30 January 2020
EMA/89372/2020
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/P46/035 (Hexaxim)

EMEA/H/C/002702/P46/035 (Hexacima)

EMEA/H/C/002796/P46/033 (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 14 November 2019, the MAH submitted a completed paediatric study MET57 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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that MET57, Immunogenicity and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly with Other Paediatric Vaccines in Healthy Toddlers is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

South Korea and Thailand: MenACYW conjugate vaccine + measles-mumps-rubella (MMR) + varicella (V)

Mexico: MenACYW conjugate vaccine + diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and Haemophilus influenzae type-b (DTaP-IPV-HB-Hib)

Russian Federation: MenACYW conjugate vaccine + pneumococcal conjugate vaccine (PCV13)

2.3. 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:

MET57:

"Immunogenicity and safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine administered concomitantly with other pediatric vaccines in healthy toddlers"

(South Korea, Thailand, the Russian Federation, and Mexico)

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

The primary objective of this study is to describe the immunogenicity profile of MenACYW conjugate vaccine administered alone or concomitantly with licensed paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13). Due to the study focus on MenACWY only results from the two groups (Groups 4 + 6, in Mexico) receiving Hexacima (licensed in Mexico) will be discussed in detail in this report. A general overview of the study is given below with the information regarding those two groups bolded.

2.3.1. Clinical study

MET57: "Immunogenicity and safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine administered concomitantly with other pediatric vaccines in healthy toddlers"

Description

The purpose of MET57 was to demonstrate that the immunogenicity and safety profiles of a single dose of MenACYW conjugate vaccine when administered alone in toddlers 12 to 23 months old were comparable to when MenACYW conjugate vaccine was given concomitantly with licensed paediatric vaccine(s) (measles-mumps-rubella [MMR] + varicella [V], diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and Haemophilus influenzae type-b [DTaPIPV- HB-Hib], or pneumococcal conjugate vaccine [PCV13]), and that the immunogenicity and safety of vaccines routinely administered to toddlers were not affected by concomitant administration with MenACYW conjugate vaccine.

Methods

Objectives

The primary objective is to describe the immunogenicity profile of MenACYW conjugate vaccine administered alone or concomitantly with licensed paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13.

The secondary objective is to describe the immunogenicity profile of licensed paediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine.

Observational Objectives

Immunogenicity

To describe the Ab responses to the meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) after vaccination with MenACYW conjugated vaccine measured by serum bactericidal assay using baby rabbit complement (rSBA) in all subjects in Group 1 and Group 2 and in a subset of subjects in Group 4, Group 5, Group 7, and Group 8 (100 subjects per group in Groups 1, 4, and 7; 50 subjects per group in Groups 2, 5, and 8) (South Korea, Mexico, and the Russian Federation only).

Safety

- To describe the safety profile of MenACYW conjugate vaccine when administered alone or concomitantly with licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13)
- To describe the safety profile of licensed pediatric vaccine(s) (MMR+V, DTaP-IPV-HB-Hib, or PCV13) when administered alone or concomitantly with MenACYW conjugate vaccine

Study design

Phase III, open-label, randomized, parallel-group, active-controlled, multicentre study.

Two groups out of the 12 of the study have received either MenACYW conjugate vaccine and DTaP IPV HB-Haemophilus influenzae Type b (PRP)~T vaccine (200 subjects), or DTaP IPV HB-PRP~T vaccine alone (100 subjects), at 12 to 23 months of age. This study took place in Mexico.

In South Korea and Mexico, healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months on the day of enrolment were randomized in a 2:1:1 ratio (by country) to the following groups:

Mexico:

Group 4: MenACYW conjugate vaccine + DTaP-IPV-HB-Hib on D0

Group 5: MenACYW conjugate vaccine on D0

Group 6: DTaP-IPV-HB-Hib on D0

South Korea:

Group 1: MenACYW conjugate vaccine + MMR + V on Day (D) 0

Group 2: MenACYW conjugate vaccine on D0

Group 3: MMR + V on D0

In the Russian Federation, healthy, meningococcal-vaccine naïve toddlers aged 12 to 14 months or 16 to 23 months on the day of enrolment were assigned to Group 8 with a balanced population distribution of half of the subjects aged 12 to 14 months and half of the subjects aged 16 to 23 months. Healthy, meningococcal-vaccine naïve toddlers, who had not received the 3rd dose of PCV13, aged 15 to 23 months on the day of enrolment were randomized in a 2:1 ratio to Groups 7 and 9, in order to comply with the National Immunization Calendar of the Russian Federation:

The Russian Federation:

Group 7: MenACYW conjugate vaccine + PCV13 on D0

Group 8: MenACYW conjugate vaccine on D0

Group 9: PCV13 on D0 (Visit 1)

> Note about Visits:
>
> Visit 0=Screening visit for subjects in the Russian Federation only
>
> Visit 1=D0, vaccination visit (all countries)
>
> Visit 2=D30 (+14 days), 30 to 44 days after D0 (all countries)
>
> In the Russian Federation, Visit 0 and Visit 1 may have taken place on the same day, or Visit 1 may have taken place up to 5 days after Visit 0.

In Thailand, healthy, meningococcal-vaccine naïve toddlers aged 12 to 23 months on the day of enrolment were randomized in a 2:1:1 ratio to the following groups:

Thailand:

Group 10: MenACYW conjugate vaccine + MMR + V on D0

Group 11: MenACYW conjugate vaccine on D0

Group 12: MMR + V on D0

All Subjects:

All subjects were to provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at Visit 2 (30 to 44 days after vaccination[s]). Solicited adverse event (AE) information was collected for 7 days after vaccination(s); unsolicited AE information was collected from

Visit 1 (D0) to Visit 2, and serious adverse event (SAE) information was collected throughout the study period from Visit 1 through Visit 2. Upon completion of all study procedures and termination from the trial at Visit 2, study participants were to receive the remainder of the recommended toddler vaccines, which were part of the respective National Immunization Programs (NIP) for each country, from their health care provider.

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 of Hexacima (source: study report)

Antigen	Assays and reference standards	Units
Diphtheria	ECL multiplex	IU/ml
Tetanus	ECL multiplex	IU/ml
Pertussis (PT, FHA)	ECL multiplex	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

Products used

MenACYW conjugate vaccine: Meningococcal PS (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA)

Form: Liquid solution

M-M-RII (MMR): Measles, Mumps, and Rubella Virus Vaccine Live (Merck & Co., Inc., Whitehouse Station, NJ, USA); (licensed in South Korea and Thailand)

Form: Solution for injection supplied as lyophilized vaccine and diluent for reconstitution

VARIVAX (V): Varicella Virus Vaccine Live (Merck, Sharp & Dohme, Haarlem, The Netherlands); (licensed in South Korea and Thailand)

Form: Suspension for injection supplied as lyophilized vaccine to be reconstituted using the accompanying sterile diluent

Hexaxim (DTaP-IPV-HB-Hib): Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (recombinant deoxyribonucleic acid [rDNA]), poliomyelitis (inactivated), and Haemophilus influenzae type b conjugate vaccine (adsorbed); (Sanofi Pasteur SA, Marcy l'Etoile, France); (licensed in Mexico as Hexacima)

Form: Suspension for injection

Prevenar 13 (PCV13): Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (Pfizer Ireland Pharmaceuticals, Ireland) (licensed in the Russian Federation)

Form: Suspension for IM injection

Outcomes/endpoints

Primary Endpoint:

Antibody (Ab) titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) for Groups 1, 2, 4, 5, 7, 8, 10, and 11 at Visit 0 (for subjects in the Russian Federation) or Visit 1 (for subjects in Mexico, South Korea, or Thailand) (before vaccination[s]) and 30 days (+14 days) after vaccination(s) (all subjects).

Secondary objectives:

- Abs to the antigens contained in MMR vaccine measured before and 30 days (+14 days) after vaccination with MMR vaccine for Groups 1, 3, 10, and 12.
- Anti-varicella Ab concentrations measured before and 30 days (+14 days) after vaccination with V vaccine for Groups 1, 3, 10, and 12.
- Abs to the tetanus and acellular pertussis antigens (PT and FHA) contained in DTaPIPV-HB-Hib vaccine measured before and 30 days (+14 days) after vaccination with DTaP-IPV-HB-Hib vaccine for Groups 4 and 6.
- Abs to the diphtheria, inactivated polio, hepatitis B, and Haemophilus influenza antigens contained in DTaP-IPV-HB-Hib vaccine measured 30 days (+14 days) after vaccination with DTaP-IPV-HB-Hib vaccine for Groups 4 and 6.
- Anti-pneumococcal Ab concentrations for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F measured before and 30 days (+14 days) after vaccination with PCV13 vaccine for Groups 7 and 9.

Observational objectives:

Immunogenicity:

Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days (+14 days) after vaccination with MenACYW conjugate vaccine in 100 subjects from each of Groups 1, 4, and 7, and in 50 subjects from each of Groups 2, 5, and 8.

Safety:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity, and relationship to vaccination(s) of any unsolicited systemic AEs reported in the 30 minutes after vaccination(s)
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) injection site reactions occurring up to 7 days after vaccination(s)
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and CRF) systemic reactions occurring up to 7 days after vaccination(s)
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to Visit 2 after vaccination(s)

- Occurrence, nature (MedDRA preferred term), time to onset, duration, seriousness criteria, relationship to vaccination, and outcome of SAEs throughout the trial and whether the SAE led to early termination from the study

Statistical Methods

All analyses were descriptive. No hypotheses were tested. All immunogenicity analyses were performed on the Per-Protocol Analysis Set (PPAS). Additional immunogenicity analyses were performed for exploratory purposes on the Full Analysis Set (FAS) according to randomization group. All safety analyses were performed on the Safety Analysis Set (SafAS).

Immunogenicity

Descriptive statistics were provided for the Ab titers against meningococcal serogroups contained in MenACYW conjugate vaccine and for the antigens contained in the licensed vaccines. In general, categorical variables were summarized and presented by frequency counts, percentages, and CIs. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper- Pearson method) for percentages. For geometric mean titers (GMTs) or geometric mean concentrations (GMCs), 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

<u>For the Primary Objective</u>

The immunogenicity descriptive analyses at least included the following:

Ab titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenACYW conjugate vaccine:

- GMT and 95% CI
- Titer distribution and reverse cumulative distribution curve (RCDCs)
- Percentage of subjects with titer ≥ 1:4 and ≥ 1:8 and 95% CI
- Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to postvaccination, and 95% CI
- Percentage of subjects with hSBA vaccine seroresponse*

* hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer had to be ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer had to be at least 4-fold greater than the pre-vaccination titer.

<u>For the Secondary Objective</u>

The analyses on the concomitant vaccines included GMTs and titer distribution or GMCs, and RCDCs, as well as percentage of subjects with:

- Abs to the antigens contained in MMR vaccine measured before and 30 days after vaccination with MMR vaccine:

    - Anti-measles Ab concentrations ≥ 255 mIU/mL
    - Anti-mumps Ab concentrations ≥ 10 Mumps Ab units/mL
    - Anti-rubella Ab concentrations ≥ 10 IU/mL
- Anti-varicella Ab concentrations before and 30 days after vaccination with V vaccine ≥ 5 glycoprotein (gp) enzyme-linked immunosorbent assay [ELISA] Ab units/mL
- Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured before and 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
    - Anti-tetanus Ab concentrations ≥ 0.01 and 0.1 IU/mL at D0 and ≥ 0.1 and 1.0 IU/mL at D30
    - Anti-pertussis (PT and FHA) Ab concentrations and pertussis vaccine response†
    - Abs to the antigens contained in DTaP-IPV-HB-Hib vaccine measured 30 days after vaccination with DTaP-IPV-HB-Hib vaccine:
        - Anti-diphtheria Ab concentrations ≥ 0.1 and 1.0 IU/mL
        - Anti-PRP Ab concentrations ≥ 0.15 and 1.0 μg/mL
        - Anti-poliovirus types 1, 2, and 3 Ab titers ≥ 1:8
        - Anti-HBsAg Ab concentrations ≥ 10 and 100 milli-international units (mIU)/mL

† Pertussis vaccine response:

- If the pre-booster vaccination concentration is < 4 x lower limit of quantification (LLOQ), then the post-booster vaccination concentration is ≥ 4 x the pre-booster concentration;
- If the pre-booster vaccination concentration is ≥ 4 x LLOQ, then the post-booster vaccination concentration is ≥ 2 x the pre-booster concentration.

- Anti-pneumococcal Ab concentrations ≥ 0.35 μg/mL and 1.0 μg/mL and 95% CI for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F measured before and 30 days after vaccination with PCV13 vaccine

<u>For the Observational Objective</u>

<u>Immunogenicity</u>

The immunogenicity descriptive analyses included the following:

Ab titers against meningococcal serogroups A, C, Y, and W measured by rSBA before and 30 days after vaccination with MenACYW conjugate vaccine:

- GMT and 95% CI
- Titer distribution and RCDCs
    - Percentage of subjects with titer ≥ 1:8 and ≥ 1:128 and 95% CI
    - Percentage of subjects with titer ≥ 4-fold rise from pre-vaccination to postvaccination, and 95% CI
- Percentage of subjects with rSBA vaccine seroresponse*

* rSBA vaccine seroresponse was defined as a post-vaccination titer ≥ 1:32 for subjects with pre-vaccination rSBA titer < 1:8, or a post-vaccination titer ≥ 4 times the prevaccination titer for subjects with pre-vaccination rSBA titer ≥ 1:8.

Safety

Safety results were described for subjects in all study groups. The main parameters for the safety endpoints were described by 95% CIs (based on the Clopper-Pearson method).

Results

In the Mexican study groups the children were comparable regarding age and ethnicity. The male/female ratio was also similar in the groups with slightly more male subjects (~53%) in each group.

Number analysed

A total of 1183 subjects were enrolled in this study and randomly allocated to one of the following groups depending on the country: Group 1 (107 subjects), Group 2 (53 subjects), and Group 3 (53 subjects) in South Korea, Group 4 (200 subjects), Group 5 (100 subjects), and Group 6 (100 subjects) in Mexico, Group 7 (200 subjects), Group 8 (100 subjects), and Group 9 (100 subjects) in the Russian Federation, and Group 10 (86 subjects), Group 11 (42 subjects), and Group 12 (42 subjects) in Thailand.

There were no early terminations due to an SAE (there was a single instance of early termination due to a non-serious AE of gastroenteritis). A total of 1177 (99.5%) subjects received vaccine and all of these subjects received the vaccine as randomized. A total of 1159 (98.0%) subjects completed the trial.

Figure 1 Subject Disposition Flow Chart for the Mexican subgroups (source: Fig. 4.1, study report)

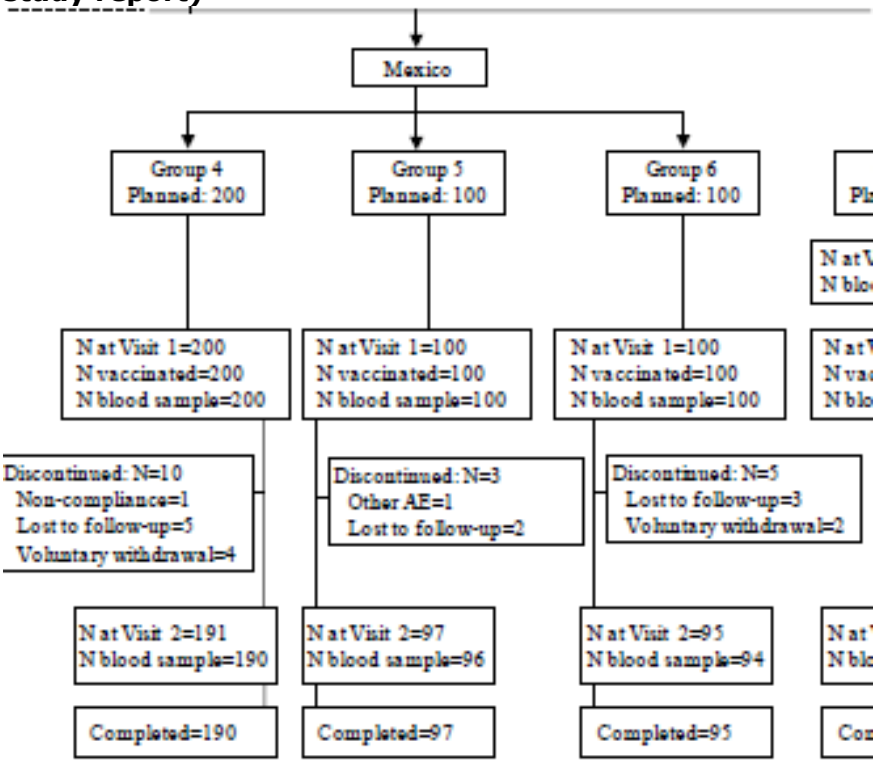

Table 2 Disposition by randomized group - All Enrolled Subjects in Mexican subgroups (source: Table 4.1, study report)

Time point		Group 4 MenACYW conjugate vaccine + DTaP-IPV-HB-Hib (N=200) n(%)	Group 5 MenACYW conjugate vaccine (N=100) n(%)	Group 6 DTaP-IPV-HB-Hib (N=100) n(%)
V00 (D-5)	Enrolled at V00	NA	NA	NA
	Provided blood sample at V00	NA	NA	NA
V01 (D0)	Enrolled at V01	200	100	100
	Randomized at V01	200 (100.0)	100 (100.0)	100 (100.0)
	Provided blood sample at V01	200 (100.0)	100 (100.0)	100 (100.0)
	Received vaccine at V01	200 (100.0)	100 (100.0)	100 (100.0)
	Received vaccine at V01 as randomized	200 (100.0)	100 (100.0)	100 (100.0)
V02 (D30)	Present at V02	191 (95.5)	97 (97.0)	95 (95.0)
	Provided blood sample at V02	190 (95.0)	96 (96.0)	94 (94.0)
Termination	Completed trial	190 (95.0)	97 (97.0)	95 (95.0)
	Discontinued	10 (5.0)	3 (3.0)	5 (5.0)
	Early termination reason			
	SAE	0 (0.0)	0 (0.0)	0 (0.0)
	Other AE	0 (0.0)	1 (1.0)	0 (0.0)
	Non-compliance with the protocol	1 (0.5)	0 (0.0)	0 (0.0)
	Lost to follow-up	5 (2.5)	2 (2.0)	3 (3.0)
	Voluntary withdrawal not due to an AE	4 (2.0)	0 (0.0)	2 (2.0)

Immunogenicity results

Table 3 Summary of response rates for DTaP-IPV-HB-Hib vaccine administrated alone or concomitantly with MenACYW vaccine – Per protocol Analysis Set (source: table 5.27, study report)

			Group 4 MenACYW conjugate vaccine + DTaP-IPV-HB-Hib (N=155)			Group 6 DTaP-IPV-HB-Hib (N=68)		
Antigens	**Time point**	**Criteria**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Diphtheria	**D30**	**>=0.1 IU/mL**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
		>=1 IU/mL	153/155	98.7	(95.4; 99.8)	68/68	100.0	(94.7; 100)
Tetanus	**D0**	**>=0.01 IU/mL**	155/155	100.0	(97.6; 100)	67/67	100.0	(94.6; 100)
		>=0.1 IU/mL	126/155	81.3	(74.2; 87.1)	52/67	77.6	(65.8; 86.9)
	D30	**>=0.1 IU/mL**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
		>=1 IU/mL	152/155	98.1	(94.4; 99.6)	67/68	98.5	(92.1; 100.0)
PT	**D30/D0**	**Vaccine response***	141/155	91.0	(85.3; 95.0)	63/68	92.6	(83.7; 97.6)
FHA	**D30/D0**	**Vaccine response***	138/155	89.0	(83.0; 93.5)	60/68	88.2	(78.1; 94.8)
Polio 1	**D30**	**>=8 (1/dil)**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
Polio 2	**D30**	**>=8 (1/dil)**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
Polio 3	**D30**	**>=8 (1/dil)**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
Hep B	**D30**	**>=10 mIU/mL**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
		>=100 mIU/mL	153/155	98.7	(95.4; 99.8)	68/68	100.0	(94.7; 100)
PRP	**D30**	**>=0.15 µg/mL**	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)
		>=1.0 µg/mL	155/155	100.0	(97.6; 100)	68/68	100.0	(94.7; 100)

N: Number of subjects analyzed according to PPAS
n: number of subjects;
M: number of subjects with valid serology results for the particular antigen and time point
%: percentages and 95% CI are calculated according to the subjects available for the endpoint
*Pertussis vaccine response: If the pre-vaccination concentration is < 4 x LLOQ, then the post-booster vaccination concentration is ≥ 4 x the pre-vaccination concentration;
If the pre-vaccination concentration is ≥ 4 x LLOQ, then the post-vaccination concentration is ≥ 2 x the pre- vaccination concentration

Table 4 Summary of geometric means for DTaP-IPV-HB-Hib vaccine administrated alone or concomitantly with MenACYW vaccine – Per-protocol Analysis Set (source: table 5.28, study report)

		Group 4 MenACYW conjugate vaccine + DTaP-IPV-HB-Hib (N=155)			Group 6 DTaP-IPV-HB-Hib (N=68)		
Antigens	**Time Point**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
Diphtheria	**D30**	155	5.52	(4.94; 6.17)	68	6.34	(5.51; 7.30)
Tetanus	**D0**	155	0.238	(0.196; 0.289)	67	0.234	(0.177; 0.309)
	D30	155	7.06	(6.01; 8.29)	68	7.11	(5.79; 8.74)
PT	**D0**	155	17.9	(15.1; 21.3)	68	20.4	(15.3; 27.0)
	D30	155	144	(130; 159)	68	169	(144; 198)
FHA	**D0**	155	45.5	(37.0; 55.9)	68	57.4	(41.4; 79.5)
	D30	155	299	(265; 337)	68	391	(319; 480)
Polio 1	**D30**	155	4560	(3870; 5373)	68	4034	(3052; 5332)
Polio 2	**D30**	155	7244	(6208; 8453)	68	5618	(4578; 6895)
Polio 3	**D30**	155	5977	(4958; 7205)	68	5100	(3840; 6772)
Hep B	**D30**	155	5171	(4104; 6515)	68	7308	(5135; 10401)
PRP	**D30**	155	46.6	(39.6; 54.9)	68	56.2	(41.5; 76.1)

M: number of subjects with valid serology results for the particular antigen and time point
N: number of subjects in PPAS

Assessor's comment:
Serological protection thresholds are reached in all cases and for all antigens of Hexyon regardless of concomitant or staggered use of Hexyon and MenACWY.
GMTs are often slightly higher in the staggered use group (6) but the Polio antibody GMTs are slightly higher in concomitant use.
Overall, the results confirm the information already to be found in the Hexyon SmPC.

Safety results

Table 5 Safety overview after vaccine injection in Groups 4, 5, and 6 - Safety Analysis Set (source: table 6.4, study report)

	Group 4 MenACYW conjugate vaccine + DTaP-IPV-HB-Hib (N=200)			Group 5 MenACYW conjugate vaccine (N=100)			Group 6 DTaP-IPV-HB-Hib (N=100)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Within 30 min after vaccine injections									
Immediate unsolicited AE	0/200	0.0	(0.0; 1.8)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)
Immediate unsolicited AR	0/200	0.0	(0.0; 1.8)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)
Solicited reaction	133/191	69.6	(62.6; 76.1)	57/98	58.2	(47.8; 68.1)	75/95	78.9	(69.4; 86.6)
Solicited injection site reaction	111/191	58.1	(50.8; 65.2)	32/98	32.7	(23.5; 42.9)	62/95	65.3	(54.8; 74.7)
MenACYW	85/191	44.5	(37.3; 51.9)	32/98	32.7	(23.5; 42.9)	NA	NA	NA
DTaP-IPV-HB-Hib	104/191	54.5	(47.1; 61.7)	NA	NA	NA	62/95	65.3	(54.8; 74.7)
Solicited systemic reaction	98/191	51.3	(44.0; 58.6)	49/98	50.0	(39.7; 60.3)	48/95	50.5	(40.1; 60.9)
Within 30 days after vaccine injection									
Unsolicited AE	86/200	43.0	(36.0; 50.2)	45/100	45.0	(35.0; 55.3)	46/100	46.0	(36.0; 56.3)
Unsolicited AR	2/200	1.0	(0.1; 3.6)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)
Unsolicited non-serious AE	86/200	43.0	(36.0; 50.2)	45/100	45.0	(35.0; 55.3)	45/100	45.0	(35.0; 55.3)
Unsolicited non-serious AR	2/200	1.0	(0.1; 3.6)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)
Unsolicited non-serious injection AR	2/200	1.0	(0.1; 3.6)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)
MenACYW	0/200	0.0	(0.0; 1.8)	0/100	0.0	(0.0; 3.6)	NA	NA	NA
DTaP-IPV-HB-Hib	2/200	1.0	(0.1; 3.6)	NA	NA	NA	0/100	0.0	(0.0; 3.6)
Unsolicited non-serious systemic AE	86/200	43.0	(36.0; 50.2)	45/100	45.0	(35.0; 55.3)	45/100	45.0	(35.0; 55.3)
Unsolicited non-serious systemic AR	0/200	0.0	(0.0; 1.8)	0/100	0.0	(0.0; 3.6)	0/100	0.0	(0.0; 3.6)

n: number of subjects experiencing the endpoint listed in the 1st column
M: number of subjects with available data for the relevant endpoint
N: number of subjects in SafAS
Percentages are based on M.
'Immediate unsolicited AE' is collected only for immediate unsolicited systemic AE

'Unsolicited AE' also includes immediate and serious unsolicited AEs. 'Unsolicited non-serious AE' includes any unsolicited AE that is non-serious.

Assessor's comment:
Solicited AEs were not more frequent in the concomitant versus staggered groups.

No deaths occurred in this study.

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 as already known from other trials with this vaccine.

No safety issues are identified.

The safety profile remains unchanged.

Discussion on clinical aspects

For both safety and immunogenicity the results of this study confirm the information known and already reflected in the product information.

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

CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.