EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

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

Hexaxim / Hexacima / Hexyon

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/W/002495 / P46 020 (Hexaxim)
EMEA/H/C/002702 / P46 020 (Hexacima)
EMEA/H/C/002796 / P46 018 (Hexyon)

Note

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

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1. Introduction

On 30 October 2016, the MAH submitted a completed paediatric study **A3L40** for Hexaxim/ Hexacima/ Hexyon, 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 balance for Hexaxim™/Hexacima™/Hexyon™ and that no consequential regulatory action is required.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A3L40 "Booster Effect and Safety of a DTaP-IPV-Hib Combined Vaccine, with or without Hep B, in Healthy Subjects 11 to 18 Months of Age Who Received a Hexavalent or Hexavalent/Pentavalent Combined Vaccine during the Primary Series" is a standalone study.

This study is the immunogenicity follow-up and booster study for the previously assessed study A3L39.

2.2. Information on the pharmaceutical formulation used in the study

As in initial MAA

2.3. Clinical aspects

2.3.1. Introduction

Hexaxim™/Hexacima™/Hexyon™ is indicated for active immunisation (primary and booster vaccination) of infants and toddlers from six weeks of age against diphtheria (D), tetanus (T), pertussis, Hepatitis B (Hep B), poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

The MAH submitted the final report for:

A3L40:

"Booster Effect and Safety of a DTaP-IPV-Hib Combined Vaccine, with or without Hep B, in Healthy Subjects 11 to 18 Months of Age Who Received a Hexavalent or Hexavalent/Pentavalent Combined Vaccine during the Primary Series"

This clinical study A3L40 is a Phase III long-term antibody persistence and booster effect study and was conducted in Czech Republic, Germany and Spain with 663 children who completed a 3-dose primary series (DTaPIPV-Hep B-PRP-T or Infanrix™ hexa), concomitantly administered with Prevenar™ (PCV7) (3 doses) and Rotateq™ (3 doses) in study A3L39.

This study was not conducted as part of the EU-approved Paediatric Investigational Plan for this product (EMEA 001201-PIP01-11-M02).

2.3.2. Clinical study

A3L40: "Booster Effect and Safety of a DTaP-IPV-Hib Combined Vaccine, with or without Hep B, in Healthy Subjects 11 to 18 Months of Age Who Received a Hexavalent or Hexavalent/Pentavalent Combined Vaccine during the Primary Series"

Description

Primary immunization (Hexacim or Infanrix hexa both concomitantly given with Prevenar and RotaTeq) had been done in study A3L39. Subjects now in this study kept the subject number from A3L39 and received a booster vaccination. Of note is the age of participants in the different groups: Groups 1 + 2 were~12 months old children whilst in Group 3 the children were ~18 months old. This was due to the structure of the different vaccination schedules used in study A3L39.

Methods

Study design

Inclusion and exclusion criteria followed that of the previous studies. Medical history was checked prior to inclusion as well as further vaccinations made between studies (HepA vaccination allowed).

Diary cards were provided.

Laboratory assays were the same as for the previous studies; analysis was done at the sponsor's laboratory in Swiftwater, USA or at Institute of Child Health in the United Kingdom (University College London).

Table 1 Assays and Units for Immunogenicity (source: study report)

Antigen	Assays and reference standards	Units
Diphtheria	Toxin neutralization test (WHO standard)	IU/ml
Tetanus	ELISA (WHO standard)	IU/ml
Pertussis (PT, FHA)	ELISA	EU/ml
Hib (PRP)	Farr-type radioimmunoassay (CBER standard)	µg/mL
HepB	VITROS ECi/ECiQ (WHO standard)	mIU/mL
Polio (IPV1, 2, 3)	Vero cell neutralization test	1/dilution

Study population /Sample size

As this was the extension study of the then not yet analysed A3L39 the group allocation of the subjects (G1 and G2 observer-blind in DE and CS, G3 open only in ES) stayed the same for all children continuing with this study. Allocation numbers in DE and CS were requested via IVRS.

Concomitant use of Prevenar 13 was only done for G1 and G2, for G3 this was optional.

Vaccination scheme:

G1: **Hexyon** + Prevenar13 at 11-15 Month of Age (MoA)
G2: **Infanrix hexa** + Prevenar13 at 11-15 MoA
G3: ***Pentavac*** + Prevenar13 at 18 MoA
The different booster vaccines are due to the previous study's conduct.

Inclusion and exclusion criteria continue from study A3L39, mainly all subjects are still to be generally healthy. Prerequisite was participation in study A3L39.

Blood draws for immunogenicity were planned for D0 (baseline) and D30 post vaccination.

Reactogenicity was assessed during the first 7 days after vaccination, unsolicited AEs for 30 days and SAEs as well as AESIs during the complete trial duration.

Objectives

Groups 1 and 2

- To describe the **safety profile after a booster dose** of a DTaP-IPV-HB-Hib or Infanrix hexa administered at 11 to 15 MoA concomitantly with a booster dose of PCV13Group 3To describe the safety profile after a booster dose of Pentavac vaccine administered at 18 MoA concomitantly with a booster dose of PCV13
- Assess the **antibody persistence** of DTaP-IPV-HB-Hib or Infanrix hexa following a 3-dose primary series at **2, 3, and 4 months** of age (MoA) before the administration of a booster dose of either vaccine
- Describe the **immunogenicity and booster effect** of the **DTaP-IPV-HB-Hib or Infanrix hexa** vaccine given as a booster dose **at 11 to 15 MoA** concomitantly with PCV13 (after a primary series with the same vaccine)
- To describe the **immunogenicity of a booster dose of PCV13** given from 11 to 15 MoA

Group 3

- Assess the **antibody persistence** of all valences contained in the vaccines administered in a mixed schedule following a 3-dose primary series at **2, 4, and 6 MoA** before the administration of a booster dose of Pentavac
- Describe the **immunogenicity and booster effect of Pentavac** given **at 18 MoA** after the administration of a mixed schedule primary series combining a hexavalent and a pentavalent vaccine

Outcomes/endpoints

Primary:

Ab Persistence
The following endpoints will be used to assess the Ab persistence (for all valences except PCV13 antigens) before the booster doses at Day 0 (D0) (Visit 1 [V01]) of the study vaccines:
• Ab concentrations/titers for each valence
• Ab concentrations/titers above a pre-determined cut-off:

• Anti-D Ab concentrations ⩾ 0.01 IU/mL and ⩾ 0.1 IU/mL
• Anti-T Ab concentrations ⩾ 0.01 IU/mL and ⩾ 0.1 IU/mL
• Anti-poliovirus 1, 2 and 3 titers ⩾ 8 (1/dil)
• Anti-Hep B Ab concentrations ⩾ 10 mIU/mL and ⩾ 100 mIU/mL
• Anti-PRP Ab concentrations ⩾ 0.15 µg/mL and ⩾ 1.0 µg/mL
• Anti-PT and anti-FHA Ab concentrations ⩾ Lower Limit Of Quantitation (LLOQ)

Booster Effect:
The following endpoints will be used to assess the booster response for all antigens at D30 (V02):
• Ab concentrations/titers for each valence (including PCV13 for Groups 1 and 2 only)
• Ab concentrations/titers levels higher than a pre-determined cut-off:
• Anti-D Ab concentrations ⩾ 0.01 IU/mL, ⩾ 0.1 IU/mL, and ⩾ 1.0 IU/mL
• Anti-T Ab concentrations ⩾ 0.01 IU/mL, ⩾ 0.1 IU/mL, and ⩾ 1.0 IU/mL
• Anti-poliovirus 1, 2 and 3 titers ⩾ 8 (1/dil)
• Anti-Hep B Ab concentrations ⩾ 10 mIU/mL and ⩾ 100 mIU/mL (Groups 1 and 2 only)
• Anti-PRP Ab concentrations ⩾ 0.15 µg/mL and ⩾ 1.0 µg/mL
• Anti-pneumococcal serotype 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F concentrations ⩾ 0.35 µg/mL (Groups 1 and 2 only)
• Individual concentration/titer ratio for each valence (D30 [V02]/D0 [V01]), except for PCV13 antigens
• Seroconversion for pertussis Ab (anti-PT and anti-FHA) defined as:
• Anti-PT and anti-FHA ⩾ 4-fold Ab titers increase from D0 (V01) to D30 (V02)
• Booster response to pertussis (PT and FHA) defined as:
• Subjects whose pre-vaccination Ab concentrations are less than the < LLOQ, will demonstrate the booster response if they have postvaccination 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 Endpoints:

• Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after booster vaccination
• Occurrence of solicited, i.e. pre-listed in the subject' s diary and electronic case report form (eCRF), injection site and systemic reactions occurring up to 7 days after booster vaccination
• Occurrence of unsolicited (spontaneously reported) AEs up to 30 days after booster vaccination
• Occurrence of adverse events of special interest (AESIs) and SAEs, throughout the trial period
• Other endpoints recorded or derived will be described at the time of statistical analysis plan.
Depending on the item, these could include: nature (MedDRA preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome

Statistical Methods

Table 2 Descriptive statistics produced (source: Table 3.6, study report)

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs]) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer/data)	Log_{10}: Mean and standard deviation. Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

Ab persistence at 11 to 18 months of age following a three-dose primary series vaccination was one of the main objectives, the immunogenicity data and group variables from the A3L39 study were used.

Immunogenicity endpoints were described for available blood samples before the booster dose and 1 month after the booster dose of either study combined vaccine. The following parameters were used:

Ab Persistence (Pre-Booster Dose):

• GM of Ab concentrations/titers before the booster dose (pre-booster dose) for all antigens except PCV13 antigens

• Percentage of subjects with concentrations/titers above predefined thresholds at pre-booster dose, including thresholds used to define seroprotection for all antigens except PCV13 antigens

Booster Effect Post-Vaccination:

• GM of Ab concentrations/titers after the booster dose (post-booster dose) for all antigens in Groups 1 and 2 and for all antigens except PCV13 antigens in Group 3

• GM of individual Ab concentrations/titers ratio post/pre-booster dose for all antigens, except for PCV13 antigens

• Percentage of subjects with concentrations/titers above predefined thresholds at post-booster dose, including those thresholds that define seroprotection for all antigens in Groups 1 and 2 and for all antigens except PCV13 and Hep B antigens in Group 3

• Seroconversion rates for PT and FHA antigens

• Booster vaccine response rate for PT and FHA antigens

Subjects who received a dose of pneumococcal vaccine between the end of the primary series and before the booster dose were excluded from the analysis of PCV13 antigens.

95% confidence intervals (CIs) were calculated:

• using the exact binomial method (Clopper-Pearson method) for single proportions

• using the normal approximation of the Log10 titers, followed by a back transformation for geometric mean concentrations/titers (GMCs/GMTs)

Reverse cumulative distribution curves for each Ab criterion are presented.

Additionally for each Ab criterion, kinetic curves based on GMC or GMT at each time point were plotted including the primary series and booster time points.

Results

Number analysed

There were 662 subjects (99.8%) included in the FAS.

A total of 648 subjects (97.7%) were included in the FAS for Ab persistence, i.e., 229 subjects (97.9%), 224 subjects (97.0%), and 195 subjects (98.5%) in Group 1, 2, and 3, respectively.

A total of 632 subjects (95.3%) were included in the PP analysis set, i.e., 225 subjects (96.2%) in Group 1, 218 subjects (94.4%) in Group 2, and 189 subjects (95.5%) in Group 3.

After booster injection, 662 subjects (99.8%) were included in the SafAS, i.e., 236 subjects in Group 1, 228 subjects in Group 2 and 198 subjects in Group 3.

Male/Female ratio was near 50% in all three groups.

The mean age of the subjects was **12.4** months (± 0.5 months) in Group **1**, **12.5** months (± 0.6 months) in Group **2** and **18.1** months (± 0.3 months) in Group **3**.

Immunogenicity results

Groups 1+2 (2, 3, 4 months primary immunization)

Persistence of antibodies was similar in both groups for most antigens. After the booster dose the percentage of subjects achieving the predefined seroprotection or seroconversion threshold for each antigen is similar across the groups for most antigens regardless whether Hexyon or Infanrix hexa had been used for priming and booster. For HepB and IPV1 the lower titres known from the post primary stage of study A3L39 are continued in the Hexon groups ending in statistical significantly lower GMs pre-booster as well as after the booster dose. For HepB the rate of subjects showing seroprotection of ≥10mIU/ml is ~10% lower in the Hexyon group than in the Infanrix hexa group and for ≥100mIU/ml it is even ~20% lower (<50%). The reverse cumulation curve for HepB can be found below in Figure 1; what is important is that both curves follow the same kinetic, both curves show the same fold-increase of titres and thus a low or negative anti-HBs result does not necessarily indicate lack of immunity in vaccinated persons: it is immune memory that matters and an anamnestic response was measured shortly after offering a booster dose.

Anti-PT GMs are also lower in the Hexyon group but not as pronounced as for HepB and IPV1. A clinically relevant impact is not expected here.

Details can be found in Table 3, GMTs/GMCs are shown further below in Table 4.

Serotypes 3, 6B, 7f, 19A, 19F show statistically significantly lower GMs in the Hexyon concomitant use than with Infanrix hexa but the CI are mostly just missing the overlap. As the seroprotection rates are similar in both groups no clinical relevance is attributed to this observation. Details can be found in Table 5 and Table 6.

Table 3 Antibody persistence and booster response rates for study vaccines - Per Protocol Analysis Set (source: Table 3.2, clinical-overview)

			Group 1 (N=225)			Group 2 (N=218)		
			n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-D (IU/mL)	>=0.01 IU/mL	Primary series post-dose 3	206/206	100.0	(98.2; 100)	203/203	100.0	(98.2; 100)
		Pre-Booster (V01)	196/199	98.5	(95.7; 99.7)	200/201	99.5	(97.3; 100)
		Post-Booster (V02)	190/190	100.0	(98.1; 100)	197/197	100.0	(98.1; 100)
	>=0.1 IU/mL	Primary series post-dose 3	129/206	62.6	(55.6; 69.2)	121/203	59.6	(52.5; 66.4)
		Pre-Booster (V01)	128/199	64.3	(57.2; 71.0)	96/201	47.8	(40.7; 54.9)
		Post-Booster (V02)	190/190	100.0	(98.1; 100)	197/197	100.0	(98.1; 100)
	>=1.0 IU/mL	Primary series post-dose 3	12/206	5.8	(3.05; 9.95)	11/203	5.4	(2.74; 9.49)
		Post-Booster (V02)	179/190	94.2	(89.9; 97.1)	185/197	93.9	(89.6; 96.8)
Anti-T (IU/mL)	>=0.01 IU/mL	Primary series post-dose 3	212/212	100.0	(98.3; 100)	203/203	100.0	(98.2; 100)
		Pre-Booster (V01)	209/209	100.0	(98.3; 100)	202/202	100.0	(98.2; 100)
		Post-Booster (V02)	211/211	100.0	(98.3; 100)	209/209	100.0	(98.3; 100)
	>=0.1 IU/mL	Primary series post-dose 3	211/212	99.5	(97.4; 100)	203/203	100.0	(98.2; 100)
		Pre-Booster (V01)	179/209	85.6	(80.1; 90.1)	173/202	85.6	(80.0; 90.2)
		Post-Booster (V02)	211/211	100.0	(98.3; 100)	209/209	100.0	(98.3; 100)
	>=1.0 IU/mL	Primary series post-dose 3	77/212	36.3	(29.8; 43.2)	87/203	42.9	(36.0; 50.0)
		Post-Booster (V02)	204/211	96.7	(93.3; 98.7)	200/209	95.7	(92.0; 98.0)
Anti-PT (EU/mL)	>=LLOQ *	Primary series post-dose 3	219/219	100.0	(98.3;100)	213/213	100.0	(98.3; 100)
		Pre-Booster (V01)	207/208	99.5	(97.4; 100)	203/203	100.0	(98.2; 100)
	Post-Booster (V02) / Pre-Booster (V01)	Booster vaccine response†	197/203	97.0	(93.7; 98.9)	197/201	98.0	(95.0; 99.5)
		Seroconversion ‡	160/203	78.8	(72.5; 84.2)	160/201	79.6	(73.4; 84.9)

			Group 1 (N=225)			Group 2 (N=218)		
			n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-FHA (EU/mL)	**>=LLOQ ***	**Primary series post-dose 3**	219/219	100.0	(98.3; 100)	213/213	100.0	(98.3; 100)
		Pre-Booster (V01)	216/216	100.0	(98.3; 100)	205/205	100.0	(98.2; 100)
	Post-Booster (V02) / Pre-Booster (V01)	**Booster vaccine response†**	201/212	94.8	(90.9; 97.4)	190/202	94.1	(89.9; 96.9)
		Seroconversion ‡	128/212	60.4	(53.5; 67.0)	163/202	80.7	(74.6; 85.9)
Anti-Polio 1 (1/dil)	**>=8 (1/dil)**	**Primary series post-dose 3**	208/208	100.0	(98.2; 100)	205/205	100.0	(98.2; 100)
		Pre-Booster (V01)	169/202	83.7	(77.8; 88.5)	191/204	93.6	(89.3; 96.6)
		Post-Booster (V02)	195/196	99.5	(97.2; 100)	203/203	100.0	(98.2; 100)
Anti-Polio 2 (1/dil)	**>=8 (1/dil)**	**Primary series post-dose 3**	214/214	100.0	(98.3; 100)	206/206	100.0	(98.2; 100)
		Pre-Booster (V01)	182/206	88.3	(83.2; 92.4)	185/204	90.7	(85.8; 94.3)
		Post-Booster (V02)	207/207	100.0	(98.2; 100)	208/208	100.0	(98.2; 100)
Anti-Polio 3 (1/dil)	**>=8 (1/dil)**	**Primary series post-dose 3**	215/215	100.0	(98.3; 100)	206/206	100.0	(98.2; 100)
		Pre-Booster (V01)	188/206	91.3	(86.5; 94.7)	188/201	93.5	(89.2; 96.5)
		Post-Booster (V02)	208/208	100.0	(98.2; 100)	207/207	100.0	(98.2; 100)
Anti-Hep B (mIU/mL)	**>=10 mIU/mL**	**Primary series post-dose 3**	211/217	97.2	(94.1; 99.0)	208/211	98.6	(95.9; 99.7)
		Pre-Booster (V01)	190/221	86.0	(80.7; 90.3)	207/213	97.2	(94.0; 99.0)
		Post-Booster (V02)	224/225	99.6	(97.5; 100)	216/216	100.0	(98.3; 100)
	>=100 mIU/mL	**Primary series post-dose 3**	160/217	73.7	(67.3; 79.5)	183/211	86.7	(81.4; 91.0)
		Pre-Booster (V01)	99/221	44.8	(38.1; 51.6)	143/213	67.1	(60.4; 73.4)
		Post-Booster (V02)	212/225	94.2	(90.3; 96.9)	212/216	98.1	(95.3; 99.5)
Anti-PRP (µg/mL)	**>=0.15 µg/mL**	**Primary series post-dose 3**	192/212	90.6	(85.8; 94.1)	177/207	85.5	(80.0; 90.0)
		Pre-Booster (V01)	154/214	72.0	(65.4; 77.9)	120/208	57.7	(50.7; 64.5)
		Post-Booster (V02)	208/208	100.0	(98.2; 100)	212/213	99.5	(97.4; 100)
	>=1.0 µg/mL	**Primary series post-dose 3**	131/212	61.8	(54.9; 68.4)	77/207	37.2	(30.6; 44.2)
		Pre-Booster (V01)	58/214	27.1	(21.3; 33.6)	19/208	9.1	(5.59; 13.9)
		Post-Booster (V02)	201/208	96.6	(93.2; 98.6)	203/213	95.3	(91.5; 97.7)

*: LLOQ = 2 EU/mL.
† Booster vaccine response rate for PT and FHA antigens, defined as Post-booster Ab concentrations greater or equal to 4-fold rise if pre-booster Ab concentrations < 4x LLOQ or Post-booster Ab concentrations greater or equal to 2-fold rise if pre-booster Ab concentrations greater or equal to 4x LLOQ
‡ Seroconversion rates for PT and FHA antigens defined as: Anti-PT and anti-FHA ≥ 4-fold Ab titers increase from D0 (V01) to D30 (V02)
n: number of subjects experiencing the endpoint listed in the first three columns M: number of subjects with available data for the relevant endpoint
Group 1: DTaP-IPV-HB-Hib + PCV13 (at 11 to 15 MoA), Group 2: Infanrix hexa + PCV13 (at 11 to 15 MoA)

Table 4 Geometric means for study vaccines – Per Protocol Analysis Set (source: Table 3.3, clinical-overview)

		Group 1 (N=225)			Group 2 (N=218)		
		M	GM	(95% CI)	M	GM	(95% CI)
Anti-D (IU/mL)	Primary series post-dose 3	206	0.174	(0.151; 0.201)	203	0.155	(0.135; 0.177)
	Pre-Booster (V01)	199	0.172	(0.141; 0.208)	201	0.107	(0.091; 0.126)
	Post-Booster (V02)	190	6.08	(5.08; 7.27)	197	4.10	(3.52; 4.78)
	Post-Booster (V02)/ Pre-Booster (V01)	175	32.8	(26.6; 40.4)	186	38.4	(31.6; 46.6)
Anti-T (IU/mL)	Primary series post-dose 3	212	0.770	(0.693; 0.856)	203	0.872	(0.784; 0.971)
	Pre-Booster (V01)	209	0.272	(0.238; 0.312)	202	0.253	(0.222; 0.287)
	Post-Booster (V02)	211	4.32	(3.82; 4.88)	209	3.78	(3.39; 4.21)
	Post-Booster (V02)/ Pre-Booster (V01)	198	16.2	(14.3; 18.3)	196	15.0	(13.4; 16.8)
Anti-PT (EU/mL)	Primary series post-dose 3	219	114	(106; 123)	213	133	(123; 144)
	Pre-Booster (V01)	208	16.1	(14.5; 17.9)	203	21.4	(19.2; 23.8)
	Post-Booster (V02)	219	112	(102; 122)	216	158	(144; 173)
	Post-Booster (V02)/Pre-Booster (V01)	203	7.28	(6.54; 8.10)	201	7.38	(6.69; 8.14)
Anti-FHA (EU/mL)	Primary series post-dose 3	219	139	(129; 149)	213	85.2	(78.6; 92.3)
	Pre-Booster (V01)	216	34.2	(30.9; 37.9)	205	24.9	(22.1; 27.9)
	Post-Booster (V02)	219	172	(158; 187)	213	173	(158; 189)
	Post-Booster (V02)/Pre-Booster (V01)	212	5.07	(4.63; 5.54)	202	6.96	(6.26; 7.74)
Anti-Polio 1 (1/dil)	Primary series post-dose 3	208	110	(93.6; 130)	205	269	(224; 322)
	Pre-Booster (V01)	202	38.8	(30.8; 48.8)	204	80.6	(65.7; 99.0)
	Post-Booster (V02)	196	1070	(880; 1302)	203	2696	(2283; 3184)
	Post-Booster (V02)/Pre-Booster (V01)	181	26.8	(21.6; 33.3)	193	33.6	(27.1; 41.7)
Anti-Polio 2 (1/dil)	Primary series post-dose 3	214	192	(162; 227)	206	358	(295; 435)
	Pre-Booster (V01)	206	51.0	(41.0; 63.5)	204	75.6	(60.7; 94.1)
	Post-Booster (V02)	207	1858	(1576; 2192)	208	2887	(2449; 3403)
	Post-Booster (V02)/ Pre-Booster (V01)	192	36.8	(29.7; 45.7)	197	37.6	(31.0; 45.7)
Anti-Polio 3 (1/dil)	Primary series post-dose 3	215	300	(256; 352)	206	702	(584; 845)
	Pre-Booster (V01)	206	68.7	(56.6; 83.4)	201	135	(109; 166)
	Post-Booster (V02)	208	2301	(1924; 2752)	207	3902	(3265; 4662)
	Post-Booster (V02)/Pre-Booster (V01)	193	33.7	(27.8; 40.8)	192	29.8	(24.4; 36.3)
Anti-Hep B (mIU/mL)	Primary series post-dose 3	217	230	(188; 281)	211	376	(316; 448)
	Pre-Booster (V01)	221	74.6	(59.7; 93.2)	213	169	(140; 203)
	Post-Booster (V02)	225	2140	(1707; 2683)	216	4642	(3837; 5616)
	Post-Booster (V02)/Pre-Booster (V01)	221	29.2	(25.0; 33.9)	212	27.9	(24.3; 31.9)
Anti-PRP (µg/mL)	Primary series post-dose 3	212	1.32	(1.07; 1.62)	207	0.596	(0.497; 0.714)
	Pre-Booster (V01)	214	0.383	(0.308; 0.476)	208	0.173	(0.144; 0.209)
	Post-Booster (V02)	208	28.8	(23.6; 35.1)	213	16.5	(13.6; 19.8)
	Post-Booster (V02)/Pre-Booster (V01)	198	72.3	(59.3; 88.2)	203	91.8	(76.1; 111)

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

Group 1: DTaP-IPV-HB-Hib + PCV13 (at 11 to 15 MoA), Group 2: Infanrix hexa + PCV13 (at 11 to 15 MoA), Group 3: Pentavac + PCV13 (at 18 MoA)

Table 5 Summary of seroprotection rates for Prevenar 13 vaccine - Per Protocol Analysis Set (source: Table 5.3, study report)

		Group 1 (N=225)			Group 2 (N=218)		
Pneumococcal serotypes		n/M	%	(95% CI)	n/M	%	(95% CI)
Serotype 1 (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	206/207	99.5	(97.3; 100)
Serotype 3 (µg/mL)	Post-Booster (V02)	158/191	82.7	(76.6; 87.8)	166/184	90.2	(85.0; 94.1)
Serotype 4 (µg/mL)	Post-Booster (V02)	205/207	99.0	(96.6; 99.9)	206/207	99.5	(97.3; 100)
Serotype 5 (µg/mL)	Post-Booster (V02)	202/206	98.1	(95.1; 99.5)	205/207	99.0	(96.6; 99.9)
Serotype 6A (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	207/207	100.0	(98.2; 100)
Serotype 6B (µg/mL)	Post-Booster (V02)	202/204	99.0	(96.5; 99.9)	206/206	100.0	(98.2; 100)
Serotype 7F (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	207/207	100.0	(98.2; 100)
Serotype 9V (µg/mL)	Post-Booster (V02)	205/207	99.0	(96.6; 99.9)	206/207	99.5	(97.3; 100)
Serotype 14 (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	207/207	100.0	(98.2; 100)
Serotype 18C (µg/mL)	Post-Booster (V02)	201/207	97.1	(93.8; 98.9)	204/207	98.6	(95.8; 99.7)
Serotype 19A (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	205/205	100.0	(98.2; 100)
Serotype 19F (µg/mL)	Post-Booster (V02)	207/207	100.0	(98.2; 100)	207/207	100.0	(98.2; 100)
Serotype 23F (µg/mL)	Post-Booster (V02)	206/207	99.5	(97.3; 100)	205/207	99.0	(96.6; 99.9)

n: number of subjects experiencing the endpoint listed in the first two columns

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

Group 1: DTaP-IPV-HB-Hib + PCV13 (at 11 to 15 MoA), Group 2: Infanrix hexa + PCV13 (at 11 to 15 MoA)

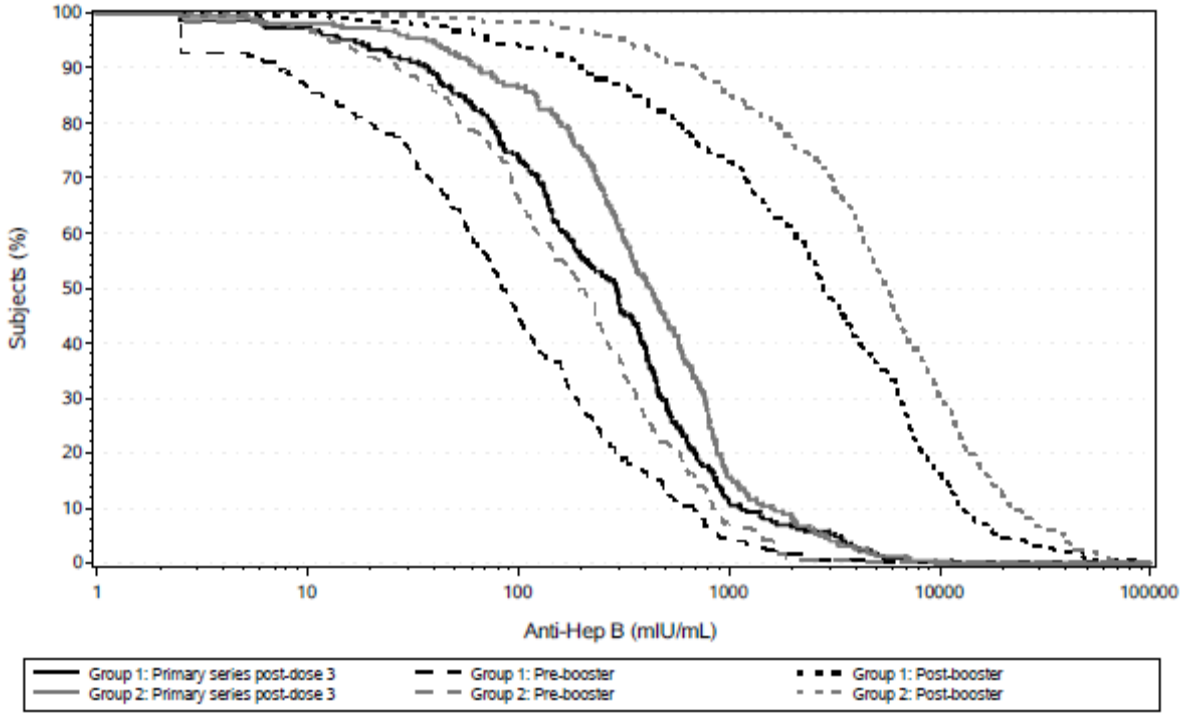
Table 6 Geometric means of concentrations for Prevenar 13 vaccine – PP Analysis Set (source: Table 5.4, study report)

		Group 1 (N=225)			Group 2 (N=218)		
Pneumococcal serotypes		M	GM	(95% CI)	M	GM	(95% CI)
Serotype 1 (µg/mL)	Post-Booster (V02)	207	2.44	(2.23; 2.67)	207	3.40	(3.09; 3.75)
Serotype 3 (µg/mL)	Post-Booster (V02)	191	0.708	(0.633; 0.791)	184	0.933	(0.828; 1.05)
Serotype 4 (µg/mL)	Post-Booster (V02)	207	2.11	(1.88; 2.37)	207	2.95	(2.63; 3.30)
Serotype 5 (µg/mL)	Post-Booster (V02)	206	1.36	(1.24; 1.49)	207	1.80	(1.63; 1.97)
Serotype 6A (µg/mL)	Post-Booster (V02)	207	6.37	(5.78; 7.03)	207	7.45	(6.75; 8.23)
Serotype 6B (µg/mL)	Post-Booster (V02)	204	5.43	(4.83; 6.11)	206	7.48	(6.79; 8.24)
Serotype 7F (µg/mL)	Post-Booster (V02)	207	4.24	(3.86; 4.65)	207	5.27	(4.80; 5.79)
Serotype 9V (µg/mL)	Post-Booster (V02)	207	1.51	(1.39; 1.65)	207	1.88	(1.72; 2.05)
Serotype 14 (µg/mL)	Post-Booster (V02)	207	9.70	(8.81; 10.7)	207	10.8	(9.86; 11.9)
Serotype 18C (µg/mL)	Post-Booster (V02)	207	1.27	(1.14; 1.42)	207	2.00	(1.78; 2.24)
Serotype 19A (µg/mL)	Post-Booster (V02)	207	8.91	(8.02; 9.89)	205	11.1	(9.96; 12.3)
Serotype 19F (µg/mL)	Post-Booster (V02)	207	7.16	(6.47; 7.92)	207	9.40	(8.52; 10.4)
Serotype 23F (µg/mL)	Post-Booster (V02)	207	2.95	(2.61; 3.33)	207	4.18	(3.70; 4.74)

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

Group 1: DTaP-IPV-HB-Hib + PCV13 (at 11 to 15 MoA), Group 2: Infanrix hexa + PCV13 (at 11 to 15 MoA)

Figure 1 Reverse cumulative distribution curves (RCDC) of anti-Hep B (Ortho-EC - mIU/mL) - Groups 1 & 2 - Full Analysis Set (source: Fig. 9.15, study report)



Group 3 (2,4,6 months primary immunization) – Pentavac+PPV13

12 months after the primary series HepB antibody titres ≥10 mIU/ml are still seen in 92.4% of the subjects of group 3 with a GM of 189 (95%CI: 144; 248). HepB is not included in Pentavac, thus no booster effect is measured.

All other antigens are present in the booster vaccine Pentavac and antibodies rise as expected post booster. In comparison with groups 1+2 GMs are widely in the same range, but for individual antigens lower or higher in the respective groups without clear relation to the vaccination scheme or vaccine used.

Defined thresholds of protection and seroconversion rates are achieved for all antigens. Details can be found in Table 7 and Table 8.

Table 7 Antibody persistence and booster response rates for study vaccines - Per Protocol Analysis Set (source: Table 5.5, study report)

			Group 3 (N=189)		
			n/M	%	(95% CI)
Anti-D (IU/mL)	Primary series post-dose 3	>=0.01 IU/mL	170/170	100.0	(97.9; 100)
		>=0.1 IU/mL	165/170	97.1	(93.3; 99.0)
		>=1.0 IU/mL	75/170	44.1	(36.5; 51.9)
	Pre-Booster (V01)	>=0.01 IU/mL	158/160	98.8	(95.6; 99.8)
		>=0.1 IU/mL	76/160	47.5	(39.6; 55.5)
	Post-Booster (V02)	>=0.01 IU/mL	183/183	100.0	(98.0; 100)
		>=0.1 IU/mL	183/183	100.0	(98.0; 100)
		>=1.0 IU/mL	177/183	96.7	(93.0; 98.8)
Anti-T (IU/mL)	Primary series post-dose 3	>=0.01 IU/mL	164/164	100.0	(97.8; 100)
		>=0.1 IU/mL	164/164	100.0	(97.8; 100)
		>=1.0 IU/mL	147/164	89.6	(83.9; 93.8)
	Pre-Booster (V01)	>=0.01 IU/mL	172/172	100.0	(97.9; 100)
		>=0.1 IU/mL	170/172	98.8	(95.9; 99.9)
	Post-Booster (V02)	>=0.01 IU/mL	182/182	100.0	(98.0; 100)
		>=0.1 IU/mL	182/182	100.0	(98.0; 100)
		>=1.0 IU/mL	182/182	100.0	(98.0; 100)
Anti-PT (EU/mL)	Primary series post-dose 3	>=LLOQ *	175/175	100.0	(97.9; 100)
	Pre-Booster (V01)	>=LLOQ *	146/170	85.9	(79.7; 90.7)
	Post-Booster (V02)/ Pre-Booster (V01)	Booster vaccine response †	166/167	99.4	(96.7; 100)
		Seroconversion ‡	160/167	95.8	(91.6; 98.3)
Anti-FHA (EU/mL)	Primary series post-dose 3	>=LLOQ *	172/172	100.0	(97.9; 100)
	Pre-Booster (V01)	>=LLOQ *	174/174	100.0	(97.9; 100)
	Post-Booster (V02)/ Pre-Booster (V01)	Booster vaccine response †	161/171	94.2	(89.5; 97.2)
		Seroconversion ‡	142/171	83.0	(76.6; 88.3)
Anti-Polio 1 (1/dil)	Primary series post-dose 3	>=8 (1/dil)	157/157	100.0	(97.7; 100)
	Pre-Booster (V01)	>=8 (1/dil)	170/171	99.4	(96.8; 100)
	Post-Booster (V02)	>=8 (1/dil)	180/180	100.0	(98.0; 100)
Anti-Polio 2 (1/dil)	Primary series post-dose 3	>=8 (1/dil)	162/163	99.4	(96.6; 100)
	Pre-Booster (V01)	>=8 (1/dil)	161/170	94.7	(90.2; 97.6)
	Post-Booster (V02)	>=8 (1/dil)	181/181	100.0	(98.0; 100)
Anti-Polio 3 (1/dil)	Primary series post-dose 3	>=8 (1/dil)	164/164	100.0	(97.8; 100)
	Pre-Booster (V01)	>=8 (1/dil)	165/170	97.1	(93.3; 99.0)
	Post-Booster (V02)	>=8 (1/dil)	181/181	100.0	(98.0; 100)
Anti-Hep B (mIU/mL)	Primary series post-dose 3	>=10 mIU/mL	176/178	98.9	(96.0; 99.9)
		>=100 mIU/mL	171/178	96.1	(92.1; 98.4)
	Pre-Booster (V01)	>=10 mIU/mL	171/185	92.4	(87.6; 95.8)
		>=100 mIU/mL	133/185	71.9	(64.8; 78.2)
	Post-Booster (V02)	>=10 mIU/mL	-	-	-
		>=100 mIU/mL	-	-	-
Anti-PRP (µg/mL)	Primary series post-dose 3	>=0.15 µg/mL	181/181	100.0	(98.0; 100)
		>=1 µg/mL	174/181	96.1	(92.2; 98.4)
	Pre-Booster (V01)	>=0.15 µg/mL	156/178	87.6	(81.9; 92.1)
		>=1.0 µg/mL	64/178	36.0	(28.9; 43.5)
	Post-Booster (V02)	>=0.15 µg/mL	177/186	95.2	(91.0; 97.8)
		>=1 µg/mL	157/186	84.4	(78.4; 89.3)

Group 3: Pentavac + PCV13 (at 18 MoA) *: LLOQ = 2 EU/mL. M: number of subjects with available data for the relevant endpoint
† Booster vaccine response rate for PT and FHA antigens, defined as Post-booster Ab concentrations greater or equal to 4-fold rise if pre-booster Ab concentrations < 4x LLOQ or Post-booster Ab concentrations greater or equal to 2-fold rise if pre-booster Ab concentrations greater or equal to 4x LLOQ
‡ Seroconversion rates for PT and FHA antigens defined as: Anti-PT and anti-FHA ≥ 4-fold Ab titers increase from D0 (V01) to D30 (V02)

n: number of subjects experiencing the endpoint listed in the first three columns

Table 8 Summary of geometric means for study vaccines - Per Protocol Analysis Set (source: Table 3.5, clinical-overview)

		Group 3 (N=189)		
		M	GM	(95% CI)
Anti-D (IU/mL)	Primary series post-dose 3	170	0.735	(0.633; 0.853)
	Pre-Booster (V01)	160	0.098	(0.082; 0.118)
	Post-Booster (V02)	183	3.43	(3.05; 3.85)
	Post-Booster (V02)/ Pre-Booster (V01)	156	35.8	(30.6; 41.8)
Anti-T (IU/mL)	Primary series post-dose 3	164	2.27	(2.04; 2.53)
	Pre-Booster (V01)	172	1.16	(1.04; 1.30)
	Post-Booster (V02)	182	6.85	(6.26; 7.49)
	Post-Booster (V02)/ Pre-Booster (V01)	165	5.77	(5.13; 6.49)
Anti-PT (EU/mL)	Primary series post-dose 3	175	99.9	(91.7; 109)
	Pre-Booster (V01)	170	5.44	(4.66; 6.35)
	Post-Booster (V02)	185	113	(101; 125)
	Post-Booster (V02)/Pre-Booster (V01)	167	21.0	(18.2; 24.2)
Anti-FHA (EU/mL)	Primary series post-dose 3	172	167	(154; 181)
	Pre-Booster (V01)	174	20.9	(17.6; 24.7)
	Post-Booster (V02)	186	210	(189; 232)
	Post-Booster (V02)/Pre-Booster (V01)	171	10.0	(8.72; 11.5)
Anti-Polio 1 (1/dil)	Primary series post-dose 3	157	866	(725; 1034)
	Pre-Booster (V01)	171	294	(239; 363)
	Post-Booster (V02)	180	1882	(1632; 2170)
	Post-Booster (V02)/Pre-Booster (V01)	162	6.26	(5.05; 7.75)
Anti-Polio 2 (1/dil)	Primary series post-dose 3	163	2119	(1707; 2631)
	Pre-Booster (V01)	170	306	(241; 390)
	Post-Booster (V02)	181	3085	(2622; 3630)
	Post-Booster (V02)/ Pre-Booster (V01)	162	9.15	(7.26; 11.5)
Anti-Polio 3 (1/dil)	Primary series post-dose 3	164	1448	(1180; 1777)
	Pre-Booster (V01)	170	258	(199; 335)
	Post-Booster (V02)	181	3501	(3039; 4033)
	Post-Booster (V02)/Pre-Booster (V01)	162	12.2	(9.63; 15.4)
Anti-Hep B (mIU/mL)	Primary series post-dose 3	178	2613	(2104; 3245)
	Pre-Booster (V01)	185	189	(144; 248)
	Post-Booster (V02)	-	-	-
	Post-Booster (V02)/Pre-Booster (V01)	-	-	-
Anti-PRP (µg/mL)	Primary series post-dose 3	181	8.85	(7.50; 10.4)
	Pre-Booster (V01)	178	0.712	(0.569; 0.891)
	Post-Booster (V02)	186	15.8	(11.6; 21.3)
	Post-Booster (V02)/Pre-Booster (V01)	175	20.0	(14.4; 27.6)

M: number of subjects with available data for the relevant endpoint
Group 3: Pentavac + PCV13 (at 18 MoA);

Safety results

No deaths or other SAEs related to the vaccines were reported. One subject in Group 2 reported extensive swelling of the limb after vaccination (Infanrix hexa); the event was resolved after 7 days One subject in Group 1 reported leg pain (Grade 1, both legs) within 30 minutes after vaccination; the event was resolved after 3 days.

Otherwise similar event rates were seen for solicited local and systemic events in all groups in known frequencies. No safety issues are identified.

The safety profile remains unchanged.

2.3.3. Discussion on clinical aspects

The data provided show the titres and concentrations following the booster dose of Hexyon versus Infanrix hexa with priming Hexyon versus Infanrix hexa and concomitantly used PCV13.

The seroprotection levels of antibodies against Diphtheria, Tetanus, HepB and Polio are adequate and similar to what is known from other vaccines.

The titres and concentrations of antibodies against all antigens vary significantly only for IPV1 and HepB depending on which vaccine has been used for priming and booster. The Infanrix hexa primed subjects show statistically significantly higher anti Hep B antibody titres post dose 3 after the primary series as well as pre and post booster. However, the general antibody kinetic is identical. Higher anti-HBs concentrations are known to take longer to decline below the minimum threshold for protection of ≤ 10mlU/ml. Of note, a low or negative anti-HBs result does not necessarily indicate lack of immunity in vaccinated persons: it is immune memory that matters and an anamnestic response was measured shortly after offering a booster dose. The clinical immunogenicity data currently do not necessarily suggest a lack of protection. To further investigate the lower anti Hep B antibody titres the applicant intents to submit clinical data of study A3L49. This study was conducted in Thailand and recently completed. The study evaluates the persistence of Anti-Hep B antibodies at 9 to 10 Years of age in subjects having received Hep B Vaccine at birth and a DTaPIPV-Hep B-PRP-T Hexavalent Vaccine at 2, 4 and 6 Months of Age. Results are not yet available but will be provided as soon as possible. The statistically significant lower GMTS for polivirus 1 and 3 are currently not considered of clinical relevance. GMTs by far exceeded the threshold of ≥ 8 (1/dil) and a good booster ability has been shown. Sufficiently high seroprotection rates have been observed. Comparable results for the polio component of DTaPIPV-Hep B-PRP-T have already been observed during licensure.

The safety profile remains unchanged as no vaccination related SAEs or even deaths occurred during this study.

3. Rapporteur's conclusion and recommendation

☒ Not fulfilled:

Based on the data submitted, the MAH should provide description of the additional clarifications requested per study as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. Regarding a potential impact of lower anti HBs antibody titres on the clinical protection against Hepatitis B infection the MAH is requested to provide a plan to further evaluate this issue.
2. The applicant is further asked to discuss the relevance of statistically significant lower anti-Polio 1 GMTs pre- and post-booster.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1

Regarding a potential impact of lower anti HBs antibody titres on the clinical protection against Hepatitis B infection the MAH is requested to provide a plan to further evaluate this issue.

MAH Response to Question 1

As pointed out by the reviewer, a low or negative (<10 mIU/mL) anti-HBs result does not necessarily indicate a lack of immunity in vaccinated persons.

The concept that it is immune memory that matters is now largely recognized. The existence of persisting immune memory against HBsAg, evidenced by anamnestic response to a booster (challenge) vaccination with a Hepatitis B containing vaccine, has been documented on several occasions in multiple cohorts of children following infant/toddler primary immunization with several types of Hepatitis B containing combination vaccine (pentavalent or hexavalent) and particularly in cohorts in which a large proportion of vaccinees presented negative (<10 mIU/mL) anti-HBs results (1-6)1.

This topic had been in the mind of the MAH since a while, and the plan to address this point has been addressed through a clinical trial (A3L492) that has been recently completed in Thailand.

The MAH plans to submit these data early next year within the context of a labelling variation which, among other objectives, will enrich the label with data on persistence of immunity.

Assessor`s comment:

The applicant intents to submit results from recently completed clinical trial A3L492 early this year to further evaluate the persistence of immunity to HBsAg. The study will evaluate persistence of Anti-Hep B Antibodies at 9 to 10 Years of Age in subjects having received Hep B Vaccine at birth and a DTaPIPV-

Hep B-PRP-T Hexavalent Vaccine at 2, 4 and 6 Months of Age. More detailed information regarding objectives and trial design of the study were not provided. The submission of the clinical trial data is appreciated. Further conclusions will depend on the submitted clinical data.

Conclusion:

The issue is solved.

Question 2

The applicant is further asked to discuss the relevance of statistically significant lower anti-Polio 1 GMTs pre- and post-booster.

MAH Response to Question 2

For trial A3L40 (as well as for trial A3L39), the immune responses against the poliovirus antigens contained in the vaccines have not been used to support pre-specified statistical comparisons, but rather to support purely descriptive analysis. The study has not been powered (sample size) for assessing the non-inferiority of the poliovirus responses between the two groups (1 and 2), therefore all post-hoc statistical comparisons are not relevant.

Nevertheless, it is true that lower responses against the three poliovirus serotypes have been observed during the course of the trial (A3L39 and A3L40) between the DTaP-IPV-HB-PRP~T (Hexyon/Hexacima/Hexaxim) vaccinees and the DTaP-IPV-HB/PRPT~T vaccinees (Infanrix hexa), and that these differences were the most marked with poliovirus type 1.

The clinical relevance of this observation can be analyzed through the following elements:

- It is well established that a level of poliovirus neutralizing antibodies above the threshold of 1/8 is a good correlate of protection against paralysis (7), and that this parameter is the most clinically relevant compared to GMT that can be achieved during the course of immunization.
- The observation that GMT and consequently proportions of subjects with poliovirus neutralizing antibodies $\geq$ 1/8 can decrease from post-dose 3 to the pre-dose 4 (booster) is not new (8), and it is known that the type of infant regimen (2,3,4 months of age versus 2,4,6 months of age) is a key driver of this observation (9).
- While it is true that 83.7 % of the DTaP-IPV-HB-PRP~T (Hexyon/Hexacima/Hexaxim) vaccinees presented poliovirus neutralizing antibodies below the 1/8 threshold before booster (as well as 93.6% of the Infanrix hexa subjects), and with as expected lower GMT, all of them (except one) did develop antibodies above this threshold after booster, indicating a good persisting immune memory. Since the early fifties Jonas Salk hypothetized that as immune memory is established by primary vaccination, and that no further immunizations (boosters) are necessary (10-12).
- In the two countries where the trial has been conducted (Germany and Czech Republic), the polio immunization regimen is a "3+1+1" regimen that is to say that a pre-school vaccination for boosting immunity against polio is recommended (generally with a DTaP-IPV vaccine). Therefore, this will further increase antibodies levels in infants who may have developed the lowest level of antibodies following their initial infant/toddler immunization. In addition, in

some circumstances, additional boosters with IPV-containing vaccines may be given in older ages with Tdap-IPV or Td-IPV products.

- The current epidemiological data regarding poliovirus circulation (13) do show that the level of risk has drastically decreased in all countries. The absence of Sabin-like viruses isolated in environmental sampling done in many European countries (indicative of the presence of a low number of recently OPV-vaccinees and/ or of recently OPV-vaccinees' contacts), the high polio vaccination coverage reached in these countries, and the lowest ever reported number of AFP cases (only due to WPV1) in the last two remaining endemic countries (Pakistan and Afghanistan) do illustrate this low risk.

Based on all these elements, the MAH consider this observation as clinically not relevant.

Assessor`s comment:

The applicant`s conclusion not considering the finding of statistically significant lower GMTS for poliovirus type 1 and 3 as clinical relevant is comprehensible explained. References were provided. The conclusion can be agreed upon.

The GMTs post dose 3 and pre-booster by far exceeded the threshold of ≥ 8 (1/dil) and booster ability was shown. Furthermore sufficiently high seroprotection rates were shown.

Conclusion:

The issue is solved.

6. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.