26 May 2016
EMA/389260/2016
Procedure Management and Committees Support Division

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

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Hexaxim

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/P46/004

Note

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

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Introduction

On 11 March 2016, the MAH submitted a completed paediatric study **A3L28** 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.

Scientific discussion

Information on the development program

The MAH stated that A3L28 "Evaluation of Antibody Persistence at 3.5 and 4.5 Years of Age in Healthy Children After Primary Series and Booster Vaccination with Investigational (DTaP-IPV-Hep B-PRP-T) or Infanrix™ hexa vaccines in Latin America" is a standalone study.

This study is the immunogenicity follow-up of two previously assessed studies: A3L24 and A3L27.

Information on the pharmaceutical formulation used in the study

No vaccines were given in this extension study A3L28. In the original studies A3L24 and A3L27 commercial products of Prevenar, Rotarix and Infanrix hexa were given.

Clinical aspects

Introduction

Hexaxim™/Hexacima™/Hexyon™ is indicated for active immunisation (primary and booster vaccination) of infants and toddlers from six weeks to 24 months 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:

A3L28:

"Evaluation of Antibody Persistence at 3.5 and 4.5 Years of Age in Healthy Children After Primary Series and Booster Vaccination with Investigational (DTaP-IPV-Hep B-PRP-T) or Infanrix™ hexa vaccines in Latin America"

This clinical study A3L28 is a Phase III long-term antibody persistence study and was conducted in Colombia with a maximum of 699 children who completed a 3-dose primary series (DTaPIPV-Hep B-PRP-T or Infanrix™ hexa), concomitantly administered with Prevenar™ (PCV7) (3 doses) and Rotarix™ (2 doses) in study A3L24, and the booster (DTaP-IPV-Hep B-PRP-T or Infanrix™ hexa, concomitantly administered with Prevenar™ [PCV7]) in study A3L27. All subjects received also hepatitis B vaccination at birth.

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

Clinical study

Description

Primary immunization (Hexacim or Infanrix hexa both concomitantly given with Prevenar and Rotarix) had been done in study A3L24, the booster dose (Hexacim or Infanrix hexa both with Prevenar) was given in study A3L27. Subjects now in this study kept the subject number from A3L27 and no further vaccinations were given. Blood draws were now made at the age of 3.5y and the second at the age of 4.5y (each +/- 60 days), i.e. ~2 and 3 years post booster vaccination. SAEs from A3L27 were followed and collected as well as newly developed SAEs during this trial.

Methods

Study design

Only subjects from Colombia participated in this follow-up study.

Table 1 Group allocation and prior vaccinations of subjects in study A3L28 (source: study report)

Group	Primary series administration (A3L24) 3 doses* at 2, 4, 6 MoA	Booster series administration (A3L27) Booster dose at 12 to 24 MoA
Group 1	DTaP-IPV-HB-Hib (3 batches) +Prevenar™ (PCV7) +Rotarix™	DTaP-IPV-HB-Hib (3 batches, same as in primary series) +PCV7
Group 2	DTaP-IPV-HB-Hib (3 batches) +PCV7 +Rotarix™	Infanrix™ hexa +PCV7
Group 3	Infanrix™ hexa +PCV7 +Rotarix™	DTaP-IPV-HB-Hib (3 batches) +PCV7

* Only 2 doses of Rotarix™ were administered in the primary series at 2 and 4 MoA.

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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 qualified laboratories.

Table 2 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

A maximum of 699 subjects (who completed A3L24 primary series study and A3L27 booster study in Colombia) were planned to be enrolled in this study.

The following distribution per group was expected based on the groups of the booster study A3L27.

• Group 1: maximum of 264 children who received 3 doses of DTaP-IPV-HB-Hib vaccine at 2, 4, 6 months of age (MoA) concomitantly with PCV7 and Rotarix™ (2 doses at 2 and 4 MoA), and a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with PCV7 at 12 to 24 MoA.

• Group 2: maximum of 264 children who received 3 doses of DTaP-IPV-HB-Hib vaccine at 2, 4, 6 MoA concomitantly with PCV7 and Rotarix™ (2 doses at 2 and 4 MoA), and a booster dose of Infanrix™ hexa vaccine concomitantly with PCV7 at 12 to 24 MoA.

• Group 3: maximum of 171 children who received 3 doses of Infanrix™ hexa vaccine at 2, 4, 6 MoA concomitantly with PCV7 and Rotarix™ (2 doses at 2 and 4 MoA), and a booster dose of DTaP-IPV-HB-Hib vaccine concomitantly with PCV7 at 12 to 24 MoA.

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Objective(s)

Primary:

To describe the long-term antibody (Ab) persistence at 3.5 and 4.5 years of age following a 3-dose primary series vaccination of either DTaP-IPV-HB-Hib+Prevenar™ (PCV7)+Rotarix™ or Infanrix™ hexa+Prevenar™ (PCV7)+Rotarix™ vaccination at 2, 4, 6 months of age and a booster vaccination of DTaP-IPV-HB-Hib+Prevenar™ (PCV7) or Infanrix™ hexa+Prevenar™ (PCV7) at 12 to 24 months of age. Only 2 doses of Rotarix™ were administered in the primary series at 2 and 4 months of age.

Observational:

To describe the long-term Ab persistence by group and by stratification on the age at inclusion of the A3L27 booster study.

Outcomes/endpoints

Primary:

The following serological endpoints were assessed in children aged 3.5 years (months [M]18 to M30 post-booster dose) and 4.5 years of age (M30 to M42 post-booster dose) according to the groups assigned in A3L27 study:

- Ab concentrations/titers for each valence (except PCV7 and Rotarix™ valences)

- Ab concentrations/titers above a 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-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-pertussis toxin (PT) and anti-filamentous hemagglutinin (FHA) Ab concentrations ≥ LLOQ* (Lower Limit of Quantitation), ≥ 2x LLOQ and ≥ 4x LLOQ
    - Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)

(* LLOQ = 2 enzyme-linked immunosorbent assay [ELISA] units [EU]/mL for PT and FHA)

Observational:

The following serological endpoints were assessed in children aged 3.5 years (months [M]18 to M30 post-booster dose) and 4.5 years of age (M30 to M42 post-booster dose):

- Ab concentrations/titers for each valence (except PCV7 and Rotarix™ valences)
- Ab concentrations/titers above a 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-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 ≥ LLOQ, ≥ 2x LLOQ and ≥ 4x LLOQ
    - Anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dil)

Statistical Methods

For the main objective:

The analysis was descriptive according to the group subjects were assigned to in the A3L27 booster trial. Immunogenicity endpoints were described at 3.5 and 4.5 years of age on all available blood samples.

The following parameters were used:

• Geometric mean (GM) of Ab concentrations/titers

• Percentage of subjects with concentrations/titers above predefined thresholds, including those of pre-defined seroprotection

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.

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

For the observational objective:

Descriptive statistics are produced.

Immunogenicity endpoints are additionally presented by vaccine group and age stratum based on the age at inclusion in the A3L27 booster phase study. The stratification on the age is as follows: 12 months included till 15 months excluded (simplified as [12 months, 15 months[), [15 months, 19 months[and [19 months, 24 months].

The same statistical method as the one described for the main objective was used.

Results

Number analysed

Table 3 Subject Disposition for Immunogenicity Analyses Set – All Included Subjects (source: Table 4.2, study report)

Primary vaccination	DTaP-IPV-HB-Hib		Infanrix™ hexa					
Booster vaccination	DTaP-IPV-HB-Hib Group 1 (N=220)		Infanrix™ hexa Group 2 (N=208)		DTaP-IPV-HB-Hib Group 3 (N=130)		Overall (N=558)	
	n	%	n	%	n	%	n	%
Subjects Present at V01	220	100.0	208	100.0	130	100.0	558	100.0
Immunogenicity analysis set at V01	219	99.5	206	99.0	130	100.0	555	99.5
Subjects Present at V02	213	100.0	200	100.0	125	100.0	538	100.0
Immunogenicity Analysis Set at V02	208	97.7	199	99.5	125	100.0	532	98.9

N: number of subjects analyzed according to All Included Subjects n: number of subjects

%: percentages are calculated according to subjects present at V01 or V02

All subjects were co-administrated with PCV7 (at 2, 4 and 6 MoA) and Rotarix™ (at 2 and 4 MoA) at primary series and with PCV7 at booster phase

Male/Female ratio was near 50% in all three groups and Hispanic was the predominant ethnic origin (>80%) similar to the previous studies.

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Immunogenicity results

The percentage of subjects achieving the predefined seroprotection or seroconversion threshold for each antigen is similar across the groups so that there is also no difference between the two vaccines used for priming. Details can be found in Table 4, GMTs/GMCs are shown further below.

Table 4 Summary of Descriptive Antibody Levels Results at V01 (Year 1) and V02 (Year 2) – Immunogenicity Analysis Set (source: Table 5.1, study report)

Primary vaccination with			DTaP-IPV-HB-Hib						Infanrix™ hexa		
Booster vaccination with			DTaP-IPV-HB-Hib Group 1 (N=220)			Infanrix™ hexa Group 2 (N=208)			DTaP-IPV-HB-Hib Group 3 (N=130)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-D (MIT-IU/mL)	Year 1 - V01	>=0.01 IU/mL	217/217	100.0	(98.3; 100.0)	205/206	99.5	(97.3; 100.0)	130/130	100.0	(97.2; 100.0)
		>=0.1 IU/mL	158/217	72.8	(66.4; 78.6)	138/206	67.0	(60.1; 73.4)	95/130	73.1	(64.6; 80.5)
		>=1.0 IU/mL	28/217	12.9	(8.7; 18.1)	17/206	8.3	(4.9; 12.9)	16/130	12.3	(7.2; 19.2)
	Year 2 - V02	>=0.01 IU/mL	208/208	100.0	(98.2; 100.0)	195/199	98.0	(94.9; 99.4)	124/125	99.2	(95.6; 100.0)
		>=0.1 IU/mL	119/208	57.2	(50.2; 64.0)	96/199	48.2	(41.1; 55.4)	74/125	59.2	(50.1; 67.9)
		>=1.0 IU/mL	21/208	10.1	(6.4; 15.0)	14/199	7.0	(3.9; 11.5)	13/125	10.4	(5.7; 17.1)
Anti-T (ELISA-IU/mL)	Year 1 - V01	>=0.01 IU/mL	217/217	100.0	(98.3; 100.0)	205/205	100.0	(98.2; 100.0)	130/130	100.0	(97.2; 100.0)
		>=0.1 IU/mL	192/217	88.5	(83.5; 92.4)	178/205	86.8	(81.4; 91.1)	115/130	88.5	(81.7; 93.4)
		>=1.0 IU/mL	49/217	22.6	(17.2; 28.7)	29/205	14.1	(9.7; 19.7)	44/130	33.8	(25.8; 42.7)
	Year 2 - V02	>=0.01 IU/mL	208/208	100.0	(98.2; 100.0)	196/198	99.0	(96.4; 99.9)	125/125	100.0	(97.1; 100.0)
		>=0.1 IU/mL	168/208	80.8	(74.7; 85.9)	152/198	76.8	(70.3; 82.5)	102/125	81.6	(73.7; 88.0)
		>=1.0 IU/mL	36/208	17.3	(12.4; 23.1)	12/198	6.1	(3.2; 10.3)	27/125	21.6	(14.7; 29.8)

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Primary vaccination with			DTaP-IPV-HB-Hib						Infanrix™ hexa		
Booster vaccination with			DTaP-IPV-HB-Hib Group 1 (N=220)			Infanrix™ hexa Group 2 (N=208)			DTaP-IPV-HB-Hib Group 3 (N=130)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-PT (ELISA-EU/mL)	Year 1 - V01	>= LLOQ	171/216	79.2	(73.1; 84.4)	164/200	82.0	(76.0; 87.1)	103/128	80.5	(72.5; 86.9)
		>= 2xLLOQ	139/216	64.4	(57.6; 70.7)	129/200	64.5	(57.4; 71.1)	80/128	62.5	(53.5; 70.9)
		>= 4xLLOQ	70/216	32.4	(26.2; 39.1)	69/200	34.5	(27.9; 41.5)	38/128	29.7	(21.9; 38.4)
	Year 2 - V02	>= LLOQ	136/207	65.7	(58.8; 72.1)	122/196	62.2	(55.1; 69.1)	71/124	57.3	(48.1; 66.1)
		>= 2xLLOQ	89/207	43.0	(36.2; 50.0)	89/196	45.4	(38.3; 52.7)	54/124	43.5	(34.7; 52.7)
		>= 4xLLOQ	46/207	22.2	(16.8; 28.5)	49/196	25.0	(19.1; 31.7)	25/124	20.2	(13.5; 28.3)
Anti-FHA (ELISA-EU/mL)	Year 1 - V01	>= LLOQ	217/218	99.5	(97.5; 100.0)	204/204	100.0	(98.2; 100.0)	127/129	98.4	(94.5; 99.8)
		>= 2xLLOQ	207/218	95.0	(91.2; 97.5)	199/204	97.5	(94.4; 99.2)	120/129	93.0	(87.2; 96.8)
		>= 4xLLOQ	185/218	84.9	(79.4; 89.3)	173/204	84.8	(79.1; 89.4)	105/129	81.4	(73.6; 87.7)
	Year 2 - V02	>= LLOQ	207/208	99.5	(97.4; 100.0)	199/199	100.0	(98.2; 100.0)	123/125	98.4	(94.3; 99.8)
		>= 2xLLOQ	199/208	95.7	(91.9; 98.0)	192/199	96.5	(92.9; 98.6)	117/125	93.6	(87.8; 97.2)
		>= 4xLLOQ	178/208	85.6	(80.1; 90.1)	168/199	84.4	(78.6; 89.2)	99/125	79.2	(71.0; 85.9)
Anti-polio 1 (MIT-WT-1/dil)	Year 1 - V01	>=8 1/dil	216/216	100.0	(98.3; 100.0)	205/205	100.0	(98.2; 100.0)	130/130	100.0	(97.2; 100.0)
	Year 2 - V02	>=8 1/dil	207/208	99.5	(97.4; 100.0)	198/199	99.5	(97.2; 100.0)	125/125	100.0	(97.1; 100.0)
Anti-polio 2 (MIT-WT-1/dil)	Year 1 - V01	>=8 1/dil	216/216	100.0	(98.3; 100.0)	205/205	100.0	(98.2; 100.0)	130/130	100.0	(97.2; 100.0)
	Year 2 - V02	>=8 1/dil	208/208	100.0	(98.2; 100.0)	199/199	100.0	(98.2; 100.0)	125/125	100.0	(97.1; 100.0)
Anti-polio 3 (MIT-WT-1/dil)	Year 1 - V01	>=8 1/dil	216/216	100.0	(98.3; 100.0)	202/205	98.5	(95.8; 99.7)	129/129	100.0	(97.2; 100.0)
	Year 2 - V02	>=8 1/dil	208/208	100.0	(98.2; 100.0)	197/199	99.0	(96.4; 99.9)	125/125	100.0	(97.1; 100.0)

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Primary vaccination with			DTaP-IPV-HB-Hib						Infanrix™ hexa		
Booster vaccination with			DTaP-IPV-HB-Hib Group 1 (N=220)			Infanrix™ hexa Group 2 (N=208)			DTaP-IPV-HB-Hib Group 3 (N=130)		
Component	Timepoint	Criteria	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-Hep B (VITROS ECi-mIU/mL)	Year 1 - V01	>=10 mIU/mL	209/219	95.4	(91.8; 97.8)	196/206	95.1	(91.3; 97.6)	125/130	96.2	(91.3; 98.7)
		>=100 mIU/mL	176/219	80.4	(74.5; 85.4)	172/206	83.5	(77.7; 88.3)	107/130	82.3	(74.6; 88.4)
	Year 2 - V02	>=10 mIU/mL	192/208	92.3	(87.8; 95.5)	185/199	93.0	(88.5; 96.1)	117/124	94.4	(88.7; 97.7)
		>=100 mIU/mL	154/208	74.0	(67.5; 79.9)	143/199	71.9	(65.1; 78.0)	93/124	75.0	(66.4; 82.3)
Anti-PRP (RIA-µg/mL)	Year 1 - V01	>=0.15 µg/mL	219/219	100.0	(98.3; 100.0)	206/206	100.0	(98.2; 100.0)	129/130	99.2	(95.8; 100.0)
		>=1.0 µg/mL	190/219	86.8	(81.5; 90.9)	185/206	89.8	(84.8; 93.6)	118/130	90.8	(84.4; 95.1)
	Year 2 - V02	>=0.15 µg/mL	208/208	100.0	(98.2; 100.0)	199/199	100.0	(98.2; 100.0)	125/125	100.0	(97.1; 100.0)
		>=1.0 µg/mL	178/208	85.6	(80.1; 90.1)	168/199	84.4	(78.6; 89.2)	113/125	90.4	(83.8; 94.9)

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

%: percentages and 95% CIs are calculated according to the subjects available for the endpoint LLOQ value for anti-PT and anti-FHA is 2 EU/mL

Year 1 (V01) and Year 2 (V02) are the first and second time points of follow-up that correspond to the follow-up when subjects were aged, respectively, 3.5 and 4.5 years, both time points following a 3-dose primary series vaccination of either DTaP-IPV-HB-Hib vaccine or Infanrix™ hexa at 2, 4, and 6 MoA (both concomitantly administered with PCV7 at 2, 4, and 6 MoA, and Rotarix™ at 2 and 4 MoA), and a booster vaccination of DTaP-IPV-HB-Hib vaccine or Infanrix™ hexa at 12 to 24 MoA (both concomitantly administered with PCV7).

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The GMTs and GMCs of antibodies against all antigens except Polio were similar in all three groups. For Polio the group primed with Infanrix hexa showed significantly higher titres than the Hexaxim primed groups. Details can be found in Table 5 and Figure 5.

Table 5 Summary of Geometric Means– Immunogenicity Analysis Set (source: Table 5.2, study report)

Primary vaccination with		DTaP-IPV-HB-Hib						Infanrix™ hexa		
Booster vaccination with		DTaP-IPV-HB-Hib Group 1 (N=220)			Infanrix™ hexa Group 2 (N=208)			DTaP-IPV-HB-Hib Group 3 (N=130)		
Component	Timepoint	M	GMC/GMT	(95% CI)	M	GMC/GMT	(95% CI)	M	GMC/GMT	(95% CI)
Anti-D (MIT-IU/mL)	Year 1 - V01	217	0.256	(0.216; 0.303)	206	0.187	(0.159; 0.220)	130	0.231	(0.188; 0.284)
	Year 2 - V02	208	0.164	(0.136; 0.197)	199	0.119	(0.098; 0.145)	125	0.143	(0.112; 0.183)
Anti-T (ELISA-IU/mL)	Year 1 - V01	217	0.433	(0.372; 0.503)	205	0.323	(0.281; 0.372)	130	0.579	(0.465; 0.722)
	Year 2 - V02	208	0.297	(0.252; 0.350)	198	0.221	(0.189; 0.260)	125	0.381	(0.302; 0.481)
Anti-PT (ELISA-EU/mL)	Year 1 - V01	216	4.75	(4.07; 5.56)	200	5.08	(4.32; 5.98)	128	4.62	(3.78; 5.65)
	Year 2 - V02	207	3.16	(2.71; 3.69)	196	3.13	(2.67; 3.68)	124	3.06	(2.45; 3.82)
Anti-FHA (ELISA-EU/mL)	Year 1 - V01	218	26.1	(21.8; 31.1)	204	26.3	(22.2; 31.1)	129	19.9	(15.9; 24.9)
	Year 2 - V02	208	33.8	(28.5; 40.1)	199	35.1	(29.2; 42.1)	125	27.3	(21.3; 34.9)
Anti-polio 1 (MIT-WT-1/dil)	Year 1 - V01	216	285	(245; 332)	205	294	(250; 345)	130	508	(410; 630)
	Year 2 - V02	208	211	(180; 249)	199	207	(173; 247)	125	417	(331; 525)
Anti-polio 2 (MIT-WT-1/dil)	Year 1 - V01	216	694	(587; 822)	205	553	(470; 652)	130	997	(788; 1261)
	Year 2 - V02	208	543	(458; 647)	199	403	(332; 490)	125	700	(555; 883)
Anti-polio 3 (MIT-WT-1/dil)	Year 1 - V01	216	691	(570; 838)	205	508	(414; 622)	129	1213	(962; 1530)
	Year 2 - V02	208	408	(338; 493)	199	307	(254; 372)	125	696	(554; 875)
Anti-Hep B (VITROS ECi-mIU/mL)	Year 1 - V01	219	500	(379; 658)	206	475	(364; 619)	130	671	(463; 971)
	Year 2 - V02	208	299	(223; 401)	199	277	(210; 365)	124	399	(271; 589)
Anti-PRP (RIA-µg/mL)	Year 1 - V01	217	4.55	(3.84; 5.40)	206	5.22	(4.37; 6.23)	130	5.37	(4.32; 6.69)
	Year 2 - V02	208	4.02	(3.39; 4.78)	199	4.34	(3.59; 5.26)	125	4.87	(3.83; 6.19)

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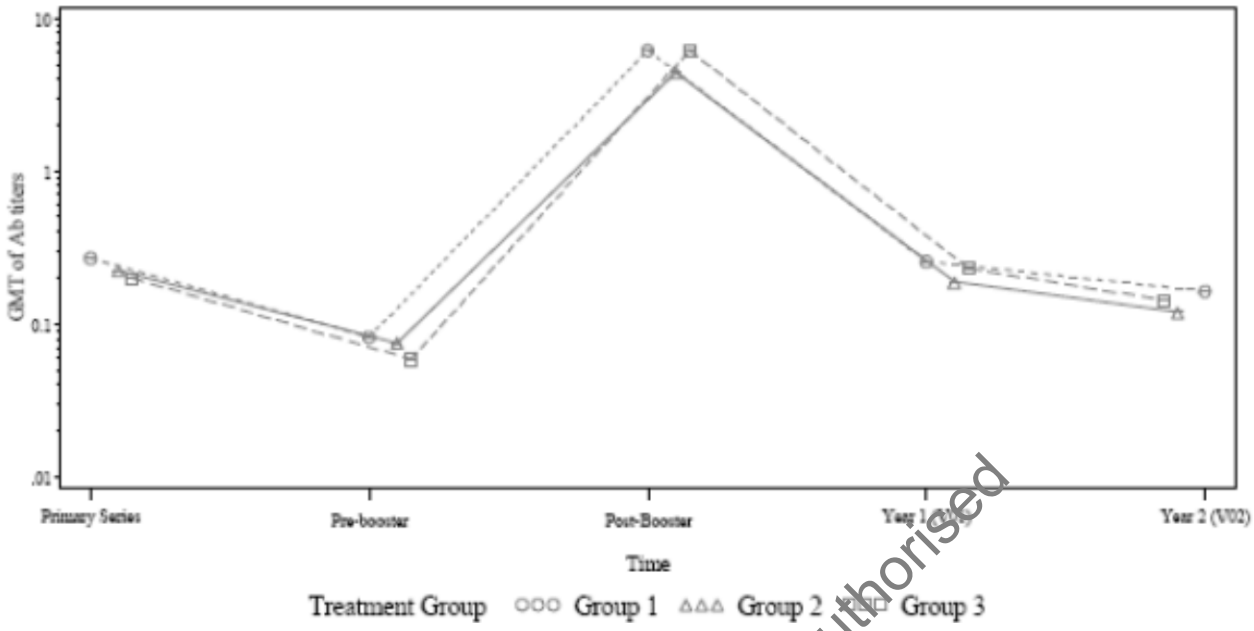
N: Number of subjects analyzed according to Immunogenicity Analysis Set n: number of subjects M: number of subjects available for the endpoint

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

Year 1 (V01) and Year 2 (V02) are the first and second time points of follow-up that correspond to the follow-up when subjects were aged, respectively, 3.5 and 4.5 years, both time points following a 3-dose primary series vaccination of either DTaP-IPV-HB-Hib vaccine or Infanrix™ hexa at 2, 4, and 6 MoA (both concomitantly administered with PCV7 at 2, 4, and 6 MoA, and Rotarix™ at 2 and 4 MoA), and a booster vaccination of DTaP-IPV-HB-Hib vaccine or Infanrix™ hexa at 12 to 24 MoA (both concomitantly administered with PCV7).

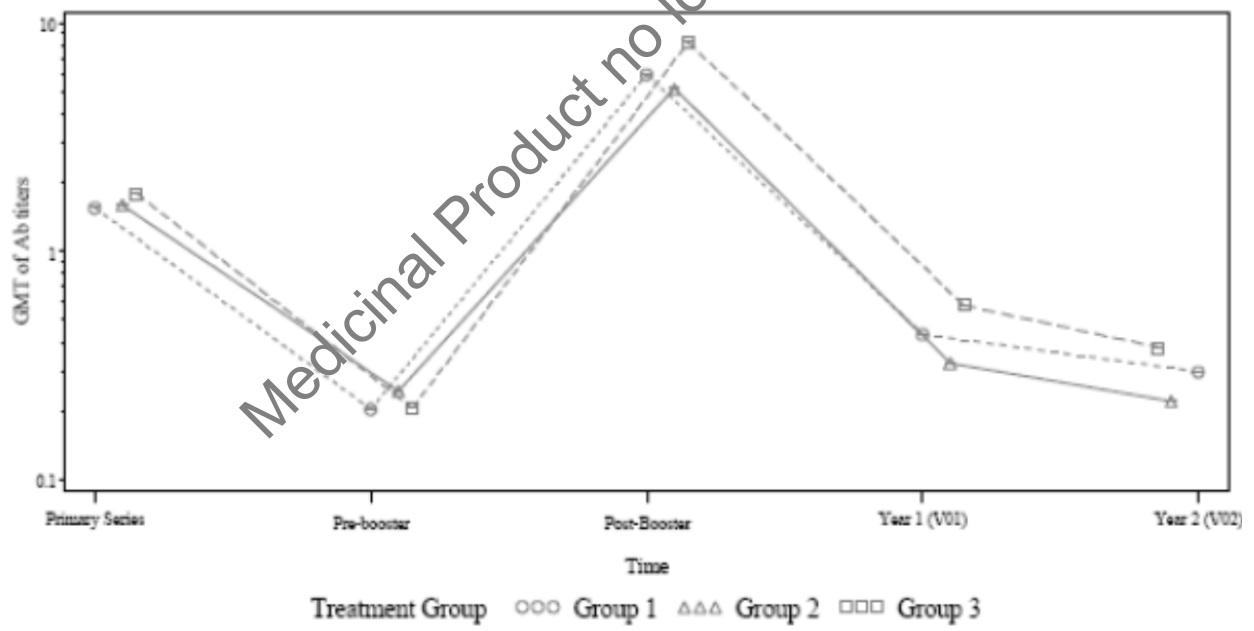
Kinetic curves (Groups 1+2: Hexyon primed; Group 3: Infanrix hexa primed)

Figure 1 Kinetic Curves on GMCs of Anti-D (source: Fig.5.1, study report)



Data can be found in Table 5.4 of the study report.

Figure 2 Kinetic Curves on GMCs of Anti-T (source: Fig.5.2, study report)



Data can be found in Table 5.6 of the study report.

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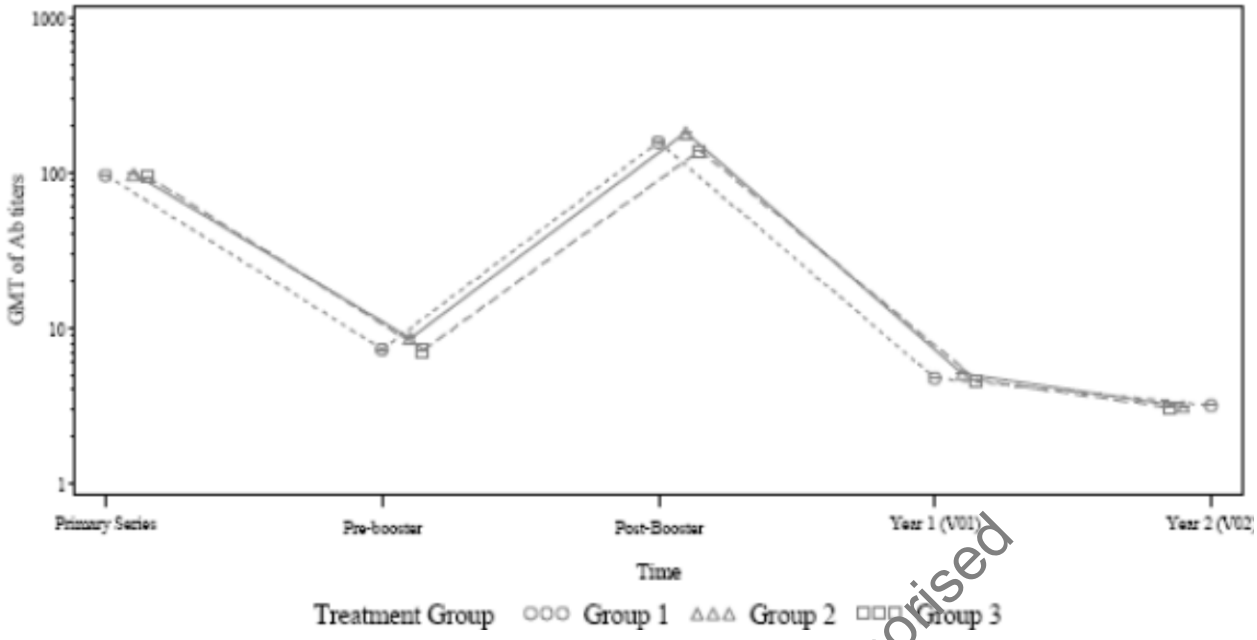
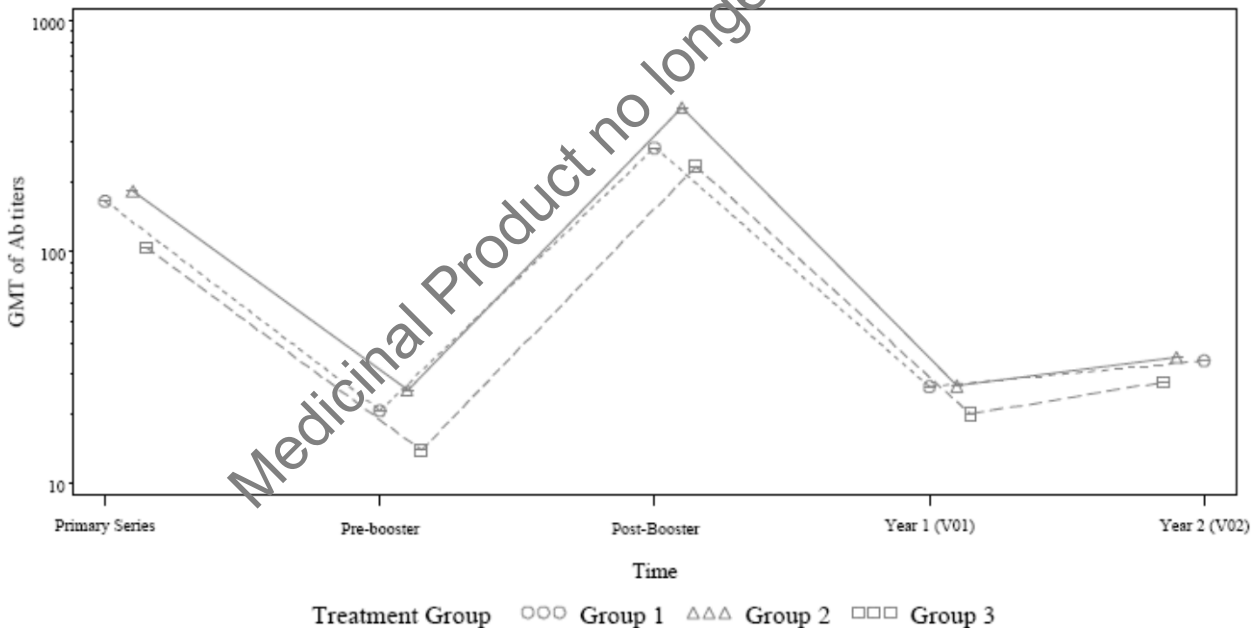
Figure 3 Kinetic Curves on GMCs of Anti-PT (source: Fig.5.3, study report)



Data can be found in Table 5.8 of the study report.

Figure 4 Kinetic Curves on GMCs of Anti-FHA (source: Fig.5.4, study report)



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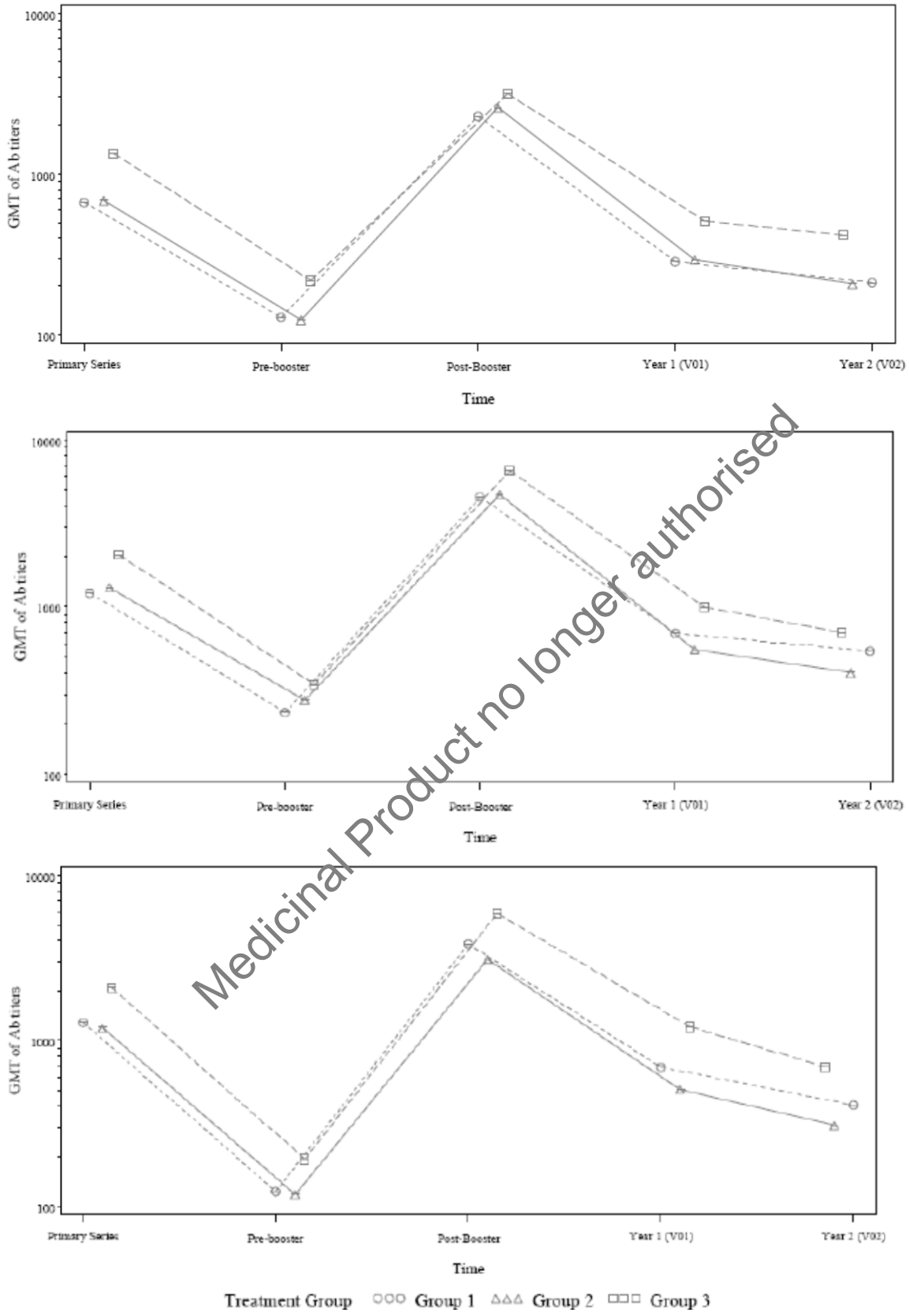
Data can be found in Table 5.10 of the study report.

Figure 5 Kinetic Curves on GMTs of Anti-Polio 1-3 (source: Fig.5.5-5.7, study report)



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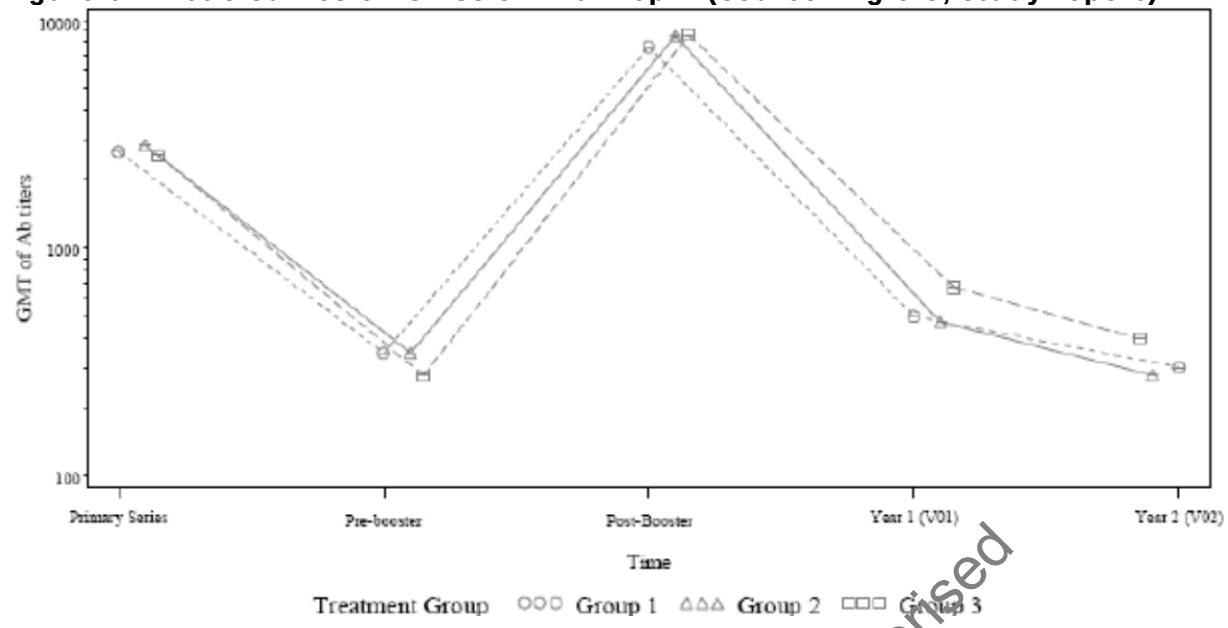
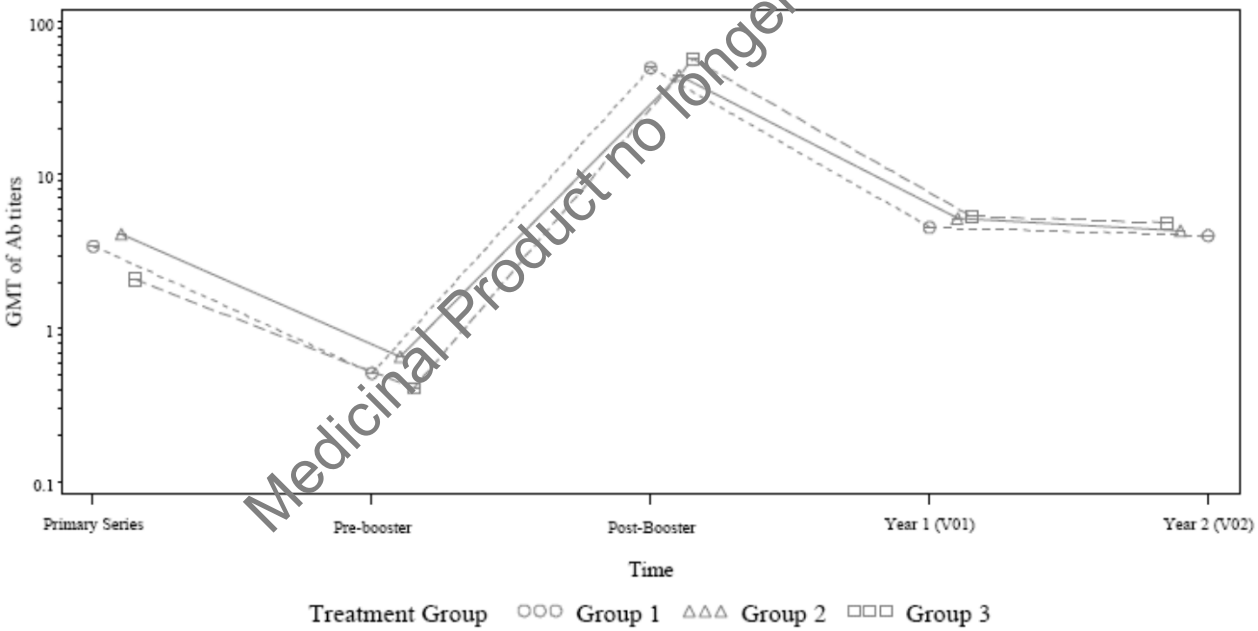
Data can be found in Table 5.12 of the study report.

Figure 6 Kinetic Curves on GMCs of Anti-Hep B (source: Fig.5.8, study report)



Data can be found in Table 5.14 of the study report.

Figure 7 Kinetic Curves on GMCs of Anti-PRP (source: Fig.5.9, study report)



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Data can be found in Table 5.16 of the study report.

Considering that the booster dose was given at some time point between 12 and 24 months of age an analysis was also done for the different age increments (12-15m, 15-19m, 19-24m) but the results still show a high similarity between groups (with the same exceptions described above) and the expected higher titres/concentrations in the older subgroups.

Safety results

No deaths or other SAEs were reported. The safety profile remains unchanged.

Discussion on clinical aspects

The data provided show the titres and concentrations including antibody kinetics 2-3 years following the booster dose of Hexyon versus Infanrix hexa with priming Hexyon versus Infanrix hexa and concomitantly used vaccines.

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 only for IPV and Pertussis depending on which vaccine has been used for priming (IPV) or for priming and/or booster. For IPV the Infanrix hexa primed subjects show statistically significantly higher concentrations the general antibody kinetic is identical nevertheless. For the Pertussis antigens slightly higher titres can be found in the Hexyon primed groups. The scale of all those differences is not clinically relevant for the timeframe of 3 to 4 years after primary immunization with Hexaxim so this is just an observation and not an issue for the moment. Nevertheless, the company should continue to monitor the long-term antibody values in the EU studies.

The safety profile remains unchanged as no SAEs or even deaths occurred during the 2 years of this study.

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CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.