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, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inact.) and Haemophilus type B conjugate vaccine (adsorbed)

Procedure no: EMEA/H/W/002495 / P46 021 (Hexaxim)
EMEA/H/C/002702 / P46 021 (Hexacima)
EMEA/H/C/002796 / P46 019 (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 12 Decemberr 2016, the MAH submitted a completed paediatric study **A3L31** 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 A3L31 "Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-HB-PRP~T Combined Vaccine at 2, 4, and 6 Months of Age versus Sanofi Pasteur's DTaP-IPV//PRP~T Combined Vaccine at 2, 4, and 6 Months of Age + Hep B Vaccine at 1 and 6 Months of Age, in South Korean Infants Primed with Hep B at Birth" is a standalone study.

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 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:

A3L31:

"Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-HB-PRP~T Combined Vaccine at 2, 4, and 6 Months of Age versus Sanofi Pasteur's DTaP-IPV//PRP~T Combined Vaccine at 2, 4, and 6 Months of Age + Hep B Vaccine at 1 and 6 Months of Age, in South Korean Infants Primed with Hep B at Birth"

This clinical study A3L31 is a Phase III, randomized, open-label, multi-center, controlled, two-arm study in 310 infants aged 1 month who received a dose of recombinant hepatitis B vaccine at birth according to the National Immunization Program in Republic of Korea. Subjects in the first arm received Sanofi Pasteur's DTaP-IPV-HepB-PRP~T vaccine at 2, 4, and 6 months of age. Subjects in the second arm received DTaP-IPV//PRP~T (Pentaxim™) at 2, 4, and 6 months of age and hepatitis B vaccine (Euvax B®) at 1 and 6 months of age.

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

Description

Infants, males and females, 1 month of age, born from confirmed Hep B surface antigen (HBsAg) seronegative mothers (documented by a laboratory test done during the last trimester of pregnancy or immediately post-delivery) or from HBsAb seropositive mothers (documented by a laboratory test done before the last trimester of pregnancy) were to be included in the study and randomly allocated to one of the following two study groups in a balanced allocation (1:1 ratio):

• Group A: were to receive DTaP-IPV-HB-PRP~T combined vaccine (study vaccine) at 2, 4 and 6 months of age.

• Group B: were to receive Hep B vaccine (Euvax B®) at 1 and 6 months of age and DTaP-IPV//PRP~T combined vaccine (Pentaxim™) at 2, 4, and 6 months of age, according to the official vaccination schedule in place in Republic of Korea.

In accordance with the National Immunization Program, a booster injection against diphtheria (D), tetanus (T), pertussis, and Haemophilus influenzae type b (Hib) infections had to be administered to study subjects during their second year of life (at 15 to 18 months of age). The booster immunization was **not part of this study**. Booster administration was to be performed using any commercially available DTaP and Hib vaccine(s) as per routine practice.

Methods

Study design

Medical history was checked prior to inclusion as well as further vaccinations made between studies (HepA vaccination allowed).

Inclusion and exclusion criteria are as standard for vaccine trials in the EU. Diary cards were provided.

Blood draws for immunogenicity were done D0 (baseline) and D30 post the 3rd dose.

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.

Laboratory assays were the same as for the previous studies; analysis was done at the sponsor's laboratory in Swiftwater, USA.

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	µg/mL

	standard)	
HepB	VITROS ECi/ECiQ (WHO standard)	mIU/mL
Polio (IPV1, 2, 3)	Vero cell neutralization test	1/dilution

Study population /Sample size

310 healthy male and female infants in two groups:

• Group A: DTaP-IPV-HB-PRP~T combined vaccine (study vaccine) at 2, 4 and 6 months of age.

• Group B: Hep B vaccine (Euvax B®) at 1 and 6 months of age and DTaP-IPV//PRP~T combined vaccine (Pentaxim™) at 2, 4, and 6 months of age

Objective(s)

- To demonstrate the non-inferiority in terms of seroprotection (D, T, poliovirus types 1, 2, and 3, PRP~T, Hep B) and seroconversion (≥ 4 fold rise) for pertussis antigens (pertussis toxoid [PT] and filamentous haemagglutinin [FHA]) of Group A versus Group B, one month after the third dose of combined vaccines.

Outcomes/endpoints

Primary:

One month after the third dose of study combined vaccines (day (D)180, Visit 5, at approximately 7 months of age):

- anti-D Ab concentrations ≥ 0.01 International Units (IU) /mL
- anti-T Ab concentrations ≥ 0.1 IU/mL
- anti-PRP Ab concentrations ≥ 0.15 μg/mL
- anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dilution [dil])
- ≥ 4-fold increase in anti-PT and anti-FHA Ab concentrations (ELISA Unit [EU]/mL) from 1 month pre-dose 1 (Visit 1) to 1 month post-dose 3 (Visit 5)
- anti-Hep B Ab concentrations ≥ 10 mIU/mL

Secondary:

Immunogenicity:

1. At D0 (Visit 1, at 1 month of age), before the first dose of vaccines:

- anti-D Ab concentrations ≥ 0.01 IU/mL and ≥ 0.1 IU/mL
- anti-Hep B Ab concentrations ≥ 10 mIU/mL
- individual Ab concentrations: anti-PT, anti-FHA, anti-Hep B, anti-D
- anti-PT and anti-FHA Ab concentrations ≥ Lower Limit of Quantitation (LLOQ)

2. One month after the third dose of study vaccine (D180, Visit 5, at approximately 7 months of age):

- anti-D Ab concentrations ⩾ 0.1 IU/mL
- anti-T Ab concentrations ⩾ 0.01 IU/mL
- anti-PRP Ab concentrations ⩾ 1.0 µg/mL
- individual Ab concentrations/titers: all Abs
- vaccine response for PT and FHA antigens defined as post-dose 3 anti-PT and anti- FHA Ab concentrations in ELISA units (EU)/mL ⩾ 4 x LLOQ if pre-vaccination concentration is < 4 x LLOQ or ⩾ pre-vaccination concentration if pre-vaccination concentrations ⩾ 4 x LLOQ
- ⩾ 2-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from 1 month pre-dose 1 (Visit 1) to 1 month post-dose 3 (Visit 5)
- anti-PT and anti-FHA Ab concentrations ⩾ 5 EU/mL, ⩾ 10 EU/mL, and ⩾ 25 EU/mL
- individual post-/pre-primary vaccination Ab concentration ratios for anti-PT, anti- FHA, anti-Hep B, and anti-D

Safety:

- Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each and any vaccination
- Occurrence of solicited (prelisted in the subject's diary card and electronic Case Report Form [CRF]) injection site and systemic reactions occurring through 7 days (D0 to D7) after each and any vaccination
- Occurrence of unsolicited AEs up to 30 days after each and any vaccination, as well as up to 30 days after Visit 1 for subjects in Group A
- Occurrence of serious adverse events (SAEs) throughout the trial

Other endpoints recorded or derived were described at the time of the statistical analysis plan. Depending on the item, these could include : nature (Medical Dictionary for Regulatory Activities [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.

Observation objective and endpoints:

To demonstrate the non-inferiority of seroprotection rates (for D, T, poliovirus types 1, 2, and 3, PRP~T, Hep B) and vaccine response for pertussis Ags (PT and FHA) of DTaP-IPV-HB-PRP~T, one month after the third dose of combined vaccines (Group A) versus previous data obtained in A3L24 (Group 5 - DTaP-IPV-HB-PRP~T pooled batches) study with the same product.

One month after the third dose of study combined vaccines (D180, Visit 5, at approximately 7 months of age):

- anti-D Ab concentrations ≥ 0.01 IU/mL

- anti-T Ab concentrations ≥ 0.1 IU/mL
- anti-PRP Ab concentrations ≥ 0.15 μg/mL
- anti-poliovirus 1, 2, and 3 Ab titers ≥ 8 (1/dilution [dil])
- vaccine response for PT and FHA antigens defined as post-dose 3 anti-PT and anti-FHA Ab concentrations in ELISA units (EU)/mL ≥ 4 x LLOQ if pre-vaccination concentration is < 4 x LLOQ or ≥ pre-vaccination concentration if pre-vaccination concentrations ≥ 4 x LLOQ
- anti-Hep B Ab concentrations ≥ 10 mIU/mL

Statistical Methods

For each antigen tested, the non-inferiority of immune response was demonstrated if the 95% CI of the difference (tested study vaccine - reference vaccine) layed entirely above the clinically acceptable limit for non-inferiority (-10%) (alpha = 2.5%). The 95% CI of the differences were calculated based on the Wilson score method without continuity correction.

The primary objective was reached if the non-inferiority was proven for all the antigens. The hypothesis of non-inferiority was tested on the per protocol analysis set (PPAS) and was confirmed on the full analysis set (FAS).

The non-inferiority of the immune response to all Ags induced by the study vaccine one month after the third dose was tested against the responses observed against all Ags in a similar trial conducted in Latin America with the same study vaccine (i.e., DTaP-IPV-HB-PRP~T, study A3L24).

Non-inferiority was demonstrated if, for each Ag, the 95% CI of the seroprotection / vaccine response rate observed one month after the third dose of study vaccine lay entirely above the reference value (expected response) minus the clinically-acceptable limit for non-inferiority (set at 10%) in a one-sided equivalence test (using an alpha of 2.5%).

Immunogenicity criteria were described for available blood samples before the first dose and one month after the third dose of the combined vaccines. The following parameters were used:

• GM of Ab concentrations (GMCs)/titers (GMTs) at pre-Dose 1 (for anti-PT, anti-FHA, anti-Hep B, and anti-D) and one month post-Dose 3 (for all antigens)

• GM of individual Ab concentrations/titers ratio:

• post-Dose 3 / pre-Dose 1 (for anti-PT, anti-FHA, anti-Hep B, and anti-D)

• Percentage of subjects with concentrations/titers above predefined thresholds

- Fold-rise rates: ≥ 2-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from 1 month pre-dose 1 (Visit 1) to 1 month post-dose 3 (Visit 5)

• Vaccine response for PT and FHA antigens defined as post-dose 3 anti-PT and anti-FHA Ab concentrations in ELISA units (EU)/mL ≥ 4 x LLOQ if pre-vaccination concentration is < 4 x LLOQ or ≥ pre-vaccination concentration if pre-vaccination concentrations ≥ 4 x LLOQ

Reverse cumulative distribution Curves (RCDCs) of individual concentrations/titers were presented at Visit 1 (Day 0) and Visit 5 (Day 180).

Safety analysis

Safety was described for all subjects by vaccine group in this study, after each and any vaccine administration.

For each safety criterion, the percentage of subjects with the criterion (i.e., with a given symptom) was computed with its 95% CI.

Results

Number analysed

	Group A	Group B
Enrolled	155	155
Fully vaccinated	148	154
Full AS (= Safety AS)	149	155
Per Protocol AS	132	131

Age and weight were similarly distributed between the groups; overall there were more males (55% vs. 45%) especially in Group 1 (58% vs. 41%).

Immunogenicity results

Primary endpoint: Non-inferiority of Hexyon versus Pentaxim+HepB for seroprotection or seroconversion was achieved for all antigens (Table 2).

Secondary endpoints: GMTs in the Hexyon group were similar after doses 1 and 3 for anti-D and anti-FHA. GMs for, anti-PT are lower in the Hexyon group. For the antibodies only measured after the third dose (T, Polio 1-3 and PRP) slightly lower GMTs were seen in the Hexyon group for anti-Polio 1, anti-Polio 3 and anti-PRP. All other antibodies had similar GMTs. ***Of note: Group B received only 2 doses of Hep B (months 1 and 6) whilst Group A received 3 doses (months 2,4 and 6) till the post-dose 3 measurement, thus, GMTs are not comparable here.*** The GMTs for anti-HepB after the first dose are similar for both vaccines (Table 3). Results of the PP are similar in the FAS the data are not separately shown here.

Exploratory endpoint: Non-inferiority of seroprotection and vaccine response respectively against the results from a similar study (A3L24) is shown (Table 5.4, study report), the rates for seroprotection and vaccine response are similar.

Table 2 Summary of seroprotection and vaccine response - titers/concentrations - Per-Protocol Analysis Set (source: table 5.2, study report)

			Group A (N=132)			Group B (N=131)		
			n/M	%	(95% CI)	n/M	%	(95% CI)
Anti-D (IU/mL)	Pre-Dose 1 (V01)	≥ 0.01 IU/mL	70/128	54.7	(45.7; 63.5)	63/131	48.1	(39.3; 57.0)
		≥ 0.1 IU/mL	7/128	5.5	(2.23; 10.9)	6/131	4.6	(1.70; 9.70)
	Post-Dose 3 (V05)	≥ 0.01 IU/mL	130/130	100.0	(97.2; 100)	125/125	100.0	(97.1; 100)
		≥ 0.1 IU/mL	128/130	98.5	(94.6; 99.8)	122/125	97.6	(93.1; 99.5)
Anti-T (IU/mL)	Post-Dose 3 (V05)	≥ 0.01 IU/mL	128/128	100.0	(97.2; 100)	124/124	100.0	(97.1; 100)
		≥ 0.1 IU/mL	127/128	99.2	(95.7; 100)	124/124	100.0	(97.1; 100)
Anti-Polio 1 (1/dil)	Post-Dose 3 (V05)	≥ 8 (1/dil)	130/130	100.0	(97.2; 100)	131/131	100.0	(97.2; 100)
Anti-Polio 2 (1/dil)	Post-Dose 3 (V05)	≥ 8 (1/dil)	130/130	100.0	(97.2; 100)	128/128	100.0	(97.2; 100)
Anti-Polio 3 (1/dil)	Post-Dose 3 (V05)	≥ 8 (1/dil)	130/130	100.0	(97.2; 100)	129/129	100.0	(97.2; 100)
Anti-PRP (µg/mL)	Post-Dose 3 (V05)	≥ 0.15 µg/mL	132/132	100.0	(97.2; 100)	131/131	100.0	(97.2; 100)
		≥ 1 µg/mL	115/132	87.1	(80.2; 92.3)	127/131	96.9	(92.4; 99.2)
Anti-Hep B (mIU/mL)	Pre-Dose 1 (V01)	≥ 10 mIU/mL	97/131	74.0	(65.7; 81.3)	90/131	68.7	(60.0; 76.5)
	Post-Dose 3 (V05)	≥ 10 mIU/mL	129/132	97.7	(93.5; 99.5)	127/131	96.9	(92.4; 99.2)
Anti-PT (EU/mL)	Post-Dose 3 response based on pre-Dose 1 (V05/V01)	Vaccine response*	127/129	98.4	(94.5; 99.8)	126/128	98.4	(94.5; 99.8)
		4-fold increase	122/129	94.6	(89.1; 97.8)	119/128	93.0	(87.1; 96.7)
Anti-FHA (EU/mL)	Post-Dose 3 response based on pre-Dose 1 (V05/V01)	Vaccine response*	129/132	97.7	(93.5; 99.5)	126/131	96.2	(91.3; 98.7)
		4-fold increase	121/132	91.7	(85.6; 95.8)	117/131	89.3	(82.7; 94.0)

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Table 3 Summary of geometric means of concentrations/titers - Per-Protocol Analysis Set (source: table 5.3, study report)

		Group A (N=132)			Group B (N=131)		
		M	GM	(95% CI)	M	GM	(95% CI)
Anti-D (IU/mL)	Pre-Dose 1 (V01)	128	0.010	(0.008; 0.013)	131	0.009	(0.007; 0.012)
	Post-Dose 3 (V05)	130	1.01	(0.874; 1.16)	125	0.676	(0.582; 0.786)
	Post-Dose 3 (V05)/ Pre-dose 1 (V01)	126	99.4	(71.3; 139)	125	80.3	(58.2; 111)
Anti-T (IU/mL)	Post-Dose 3 (V05)	128	3.05	(2.67; 3.48)	124	2.53	(2.30; 2.78)
Anti-Polio 1 (1/dil)	Post-Dose 3 (V05)	130	823	(695; 975)	131	1210	(1003; 1459)
Anti-Polio 2 (1/dil)	Post-Dose 3 (V05)	130	1380	(1126; 1692)	128	1588	(1255; 2009)
Anti-Polio 3 (1/dil)	Post-Dose 3 (V05)	130	899	(721; 1120)	129	1280	(1000; 1639)
Anti-PRP (µg/mL)	Post-Dose 3 (V05)	132	5.44	(4.37; 6.77)	131	9.35	(7.67; 11.4)
Anti-Hep B (mIU/mL)	Pre-Dose 1 (V01)	131	37.3	(26.0; 53.4)	131	41.8	(29.0; 60.2)
	Post-Dose 3 (V05)	132	1068	(805; 1416)	131	827	(601; 1138)
	Post-Dose 3 (V05)/ Pre-dose 1 (V01)	131	28.7	(17.9; 46.1)	131	19.8	(12.0; 32.7)
Anti-PT (EU/mL)	Pre-Dose 1 (V01)	132	2.84	(2.35; 3.43)	131	2.98	(2.40; 3.69)
	Post-Dose 3 (V05)	129	99.0	(90.6; 108)	128	143	(129; 157)
	Post-Dose 3 (V05)/ Pre-dose 1 (V01)	129	34.4	(27.4; 43.2)	128	48.0	(37.3; 61.9)
Anti-FHA (EU/mL)	Pre-Dose 1 (V01)	132	6.30	(5.20; 7.64)	131	6.84	(5.50; 8.51)
	Post-Dose 3 (V05)	132	153	(141; 166)	131	163	(148; 180)
	Post-Dose 3 (V05)/ Pre-dose 1 (V01)	132	24.2	(19.4; 30.2)	131	23.9	(18.3; 31.0)

Safety results

No deaths occurred in this study. One case of fever (onset 6 days post vaccination, no other diagnosis) was judged as related to the Hexyon vaccination. No other SAEs related to the vaccines were reported. No (S)AEs led to discontinuation of the study.

Otherwise similar event rates were seen for solicited local and systemic events in both groups in known frequencies. Frequencies and grades do not increase with additional doses.

No safety issues are identified.

The safety profile remains unchanged.

Discussion on clinical aspects

Regarding immunogenicity the results are similar to what is known from former studies:

Established thresholds of protection and accepted vaccine responses are achieved with Hexyon as well as with the comparator. GMs after the 3rd dose tend to be lower for Hexyon concerning different anti-Polio serotypes and this time anti-PT and anti-PRP. Sadly, the results for anti-HB cannot be compared due to a difference in doses between the two groups. After the one dose GMs are similar at least.

Overall, this study does not add new information regarding the immunogenicity. The clinical relevance of the tendency to lower titres is unknown but as thresholds are reached not expected to be dramatic.

The safety profile remains unchanged.

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.

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