22 June 2017
EMA/CHMP/345017/2017
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 022 (Hexaxim)
EMEA/H/C/002702 / P46 022 (Hexacima)
EMEA/H/C/002796 / P46 020 (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 07 April 2017, the MAH submitted a completed paediatric study **A3L45** 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 **A3L45** "Safety and Immunogenicity of Sanofi Pasteur's DTaP-IPV-HBPRP~T combined Vaccine given as a Primary Series of Vaccination in Infants" is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Licensed product

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:

A3L45:

"Safety and Immunogenicity of Sanofi Pasteur's DTaP-IPV-HBPRP~T combined Vaccine given as a Primary Series of Vaccination in Infants" (Russian Federation, Poland)

Intent of this study was licensure in the Russian Federation. Only one dose of the vaccine was given in that country but immunogenicity and safety were assessed. In Poland three doses were given but due to the vaccine being licensed here already only safety was assessed.

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

Methods

Study design

This clinical study A3L45 is a Phase III, open-label, multi-center one-arm study in 150 infants.

- In the Russian Federation, 1 single dose of DTaP-IPV-HB-PRP~T vaccine was administered between 6 months and 6 months and 29 days of age in infant subjects who had previously received through routine medical practice 2 doses of a DTaP-IPV//PRP~T vaccine (Pentaxim) at 3 and 4.5 months of age (MoA) and 2 doses of a standalone HB vaccine administered within 24 hours of birth and at 1 MoA per the national vaccination calendar of the Russian Federation.
- In Poland, a 3-doses primary series of DTaP-IPV-HB-PRP~T vaccine was administered at 6 to 8 weeks of age, at 3 to 4 MoA, and at 5 to 6 MoA in infant subjects who had received 1 dose of HB vaccine administered within 24 hours of birth per the national vaccination calendar of Poland.

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 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

100 infant subjects in the Russian Federation were enrolled and received 1 dose of DTaP-IPV-HB-PRP~T vaccine and 50 subjects in Poland were enrolled and received a 3-doses primary series of DTaP-IPV-HB-PRP~T vaccine

Objectives

Russian Federation

- To describe the safety and reactogenicity of DTaP-IPV-HB-PRP~T vaccine after a single injection in infants between 6 months and 6 months 29 days of age who had previously received 2 vaccinations with DTaP-IPV//PRP~T (Pentaxim) and 2 doses with HB vaccines administered at ages recommended by the Russian National Immunization Program.
- To evaluate the immunogenicity of DTaP-IPV-HB-PRP~T vaccine 1 month after vaccination.

Poland

- To describe the safety and reactogenicity after each and all doses of DTaP-IPV-HB-PRP~T vaccine administered as a 3-dose primary series.

Outcomes/endpoints

Primary:

- Occurrence of any unsolicited systemic AEs reported in the 30 minutes after each and all dose(s).
- Occurrence of solicited (prelisted in the subject's DC and CRF) injection site and systemic reactions occurring through 7 days (D0-D7) following each and all dose(s).
- Occurrence of unsolicited AEs through 30 days following each and all dose(s).
- Occurrence of SAEs throughout the trial
- Other endpoints recorded or derived as described in the statistical analysis plan (SAP). Depending on the item, these 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

Secondary:

One month (30 to 42 days) after the single dose of study vaccine (D30, Visit 2):

- anti-D Ab concentrations $\geq$ 0.01 International Units (IU) /mL, 0.1 IU/ml, 1.0 IU/ml
- anti-T Ab concentrations $\geq$ 0.1 IU/mL, 0.1 IU/ml, 1.0 IU/ml
- anti-PRP Ab concentrations $\geq$ 0.15 μg/mL, 1.0 μg /ml
- anti-poliovirus 1, 2, and 3 Ab titers $\geq$ 8 (1/dilution [dil])
- anti-Hep B Ab concentrations $\geq$ 10 mIU/mL, 100 mIU/mL
- individual Ab concentrations/titers: all Abs

Statistical Methods

Table 2 Descriptive statistics produced (source: Table 3.3, 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% 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).

Results

Number analysed

	Russian Federation	Poland
Enrolled	100	50
Full AS (= Safety AS)	100	50
Per Protocol AS	97	50

Immunogenicity results

Table 3 Summary of seroprotection for study vaccine Post-Dose 1 (V02) – Russian Federation - Per Protocol Analysis Set (source: table 3.5, clinical overview)

		Russian Federation (N=97)		
		n/M	%	(95% CI)
Anti-D (IU/mL)	**>=0.01 IU/mL**	93/93	100.0	(96.1; 100)
	>=0.1 IU/mL	64/93	68.8	(58.4; 78.0)
	>=1.0 IU/mL	19/93	20.4	(12.8; 30.1)
Anti-T (IU/mL)	**>=0.01 IU/mL**	89/89	100.0	(95.9; 100)
	>=0.1 IU/mL	89/89	100.0	(95.9; 100)
	>=1.0 IU/mL	73/89	82.0	(72.5; 89.4)
Anti-Polio 1 (1/dil)	**>=8 (1/dil)**	92/92	100.0	(96.1; 100)
Anti-Polio 2 (1/dil)	**>=8 (1/dil)**	92/92	100.0	(96.1; 100)
Anti-Polio 3 (1/dil)	**>=8 (1/dil)**	93/93	100.0	(96.1; 100)
Anti-Hep B (mIU/mL)	**>=10 mIU/mL**	96/96	100.0	(96.2; 100)
	>=100 mIU/mL	93/96	96.9	(91.1; 99.4)
Anti-PRP (µg/mL)	**>=0.15 µg/mL**	92/94	97.9	(92.5; 99.7)
	>=1 µg/mL	87/94	92.6	(85.3; 97.0)

n: number of subjects experiencing the endpoint listed in the first three columns
M: number of subjects with available data for the relevant endpoint

Table 4 Summary of geometric means of titers/concentrations for study vaccine Post-Dose 1 (V02) - Russian Federation - Per Protocol Analysis Set (source: table 3.6, clinical overview)

	Russian Federation (N=97)		
	M	GM	(95% CI)
Anti-D (IU/mL)	93	0.278	(0.205; 0.377)
Anti-T (IU/mL)	89	2.08	(1.76; 2.46)
Anti-PT (EU/mL)	89	123	(104; 145)
Anti-FHA (EU/mL)	94	154	(135; 177)
Anti-Polio 1 (1/dil)	92	1358	(1035; 1782)
Anti-Polio 2 (1/dil)	92	2597	(2010; 3355)
Anti-Polio 3 (1/dil)	93	2749	(1904; 3969)
Anti-Hep B (mIU/mL)	96	1679	(1254; 2248)
Anti-PRP (µg/mL)	94	6.25	(4.58; 8.53)

M: number of subjects with available data for the relevant endpoint
FHA: filamentous hemagglutinin; PT: pertussis toxoid

Assessor's comment:
The manner of this study with only one dose of Hexyon after two doses of Pentaxim + HepB makes it hardly relevant which GMs are achieved. Serological protection thresholds are reached in all cases and for all antigens.

Safety results

No deaths occurred in this study.

A total of 3 unsolicited AEs reported by 2 subjects were considered as related to vaccine by the Investigator:

• A subject experienced rash of Grade 2 one day after the second injection. The subject received health care and medication. The event resolved after 9 days. This subject also experienced rash papular of Grade 1 one day after the third injection. The subject received health care and medication. The event resolved after 8 days.

• A subject experienced injection site rash of Grade 2 two days after the third injection. No action was taken. The event resolved after 30 days.

No 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 in the polish part of the study.

No safety issues are identified.

The safety profile remains unchanged.

2.3.3. Discussion on clinical aspects

Due to the nature of the study (only one dose given within immunogenicity part of the study) the immunogenicity results are hardly relevant.

Overall, this study does not add new information regarding the immunogenicity and safety. The safety profile remains unchanged.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.