152	1403	(1167; 1686)
	Post-booster - V02 (D30)	223	4200	(3702; 4765)	150	4115	(3611; 4689)
Anti-polio 3 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	219	177	(145; 217)	151	468	(372; 590)
	Post-booster - V02 (D30)	223	3697	(3218; 4247)	151	3868	(3318; 4508)

N: number of subjects analyzed according to the Per Protocol Analysis Set
n: number of subjects
M: number of subjects available for the endpoint
%: percentages are calculated according to the Per Protocol Analysis Set
All subjects were co-administered with Prevenar

Table 12 Effect of Stand Alone Oral Polio Vaccine on Anti –polio 1, 2 and 3 (MIT-WT-1/dil)-Subjects of Center 200-Seroprotection Rates-Per Protocol Analysis Set (source Table 9.77 study report

			Overall Subjects without OPV Standalone (N=231)			Overall Subjects with OPV Standalone (N=159)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-polio 1 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	>=8 (1/dil)	215/219	98.2	(95.4; 99.5)	151/152	99.3	(96.4; 100.0)
	Post-booster - V02 (D30)	>=8 (1/dil)	223/223	100.0	(98.4; 100.0)	150/150	100.0	(97.6; 100.0)
Anti-polio 2 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	>=8 (1/dil)	220/221	99.5	(97.5; 100.0)	152/152	100.0	(97.6; 100.0)
	Post-booster - V02 (D30)	>=8 (1/dil)	223/223	100.0	(98.4; 100.0)	150/150	100.0	(97.6; 100.0)
Anti-polio 3 (MIT-WT-1/dil)	Pre-booster - V01 (D0)	>=8 (1/dil)	213/219	97.3	(94.1; 99.0)	151/151	100.0	(97.6; 100.0)
	Post-booster - V02 (D30)	>=8 (1/dil)	223/223	100.0	(98.4; 100.0)	151/151	100.0	(97.6; 100.0)

N: Number of subjects analyzed according to Per Protocol Analysis Set
n: number of subjects; M: number of subjects available for the endpoint
%: percentages and 95% CI are calculated according to the subjects available for the endpoint
All subjects were co-administered with Prevenar

Table 6 and Table 7 show the persistence of the antibodies post dose three for the surrogate and correlates of protection (Table 6) as well as the GMTs (Table 7) for all antigens included in the hexavalent vaccines. Data from D140 derive from study A3L24 (MAH statement in study report page 145:" values calculated from data from the A3L24 primary series").

Diphtheria

Short-term protection threshold (≥0,01 IU/mL) was still fulfilled for nearly all subjects prior to the booster, long-term threshold (≥0,1 IU/mL) for 30-40% of all subjects with only minor differences between the groups. After the booster dose all subjects reached the long-term protection threshold. GMTs were similar for all groups at the different time-points.

Tetanus

Short-term protection threshold (≥0,01 IU/mL) was still fulfilled for nearly all subjects prior to the booster, long-term threshold (≥0,1 IU/mL) still for 70% of all subjects with only minor differences between the groups. After the booster dose all subjects reached the long-term protection threshold. GMTs were similar for all groups at the different time-points except for group 3 (Infanrix Hexa primed, Hexyon booster) that showed statistically significantly higher GMT (7,52 vs. 5,21 or 5,72 in the Hexyon primed groups). This difference is not considered clinically important as the thresholds are still met.

Hib (PRP)

Short-term protection threshold (≥0.15 µg /mL) was still fulfilled for ~70% of the subjects prior to the booster, long-term threshold (≥1 µg/mL) for ~30% of all subjects with only minor differences between the groups. After the booster dose all subjects reached the long-term protection threshold. Although the GMTs were not statistically different between the groups, group3 that had the lowest GMT after the priming with Infanrix hexa now shows the highest GMT after the Booster with Hexyon. Again, these differences are not considered clinically important.

Pertussis

A sufficient booster response (4-fold increase) after the booster was seen for both PT and FHA.

PT GMTs show that prior to the booster the GMTs have sunken from ~100 EU/ml across all groups to about 8 EU/ml across all groups. Due to the booster dose GMTs then reach values of 140-150 EU/ml with the significantly highest result of 191 UE/ml for group2 (Priming Hexyon, Booster Infanrix hexa).

FHA GMTs show that prior to the booster the GMTs have sunken from ~180-190 EU/ml across the two Hexon-primed groups (G1 + G2) and 120 for group 3 to about 14-23 EU/ml across all groups. Due to the booster dose GMTs then reach values of 260 EU/ml in group 3 and significantly higher results of 316 EU/ml for group 1 (Priming Hexyon, Booster Hexyon) and 418 EU/ml for group 2 (Priming Hexyon, Booster Infanrix hexa). Confidence intervals are not overlapping (reddened cells in Table 7). The clinical relevance of this observance (in absence of a definite threshold) can only be guessed in so far as a higher titre would be preferable. Nevertheless, given the rapid deterioration of Pertussis-antigen titres the differences observed are judged negligible.

Hepatitis B

Details on seroprotection rates can be seen in Table 6 above. Development of anti HBs response exceeding 10 mIU/mL is general accepted as a correlate for protective immunity against hepatitis, whereas 100 mIU/mL is the more conservative threshold.

Prior to the booster vaccination nearly all subjects were still seroprotected. The percentage of subjects with antibody titers above the threshold of 10mIU/mL was similar in the three groups with a range from 97.5% in group 1 to 99.2% in group 3. For the more conservative threshold seroprotection rates also were similar in the three groups with ranges from 82.2% (group 3) to 85.2% (group 2). Post-booster seroprotection rates were nearly 100% and equivalent for the three groups. 99.7% of subjects in group 1 and 99.5% of subjects in group 2 reached the threshold of 10 mIU/mL, in group 3 100% of subjects reached that threshold. The more conservative threshold was reached by 97.7% of subjects in group 1 and 2 and 99.2% of subjects in group 3, which is similar for the 3 groups.

Please see details on GMTs for hepatitis B virus in Table 7 above. GMTs have sunken about factor 10 after primary vaccination. The pre-and post-booster GMTs were of the same order of magnitude in all 3 groups

ranging from 336 (group 3) to 406 (group 2) pre-booster and 8462 (group 1) to 11218 (group 2) post-booster.

Taking together over 97% of all subjects were seroprotected with antibody titers ≥10 mIU/mL prior to the booster vaccination. The percentage of subjects with protective antibody titers was similar for the 3 groups. Immune response after booster vaccination was equivalent for the 3 groups with similar GMTs and seroprotection rates. Subjects following booster vaccination with Hexyon/Hexaxaim concomitant with Prevenar experienced a sufficient anti Hepatitis B immune response, regardless if the priming was done with Infanrix hexa or Hexaxim/Hexyon.

Polio

Details on seroprotection rates for the different polio virus types are given in Table 6 above. For polio types 1, 2 and 3 prior to the booster vaccination nearly all subjects were still seroprotected. Overall about 98% of all subjects presented antibody titers ≥ 8 (1/dil), the established correlate of protection The seroprotection rate was similar for the 3 groups, with ranges from 98.2% (group 2) to 98.8% (group 1) for anti-polio 1, from 99.4% (group 1) to 100% (group 2 and 3) for anti-polio 2, and from 94.8% (group 2) to 99.1% (group3) foranti- polio 3. After the booster vaccination all subjects were seroprotected against all poliovirus types, seroprotection rate was 100% in all 3 groups.

GMT values for the 3 poliovirus types can be seen in Table 7 above. Pre-and post-booster GMTs were higher for all 3 poliovirus types in group 3, primed with Infanrix hexa than in group 1 and group 2, primed with the investigational product Hexyon. This difference in GMTs was statistically significant for all parameters in group 3 compared to group 1 and except for the pre-booster GMT for poliovirus type 2 and post-booster GMT for poliovirus type 1 statistically significant in group 3 compared to group 2. However the achieved GMTs were high in all 3 groups and far exceeded the threshold of ≥ 8 (1/dil) so that the effect of higher GMTs in group 3 is not considered of clinical relevance.

In summary booster vaccination with Hexaxim/Hexyon concomitant with Prevenar induced a sufficient immune response against all 3 poliovirus types regardless if the priming has been done with Infanrix hexa or Hexaxim/Hexyon.

Effect of One Additional Oral Dose of Standalone Poliovirus Vaccine

From 2 to 27 May 2011, the Ministry of Health of Costa Rica and the Costa Rican Social Security

Institution scheduled a National Campaign of Intensification against Polio with OPV. The Polio campaign took place between completion of vaccinations on the primary series study (A3L24) and previous the initiation of the booster vaccination (A3L27). The effect of this additional dose of poliovirus vaccine in the immune responses to poliovirus serotypes 1, 2 and 3 in Costa Rica was therefore added as an observational objective. Subjects of Costa Rica who had participated at the National Campaign of Intensification against Polio with standalone oral poliovirus serotypes vaccine before inclusion in this trial were not included in the descriptive analysis of poliovirus 1, 2 and 3 antigens on the per protocol analysis set for the main analysis

Please find details on seroprotection rates and GMT values in the final clinical study report Table 9.70 to Table 9.77, page 451 to page 502. Exemplarily overall GMTs can be seen in Table 11 above. Prior to booster vaccination GMTs were significant higher in subjects with an additional OPV dose (5 doses of poliovirus vaccine altogether) than in subjects without (4 doses of poliovirus vaccine altogether). GMT ranged from 468 for poliovirus type 3 to 1403 for poliovirus type 2 in subjects with an additional poliovirus

vaccination and from 171 for poliovirus type 1 to 358 for poliovirus type 2 in subjects without an additional vaccination. However all pre-booster GMTs in subjects without an additional OPV vaccination exceeded the threshold of ≥ 8 (1/dil) and were equivalent for all 3 groups. After booster vaccination the GMTs were high and far exceeded the threshold of ≥ 8 (1/dil). The results regarding post-booster GMT values were similar for subjects with 4 doses compared to the subjects receiving 5 doses of poliovirus vaccination and equivalent for the 3 groups.

Pre- and post-booster seroprotection rates were similar for subjects with and without an additional poliovirus vaccination and for the three groups. Overall seroprotection rates can be seen in Table 12.above. Overall prior to the booster vaccination nearly all subjects were seroprotected. The overall pre-booster seroprotection rates in subjects without an additional OPV vaccination was more than 97% with ranges from 97.3% (poliovirus type 3) to 99.5% (poliovirus type 2). Overall pre-booster seroprotection rates for subjects who received an additional dose of poliovirus vaccine ranged from 99.3% for poliovirus type 1 to 100% for poliovirus type 2 and 3. Post-booster the seroprotection rate was 100% for all subjects in all groups against all poliovirus types.

Taking together there was no beneficial effect of an additional dose of oral polio vaccine administered between primary and booster vaccination with Hexyon/Hexaxima regarding seroprotection against any of the three poliovirus types or the GMTs. From the data presented the impact of the additional OPV vaccination on the Hexaxim/Hexyon valences cannot be assessed as there is no comparison of the Costa-Rican versus the other sites.

Pneumococcal serotypes in concomitant use with the two hexavalent vaccines

Table 8 shows that nearly all subjects reached the predefined threshold of ≥0,35 µg/ml after the booster dose regardless of which hexavalent vaccine has been concomitantly used for priming or booster. Table 9 shows the respective titres to be very similar with overlapping CIs.

Prophylactic use of antipyretics

Table 10 shows the comparison of both prime-booster combinations with and without prophylactic (-6h to 12h post booster) or later use (>12h post booster) of antipyretics in respect to the antigens contained in the hexavalent vaccines. In almost all cases the use of (prophylactic) antipyretics did not change the GMTs significantly. Only for the anti-PRP antibodies there is a statistically significant difference in GMTs in the prophylactic use regarding the combination of the hexavalent vaccines: subjects primed and boostered with Hexyon show a significantly ***lower GMT*** *(32.3 [22.5;46.5]) than subjects primed with Infanrix hexa and boostered with Hexyon (67.1 [49.4;91.2]). Nevertheless, although a slight difference regarding the threshold of long-term protection can also be seen (97.1 [90.1;99.7] versus 100 [94.4;100]) it is not statistically significant (Table 9.69 of the study protocol, data not shown in this AR). Thus, the observed difference is of doubtful clinical significance.*

For hepatitis B GMTs in group 1 (priming and booster vaccination with Hexyon) and group 3 (priming with Infanrix hexa, booster vaccination with Hexyon) were lower for subjects with antipyretic use in the 6 hours preceding the booster vaccination and 12 hours after vaccination than in subjects with no antipyretic use and subjects with antipyretic use more than 12hours after vaccination. Group 1 5138 versus 9389 and 10544 respectively, group 3 7686 versus 10189 and 12642 respectively. GMTs for the 3 poliovirus types in group 1 were also lower for subjects with antipyretic use in the 6 hours preceding the

booster vaccination and 12 hours after vaccination than in subjects with no antipyretic use and subjects with antipyretic use more than 12 hours after vaccination. In group 3 GMTs for subjects with antipyretic use more than 12 hours after vaccination were the lowest. For the detailed GMT values please also see Table 10 above.

Overall GMTs for hepatitis B and the 3 poliovirus types were high for all subjects and the observed differences were not statistically relevant. Therefore the findings seem not be of clinical relevance.

Safety

Table 13 Safety Overview After Booster Injection - Safety Analysis Set (source: Table 6.1, study report)

Primary vaccination	DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination	DTaP-IPV-Hep B-PRP-T Group 1 (N=416)			Infanrix hexa Group 2 (N=415)			DTaP-IPV-Hep B-PRP-T Group 3 (N=275)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Immediate unsolicited AE	0/416	0.0	(0.0; 0.9)	0/415	0.0	(0.0; 0.9)	0/275	0.0	(0.0; 1.3)
Immediate unsolicited AR	0/416	0.0	(0.0; 0.9)	0/415	0.0	(0.0; 0.9)	0/275	0.0	(0.0; 1.3)
Solicited reaction	322/413	78.0	(73.7; 81.9)	299/412	72.6	(68.0; 76.8)	219/272	80.5	(75.3; 85.1)
Solicited injection site reaction	271/413	65.6	(60.8; 70.2)	239/412	58.0	(53.1; 62.8)	184/272	67.6	(61.7; 73.2)
Solicited systemic reaction	270/413	65.4	(60.6; 70.0)	249/412	60.4	(55.5; 65.2)	198/272	72.8	(67.1; 78.0)
Unsolicited event	84/416	20.2	(16.4; 24.4)	97/415	23.4	(19.4; 27.7)	67/275	24.4	(19.4; 29.9)
Unsolicited reaction	5/416	1.2	(0.4; 2.8)	14/415	3.4	(1.9; 5.6)	5/275	1.8	(0.6; 4.2)
Unsolicited non-serious AE	82/416	19.7	(16.0; 23.9)	94/415	22.7	(18.7; 27.0)	66/275	24.0	(19.1; 29.5)
Unsolicited non-serious AR	5/416	1.2	(0.4; 2.8)	14/415	3.4	(1.9; 5.6)	5/275	1.8	(0.6; 4.2)
Unsolicited non-serious injection site AR	2/416	0.5	(0.1; 1.7)	2/415	0.5	(0.1; 1.7)	0/275	0.0	(0.0; 1.3)
Unsolicited non-serious systemic AE	80/416	19.2	(15.6; 23.4)	93/415	22.4	(18.5; 26.7)	66/275	24.0	(19.1; 29.5)
Unsolicited non-serious systemic AR	3/416	0.7	(0.1; 2.1)	12/415	2.9	(1.5; 5.0)	5/275	1.8	(0.6; 4.2)
AE leading to study discontinuation*	0/416	0.0	(0.0; 0.9)	0/415	0.0	(0.0; 0.9)	0/275	0.0	(0.0; 1.3)
SAE until V02	3/416	0.7	(0.1; 2.1)	5/415	1.2	(0.4; 2.8)	2/275	0.7	(0.1; 2.6)
Death until V02	0/416	0.0	(0.0; 0.9)	0/415	0.0	(0.0; 0.9)	0/275	0.0	(0.0; 1.3)
SAE during the six month follow-up period	10/416	2.4	(1.2; 4.4)	10/415	2.4	(1.2; 4.4)	7/275	2.5	(1.0; 5.2)
Death during the six month follow-up period	0/416	0.0	(0.0; 0.9)	0/415	0.0	(0.0; 0.9)	0/275	0.0	(0.0; 1.3)

N: number of subjects analyzed according to SafAS n: number of subjects M: number of subjects available for the endpoint
%: percentages and 95% CI are calculated according to the subjects available for the endpoint * Identified in the termination form as SAE or other AE
All subjects were co-administered with Prevenar

Table 14 Solicited Injection Site Reactions within 7 Days After Booster Injection – Safety Analysis Set (source: Table 6.2, study report)

Primary vaccination	DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination	DTaP-IPV-Hep B-PRP-T Group 1 (N=416)			Infanrix hexa Group 2 (N=415)			DTaP-IPV-Hep B-PRP-T Group 3 (N=275)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited injection site reaction	271/413	65.6	(60.8; 70.2)	239/412	58.0	(53.1; 62.8)	184/272	67.6	(61.7; 73.2)
Injection site pain	253/413	61.3	(56.4; 66.0)	221/412	53.6	(48.7; 58.5)	168/272	61.8	(55.7; 67.6)
Injection site erythema	127/413	30.8	(26.3; 35.4)	111/412	26.9	(22.7; 31.5)	93/272	34.2	(28.6; 40.2)
Injection site swelling	73/412	17.7	(14.2; 21.8)	63/412	15.3	(12.0; 19.1)	52/272	19.1	(14.6; 24.3)
Extensive swelling of vaccinated limb	0/413	0.0	(0.0; 0.9)	0/412	0.0	(0.0; 0.9)	0/272	0.0	(0.0; 1.3)
Grade 3 injection site reaction	17/413	4.1	(2.4; 6.5)	12/412	2.9	(1.5; 5.0)	13/272	4.8	(2.6; 8.0)

N: number of subjects analyzed according to SafAS n: number of subjects M: number of subjects available for the endpoint
%: percentages and 95% CI are calculated according to the subjects available for the endpoint
Note: For each individual solicited reaction, 'n' is based on any reaction after any of the two vaccinations (study vaccine or Prevenar)

Table 15 Solicited Systemic Reactions within 7 Days After Booster Injection – Safety Analysis Set (source: Table 6.4, study report)

Primary vaccination	DTaP-IPV-Hep B-PRP-T						Infanrix hexa		
Booster vaccination	DTaP-IPV-Hep B-PRP-T			Infanrix hexa			DTaP-IPV-Hep B-PRP-T		
	Group 1 (N=416)			Group 2 (N=415)			Group 3 (N=275)		
	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Subjects experiencing at least one:									
Solicited systemic reaction	270/413	65.4	(60.6; 70.0)	249/412	60.4	(55.5; 65.2)	198/272	72.8	(67.1; 78.0)
Pyrexia	114/413	27.6	(23.3; 32.2)	99/412	24.0	(20.0; 28.5)	91/272	33.5	(27.9; 39.4)
Vomiting	34/413	8.2	(5.8; 11.3)	39/412	9.5	(6.8; 12.7)	19/272	7.0	(4.3; 10.7)
Crying	148/413	35.8	(31.2; 40.7)	139/412	33.7	(29.2; 38.5)	102/272	37.5	(31.7; 43.5)
Somnolence	124/413	30.0	(25.6; 34.7)	113/412	27.4	(23.2; 32.0)	85/272	31.3	(25.8; 37.1)
Anorexia	118/413	28.6	(24.3; 33.2)	121/412	29.4	(25.0; 34.0)	90/272	33.1	(27.5; 39.0)
Irritability	201/413	48.7	(43.8; 53.6)	176/412	42.7	(37.9; 47.7)	146/272	53.7	(47.6; 59.7)
Grade 3 systemic reaction	6/413	1.5	(0.5; 3.1)	14/412	3.4	(1.9; 5.6)	9/272	3.3	(1.5; 6.2)

N: number of subjects analyzed according to SafAS n: number of subjects M: number of subjects available for the endpoint
%: percentages and 95% CI are calculated according to the subjects available for the endpoint
Note: For each individual solicited reaction, 'n' is based on any reaction after any of the two vaccinations (study vaccine or Prevenar)

Table 16 Summary of Non-Serious Unsolicited AEs Within 30 Days After Booster Injection - Safety Analysis Set (source: Table 6.5, study report)

Primary vaccination	DTaP-IPV-Hep B-PRP-T								Infanrix hexa			
Booster vaccination	DTaP-IPV-Hep B-PRP-T Group 1 (N=416)				Infanrix hexa Group 2 (N=415)				DTaP-IPV-Hep B-PRP-T Group 3 (N=275)			
Subjects experiencing at least one:	n	%	(95% CI)	n AEs	n	%	(95% CI)	n AEs	n	%	(95% CI)	n AEs
Unsolicited non-serious AE	82	19.7	(16.0; 23.9)	105	94	22.7	(18.7; 27.0)	113	66	24.0	(19.1; 29.5)	81
Grade 3 unsolicited non-serious AE	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 1.3)	0
Unsolicited non-serious AR	5	1.2	(0.4; 2.8)	5	14	3.4	(1.9; 5.6)	24	5	1.8	(0.6; 4.2)	6
Grade 3 unsolicited non-serious AR	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 1.3)	0
Unsolicited non-serious injection site AR	2	0.5	(0.1; 1.7)	2	2	0.5	(0.1; 1.7)	2	0	0.0	(0.0; 1.3)	0
Grade 3 unsolicited non-serious injection site AR	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 1.3)	0
Unsolicited non-serious systemic AE	80	19.2	(15.6; 23.4)	103	93	22.4	(18.5; 26.7)	111	66	24.0	(19.1; 29.5)	81
Grade 3 unsolicited non-serious systemic AE	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 1.3)	0
Unsolicited non-serious systemic AR	3	0.7	(0.1; 2.1)	3	12	2.9	(1.5; 5.0)	22	5	1.8	(0.6; 4.2)	6
Grade 3 unsolicited non-serious systemic AR	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 0.9)	0	0	0.0	(0.0; 1.3)	0

N: number of subjects analyzed according to SafAS
n AEs: number of AEs
All subjects were co-administered with Prevenar
n: number of subjects experiencing the endpoint listed in the first column
%: percentages and 95% CI are calculated according to the subjects available for the endpoint

Overall, the rate and severity of adverse events and reactions is similar between the groups (Table 13). No grade 3 solicited or unsolicited reactions were seen (Table 16) with nasopharingitis the most common AE within the first 30 days after the vaccination. The rate of both injection site and systemic reactions is very similar in all groups as can be seen in Table 14 and Table 15 with pain and irritability the most common reactions. Also, there is no significant difference between the hexavalent-vaccine-arm and the Prevenar-arm (data not shown but included in study report).

There were no deaths in this study.

"Extensive limb swelling", that had been defined as a case of special interest, was also not seen in this study.

Of the 38 SAEs that occurred during the complete study duration none were judged related to the vaccines:

One case of Kawasaki disease occurred 153 days post booster immunization with Hexyon, the child completely recovered and continued in the study.

The febrile seizures that were seen were of similar rate in the three groups (G1:1, G2:2, G3:1) and all occurred 101d, 39d, 33d and 15d after the booster vaccinations. All children had concomitant infections, all recovered and continued in the trial.The most common other SAEs were infections not related to the vaccinations. The assessor concurs with the judgement that the SAEs seen were not related to the vaccinations.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

For antigens with correlates of protection all thresholds were met after the booster dose in all groups. Booster responses against Pneumococcal and Pertussis antigens were also equivalent in all groups.

Booster vaccination with Hexaxim/Hexyon concomitant with Prevenar induced a sufficient immune response against all 3 poliovirus types regardless if the priming has been done with Infanrix hexa or Hexaxim/Hexyon. The higher GMTs seen in the group primed with Infanrix hexa are not considered of clinical relevance.

Also booster responses against hepatitis B virus were equivalent in all study groups with similar seroprotection rates and GMTs.

There was no effect on seroprotection rates or GMTs for any of the 3 poliovirus types regarding subjects with an additional dose of poliovirus vaccine compared to subjects who did not receive this additional vaccination.

The lower GMTs for hepatitis B in subjects with prophylactic antipyretic use in the 6 hours preceding the booster vaccination and 12 hours after vaccination are deemed not to be of clinical relevance.

Regarding GMTs minor differences were seen for Tetanus, Hib and Pertussis (FHA only) but are judged of negligible clinical effect. The same holds true for the observed lower anti-PRP GMT in the group using only Hexyon with antipyretics used as prophylactic.

Safety assessment shows equivalence of the rate and severity of AEs in all groups. No deaths occurred in this study. The SAEs seen were all unrelated to the vaccinations and none of the cases of special interest were seen in the study.

There is no text change necessary for the common English SmPC but it was seen that at least the German translation – which included the term "Grundimmunisierung" [primary vaccination] in the concomitant use text regarding pneumococcal polysaccharide conjugated vaccine (PCV7) – needs to be amended.

Recommendation

☒ **Fulfilled** –

The MAH is requested to amend the **German translation of the product information** in the next upcoming procedure affecting the Annexes as follows:

4.5 Wechselwirkungen mit anderen Arzneimitteln und sonstige Wechselwirkungen

Daten über die zeitgleiche Verabreichung von Hexyon mit einem Pneumokokken-Polysaccharid-Konjugatimpfstoff zeigten ~~bei der Grundimmunisierung~~ keine klinisch relevante Beeinträchtigung der Antikörperantwort auf die einzelnen Antigene.

Reason: The German translation mentions the non-interference at the time-point of primary vaccination only. The English original does not include the term, thus, needs not to be amended with the new data from the booster. Whether this change is also necessary for other languages should be checked.