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

Infanrix hexa

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/C/000296/P46/119

Note

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

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Rapporteur's assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Infanrix hexa

International non-proprietary name: 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.: EMA/H/C/296/P46 119

Marketing authorisation holder (MAH): GlaxoSmithKline Biologicals SA

Rapporteur:	Daniel Brasseur
Start of the procedure:	25/04/2016
Date of this report:	28/06/2016
Deadline for Rapporteur's AR:	27/06/2016
Deadline for CHMP member's comments:	11/07/2016
Date of the Rapporteur's final report:	14/07/2016

Introduction

On 22 March 2016, the MAH submitted the final study report of study **DTPa-HBV-IPV-119** for Infanrix hexa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study 111157 (DTPa-HBV-IPV-119) is a standalone study. The main objective of the study was to determine the safety and immunogenicity of Infanrix hexa when administered to Indian infants according to a 6-10-14 weeks of age and a 2-4-6 months of age schedule, in rder to support the marketing authorization application of Infanrix hexa in India.

The current standard of care in India recommends

- At birth: vaccination against tuberculosis (BCG), poliomyelitis (OPV), hepatitis B
- At 6, 10 and 14 weeks of age: Diphtheria, tetanus, pertussis (DTPw), poliomyelitis (OPV and IPV), Hib
- At 6 and 14 weeks of age: hepatitis B

The highest valent combination vaccines currently available in India are the 5-valent vaccines: DTPw-HBV-Hib and DTPa-IPV/Hib.

A first study has confirmed the safety profile of the vaccine in Indian infants [104005 (DTPa-HBV-IPV-106)]. The present study was performed to establish the immunogenicity and safety of the vaccine in Indian infants.

1.2. Information on the pharmaceutical formulation used in the study

All subjects received three doses of Infanrix hexa (Lot Numbers AC21B293A and AHIBC456D).

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

• Study 111157 (DTPa-HBV-IPV-119), a phase III, open-label, randomised, multicentre study to evaluate the immunogenicity and safety of the combined DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) administered to Indian infants according to a 6-10-14 weeks of age or a 2-4-6 months of age schedule.

1.3.2. Clinical study

Study 111157 (DTPa-HBV-IPV-119), a phase III, open-label, randomised, multicentre study to evaluate the immunogenicity and safety of the combined DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) administered to Indian infants according to a 6-10-14 weeks of age or a 2-4-6 months of age schedule.

Description

This was a phase III, open-label, randomised, multicentre study in India with two groups (N=112 per group), with all subjects receiving three dose of DTPa-HBV-IPV/Hib vaccine. Two blood samples were collected, one (2 mL) before the administration of the first dose and a second sample (5 mL) approximately one month after the third dose. Safety data was collected up to 30 days after administration of the study vaccine.

The first subject was enrolled in the study on 16 April 2012 and the last study visit was on 25 February 2013. The data lock point was 4 December 2015.

Methods

Objectives

Primary objective

Immunogenicity

- To assess the immunological response to the study vaccine in terms of seroprotection status for diphtheria, tetanus, polio, hepatitis B and Hib antigens, and in terms of vaccine response for the pertussis antigens, one month after the third dose of the primary vaccination.

Secondary objective

Immunogenicity

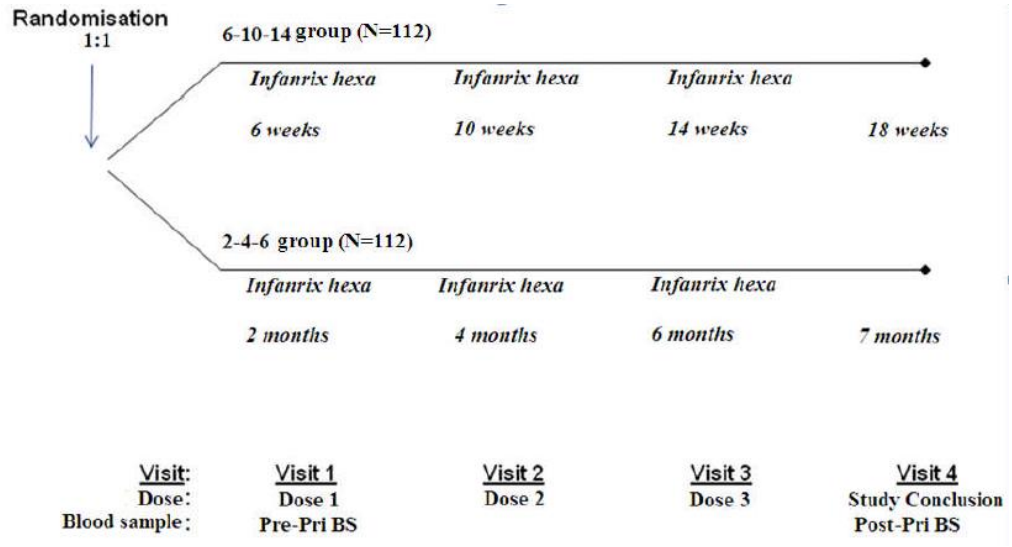
- To assess the immunological response to the study vaccine in terms of seroprotection/seropositivity status and antibody concentrations or titres for all antigens, one month after the third dose of the primary vaccination.
- To assess the immunological status towards hepatitis B, pertussis and polio antigens in terms of antibody concentrations, before the first dose of the primary vaccination.

Safety

- To assess the safety and reactogenicity of the study vaccine in terms of solicited and unsolicited, local and general symptoms and serious adverse events.

Study design

Phase III, open-label, non-randomised, multicentre study in India with two groups and all subjects receiving three doses of hexavalent vaccine. Collection of blood samples before dose 1 and one month post dose 3.



N = number of subjects planned to be enrolled
BS = Blood sample
Pre-Pri = Blood sample to be collected before the first dose of the primary vaccination course.
Post-Pri = Blood sample to be collected one month after the third dose of the primary vaccination course.

Study population

Inclusion criteria

- A male or female between, and including, 6 and 10 weeks of age at the time of the first vaccination.
- Documented administration of a hepatitis B vaccine dose at birth (from Day 0 to Day 7 after birth).
- Subjects who the investigator believed that their parent(s)/legally acceptable representative(s) could and would comply with the requirements of the protocol.
- Written informed consent was obtained from the parent(s)/ legally acceptable representative(s) of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born after a gestation period of at least 36 weeks.

Exclusion criteria

- Child in care
- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines within 30 days preceding the first dose, or planned use during the study period.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. For corticosteroids, this was meant to be prednisone ≥0.5 mg/kg/day, or equivalent. Inhaled and topical steroids were allowed.

- Administration of a vaccine not foreseen by the study protocol, within 30 days prior to the first study visit, or planned administration during the study period, with the exception of oral human rotavirus (HRV) vaccination which was allowed at any time during the study.
- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or was exposed to an investigational or a noninvestigational product (pharmaceutical product or device).
- Evidence of previous diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib vaccination or disease, with the exception of a birth dose of hepatitis B vaccine and OPV as per local standard of care.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- Family history of congenital or hereditary immunodeficiency.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine.
- Major congenital defects or serious chronic illness.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Acute disease and/or fever at the time of enrolment. Fever was defined as temperature ≥ 37.5°C/99.5°F on oral, axillary or tympanic setting, or ≥38.0° C/100.4° F on rectal setting. The preferred route for recording temperature in this study was oral/axillary.
- Subjects with a minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may have be enrolled at the discretion of the investigator.

Sample size

A total of 224 subjects were vaccinated and **223 subjects** completed the study and were therefore included in the ATP cohort for safety. Twelve subjects were excluded and therefore **211 subjects** were included in the ATP cohort for analysis of immunogenicity.

The target sample size was 200 subjects (100 subjects per group) evaluable for immunogenicity. Considering that approximately 10% of enrolled subjects might withdraw or may not be evaluable for immunogenicity, the number of subjects enrolled was 224 subjects (112 subjects per group).

Table 1. Number of subjects enrolled into the study as well as the number of subjects excluded from ATP analyses with reasons for exclusion

	Total			6-10-14 group		2-4-6 group	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**
Total cohort	225			113		112	
Study vaccine dose not administrated but subject number allocated (code 1030)	1	1		1	1	0	0
Total vaccinated cohort	224		100	112		112	
Study vaccine dose not administered according to protocol (code 1070)	1	1		0	0	1	1
ATP cohort for safety	223		99.6	112		111	
Protocol violation (inclusion/exclusion criteria) (code 2010)	7	7		5	5	2	2
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	2	2		0	0	2	2
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	2	2		1	1	1	1
Essential serological data missing (code 2100)	1	1		1	1	0	0
ATP cohort for immunogenicity	211		94.2	105		106	

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort
Codes are listed based on a ranking order

Treatments

Vaccination schedules and treatment groups: Infanrix hexa was administered at two schedules in infants who have received hepatitis B vaccination at birth;

- 6-10-14 group: Subjects in this group received Infanrix hexa at 6-10-14 weeks of age.
- 2-4-6 group: Subjects in this group received Infanrix hexa at 2-4-6 months of age.

Endpoints

All analyses are descriptive.

Primary endpoint

Immunogenicity

- Anti-diphtheria, anti-tetanus, anti-HBs, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3 and anti-PRP **seroprotection status**, one month after the third dose of primary vaccination.
- **Vaccine response** to PT, FHA and PRN, one month after the third dose of primary vaccination.

Secondary endpoint

Immunogenicity

- Anti-diphtheria, anti-tetanus, anti-HBs, anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-PRP, anti-PT, anti-FHA, anti-PRN **antibody concentrations** or titres, one month after the third dose of primary vaccination.
- Anti-PT, anti-FHA, anti-PRN antibody seropositivity status, one month after the third dose of primary vaccination.
- Anti-poliovirus type 1, anti-poliovirus type 2, anti-poliovirus type 3, anti-PT, anti-FHA, anti-PRN and anti-HBs antibody titres or concentrations and seropositivity/seroprotection status, before the first dose of primary vaccination.

Safety

- **Solicited local and general symptoms**: Occurrence of solicited local/general symptoms during the 4-day (Day 0-Day 3) follow-up period after each vaccination.
- **Unsolicited Adverse Events (AEs)**: Occurrence of unsolicited symptoms during the 31-day (Day 0-Day 30) followup period after each vaccination.
- **SAEs**: Occurrence of SAEs from Dose 1 up to study end.

Exploratory analyses

As per the request of the regulatory authorities in India, the initial study protocol was amended to include also two subgroup analyses:

- A subgroup analysis of seropositivity rates, seroprotection rates with exact 95% CI and GMC with 95% CI for hepatitis B antigen, before the first dose of primary vaccination was performed based on the hepatitis B status of the mother. However, since none of the mothers reported a hepatitis B infection, this subgroup analysis was not performed.

- A subgroup analysis of seroprotection rates with exact 95%CI and GMT with 95% CI for all three poliovirus types, before the first dose of primary vaccination was performed based on the number of OPV birth doses.

These analyses were performed for information only. In case the numbers of subjects in each subgroup were insufficient, the information was to be provided in the form of an individual data listing in the clinical study report.

The results of the exploratory group comparisons were to be interpreted with caution considering that there was no adjustment for multiplicity for these comparisons and that the clinical relevance of any differences was not accounted for in the planning of the exploratory analyses.

Statistical Methods

ATP cohort for analysis of safety

All vaccinated subjects:

- who had received at least one dose of study vaccine according to their random assignment
- for whom administration route and site of study vaccine was known and according to the protocol and
- who have not received a vaccine not specified or forbidden in the protocol.

ATP cohort for analysis of immunogenicity

All subjects from the ATP cohort for analysis of safety:

- who met all eligibility criteria
- who complied with the procedures and intervals defined in the protocol
- who did not meet any of the elimination criteria during the study
- who did not receive a product leading to exclusion from an ATP analysis
- who did not present with a medical condition leading to exclusion from an ATP analysis
- for whom data concerning immunogenicity endpoint measures were available. This included subjects for whom assay results were available for antibodies against at least one study

vaccine antigen component after vaccination. The interval between Visit 3 and Visit 4, considered for inclusion of a subject was 21–48 days.

Derived and transformed data

- A **seronegative subject** was a subject whose antibody concentration/titre was below the assay cut-off.
- A **seropositive subject** was a subject whose antibody concentration/titre was greater than or equal to the assay cut-off.
- A **seroprotected subject** was a subject whose antibody concentration/titre was greater than or equal to the level defining clinical protection. The following seroprotection thresholds are applicable:
    - Anti-diphtheria antibody concentrations ≥0.1 IU/ml.
    - Anti-tetanus antibody concentrations ≥0.1 IU/ml.
    - Anti-HBs antibody concentrations ≥10 mIU/ml.
    - Anti-poliovirus types 1, 2 and 3 antibody titres ≥8.
    - Anti-PRP antibody concentrations ≥0.15 µg/ml.

  Other cut-offs were considered:

    - Anti-PRP antibody concentrations ≥1.0 µg/ml.
    - Anti-diphtheria antibody concentrations ≥1.0IU/ml.
    - Anti-tetanus antibody concentrations ≥1.0 IU/ml.
    - Anti-HBs antibody concentrations ≥100 mIU/ml.
- **Vaccine response** to PT, FHA and PRN, was defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations < cut-off value) or at least maintenance of pre-vaccination antibody concentrations in subjects who were initially seropositive (i.e. with concentrations ≥ cut-off value), taking into consideration the decreasing maternal antibodies.
- The geometric mean titres (**GMT**) /geometric mean concentrations (**GMC**) calculations were performed by taking the anti-log of the mean of the log10 titre/concentration transformations. Antibody titres/concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation. For anti-HBs GMC calculation, as per CLIA assay specification, results between 6.2 mIU/ml (assay cut-off) and 7.65 mIU/ml [Lower Limit of quantification (LLOQ)] were quantified as 6.2 mIU/ml only.

Results

Analysis of demographics/baseline characteristics

Table 1. Summary of demographic characteristics (Total vaccinated cohort)

		6-10-14 group N = 112		2-4-6 group N = 112		Total N = 224	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (weeks) at vaccination dose*	Mean	6.7	-	6.8	-	6.8	-
	SD	1.0	-	1.1	-	1.1	-
	Median	6.0	-	6.0	-	6.0	-
	Minimum	6	-	6	-	6	-
	Maximum	10	-	10	-	10	-
Gender	Female	52	46.4	52	46.4	104	46.4
	Male	60	53.6	60	53.6	120	53.6
Geographic Ancestry	Asian - Central/South Asian Heritage	112	100	112	100	224	100

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation
* Age at vaccination dose: 1

Efficacy results

- *Immunogenicity against Diphtheria and Tetanus*

Table 2. Seroprotection rates and geometric mean concentrations (GMCs) for anti-Diphtheria and anti-Tetanus antibody concentrations by groups one month after third dose of vaccination (ATP cohort for immunogenicity)

				≥ 0.1 IU/ml				≥ 1 IU/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti- Diphtheria	6-10-14 group	Post-Pri	105	105	100	96.5	100	96	91.4	84.4	96.0	2.334	2.049	2.659
	2-4-6 group	Post-Pri	106	106	100	96.6	100	102	96.2	90.6	99.0	3.726	3.260	4.258
Anti-Tetanus	6-10-14 group	Post-Pri	105	105	100	96.5	100	104	99.0	94.8	100	3.307	2.925	3.739
	2-4-6 group	Post-Pri	106	106	100	96.6	100	106	100	96.6	100	4.904	4.378	5.493

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
Seroprotection =anti-Diphtheria and anti-Tetanus antibody concentration ≥ 0.1 IU/ml
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Post-Pri = Blood sample collected one month after the third dose of the primary vaccination course

One month post-dose 3:

- All subjects were **seroprotected against diphtheria** in 6-10-14 group and 2-4-6 group, respectively. The GMC values ranged between 2.334 IU/ml and 3.726IU/ml across two groups.
- All subjects were **seroprotected against tetanus** in 6-10-14 and 2-4-6 group. The GMC values ranged between 3.307 IU/ml and 4.904 IU/ml across two groups.

- *Immunogenicity against hepatitis B*

Table 4. Seroprotection rate and geometric mean concentrations (GMCs) for anti-HBs by groups before first dose of vaccination and one month after third dose of vaccination (ATP cohort for immunogenicity)

				≥ 6.2 mIU/ml				≥ 10 mIU/ml				≥ 100 mIU/ml				GMC		
						95% CI				95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-HBs	6-10-14 group	Pre-Pri*	80	15	18.8	10.9	29.0	14	17.5	9.9	27.6	6	7.5	2.8	15.6	5.9	4.2	8.3
		Post-Pri	101	101	100	96.4	100	101	100	96.4	100	99	98.0	93.0	99.8	1695.7	1395.2	2060.9
	2-4-6 group	Pre-Pri*	81	18	22.2	13.7	32.8	13	16.0	8.8	25.9	6	7.4	2.8	15.4	5.6	4.1	7.7
		Post-Pri	105	104	99.0	94.8	100	104	99.0	94.8	100	104	99.0	94.8	100	3314.5	2645.2	4153.1

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
Seroprotection =anti-HBs antibody concentration ≥ 10 mIU/ml
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = Blood sample collected before the first dose of the primary vaccination course
Post-Pri = Blood sample collected one month after the third dose of the primary vaccination course
*All subjects received a birth dose of hepatitis B vaccine as per local standard of care.

Before the first dose

- 17.5% of the subjects in 6-10-14 group and 16.0% of the subjects in 2-4-6 group were seroprotected for HBs antigen. The prevaccination rates were mainly due to the fact that the subjects received a birth dose of hepatitis B vaccine.

One month post-dose 3:

- All subjects in 6-10-14 group and 99% of subjects (i.e. all subjects except one) in 2-4-6 group were **seroprotected against hepatitis B**. The GMC values ranged between 1695.7mIU/ml and 3314.5mIU/ml across the two groups.

- *Immunogenicity against poliomyelitis*

All subjects had received an OPV dose at birth as per standard of care in India.

Table 2. Seroprotection rates and geometric mean titres (GMTs) for anti-Poliovirus 1, 2 and 3 antibody by groups before first dose of vaccination and one month after third dose of vaccination (ATP cohort for immunogenicity)

				≥ 8 ED50				GMT		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-Poliovirus 1	6-10-14 group	Pre-Pri*	97	71	73.2	63.2	81.7	53.5	33.5	85.3
		Post-Pri	99	99	100	96.3	100	884.3	666.6	1173.1
	2-4-6 group	Pre-Pri*	102	70	68.6	58.7	77.5	31.9	21.5	47.2
		Post-Pri	99	99	100	96.3	100	1799.2	1429.0	2265.5
Anti-Poliovirus 2	6-10-14 group	Pre-Pri*	56	38	67.9	54.0	79.7	32.5	19.2	55.0
		Post-Pri	77	77	100	95.3	100	840.2	616.9	1144.2
	2-4-6 group	Pre-Pri*	55	42	76.4	63.0	86.8	36.2	22.2	59.0
		Post-Pri	88	88	100	95.9	100	2138.7	1658.1	2758.7
Anti-Poliovirus 3	6-10-14 group	Pre-Pri*	88	23	26.1	17.3	36.6	8.0	5.9	10.8
		Post-Pri	74	73	98.6	92.7	100	923.7	691.9	1233.2
	2-4-6 group	Pre-Pri*	91	30	33.0	23.5	43.6	11.9	8.3	17.0
		Post-Pri	79	79	100	95.4	100	2245.5	1866.1	2702.1

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
Seroprotection =anti-Poliovirus 1,2 and 3 antibody titres ≥ 8 ED50
GMT = geometric mean antibody titre calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titre equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = Blood sample collected before the first dose of the primary vaccination course
Post-Pri = Blood sample collected one month after the third dose of the primary vaccination course
*All subjects received oral poliovirus vaccine as per local standard of care.

Anti-Poliovirus 1:

- Before first dose of primary vaccination, 73.2% of subjects in 6-10-14 group and 68.6% of subjects in 2-4-6 group were seroprotected against poliovirus type 1, reflecting the previous OPV vaccination received as per local standard of care.
- One month after vaccination, all the subjects in both the groups were seroprotected.
- The GMTs values increased from 53.5 ED50 to 884.3 ED50 in 6-10-14 group and from 31.9 ED50 to 1799.2 ED50 in 2-4-6 group.

Anti-Poliovirus 2:

- Before first dose of primary vaccination, 67.9% of subjects in 6-10-14 group and 76.4% of subjects in 2-4-6 group were seroprotected against poliovirus type 2, reflecting the previous OPV vaccination received as per local standard of care.
- One month after vaccination, all the subjects in both the groups were seroprotected.
- The GMT values increased from 32.5 ED50 to 840.2 ED50 in 6-10-14 group and from 36.2 ED50 to 2138.7 ED50 in 2-4-6 group.

Anti-Poliovirus 3:

- Before first dose of primary vaccination, 26.1% of subjects in 6-10-14 group and 33.0% of subjects in 2-4-6 group were seroprotected against poliovirus type 3, reflecting the previous OPV vaccination received as per local standard of care.
- One month after vaccination, 98.6% of subjects (i.e. all subjects except one) in 6-10-14 group and all subjects in 2-4-6 group were seroprotected.
- The GMT values increased from 8.0 ED50 to 923.7 ED50 in 6-10-14 group and from 11.9 ED50 to 2245.5 ED50 in 2-4-6 group.

All initially seronegative subjects (i.e. antibody concentration < 5 ELU/ml) for all three antigens (i.e. Polio 1, 2 and 3) in both groups (i.e. 6-10-14 weeks and 2-4-6 months), reached seroprotective levels at one month post-dose 3 vaccination.

- *Immunogenicity against Hib*

Table 3. Seroprotection rate and geometric mean concentrations (GMCs) for anti-PRP by groups one month after third dose of vaccination (ATP cohort for immunogenicity)

				≥ 0.15 µg/ml				≥ 1 µg/ml				GMC		
						95% CI				95% CI			95% CI	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**value**	**LL**	**UL**
Anti-PRP	6-10-14 group	Post-Pri	105	104	99.0	94.8	100	86	81.9	73.2	88.7	2.697	2.176	3.343
	2-4-6 group	Post-Pri	106	105	99.1	94.9	100	94	88.7	81.1	94.0	5.404	4.168	7.006

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
Seroprotection =anti-PRP antibody concentration ≥ 0.15 µg/ml
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Post-Pri = Blood sample collected one month after the third dose of the primary vaccination course

One month post-dose 3:

- All subjects except one in each group were seroprotected against PRP antigen.
- The GMC values ranged between 2.697 µg/ml and 5.404 µg/ml across the two groups.

- *Immunogenicity against pertussis*

Table 4. Vaccine response to anti-PT, anti-FHA and anti-PRN antibody concentrations one month after the third dose of vaccination (ATP cohort for immunogenicity)

				Vaccine response			
						95% CI	
Antibody	**Group**	**Pre-vaccination status**	**N**	**n**	**%**	**LL**	**UL**
anti-PT antibody (EL.U/ml)	6-10-14 group	S-	61	61	100	94.1	100
		S+	44	44	100	92.0	100
		Total	105	105	100	96.5	100
	2-4-6 group	S-	67	67	100	94.6	100
		S+	37	36	97.3	85.8	99.9
		Total	104	103	99.0	94.8	100
anti-FHA antibody (EL.U/ml)	6-10-14 group	S-	12	12	100	73.5	100
		S+	89	86	96.6	90.5	99.3
		Total	101	98	97.0	91.6	99.4
	2-4-6 group	S-	12	12	100	73.5	100
		S+	90	88	97.8	92.2	99.7
		Total	102	100	98.0	93.1	99.8
anti-PRN antibody (EL.U/ml)	6-10-14 group	S-	86	86	100	95.8	100
		S+	19	18	94.7	74.0	99.9
		Total	105	104	99.0	94.8	100
	2-4-6 group	S-	89	89	100	95.9	100
		S+	15	14	93.3	68.1	99.8
		Total	104	103	99.0	94.8	100

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
S- = seronegative subjects (antibody concentration < 5 EL.U/ml for Anti-FHA, Anti-PRN and Anti-PT) prior to vaccination
S+ = seropositive subjects (antibody concentration ≥ 5 EL.U/ml for Anti-FHA, Anti-PRN and Anti-PT) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as :
For initially seronegative subjects, antibody concentration ≥ 5 ELU/ml at one month after third dose
For initially seropositive subjects : antibody concentration at one month after third dose≥ 1 fold the pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit

One month post-dose 3:

- All subjects in 6-10-14 group and 99% of subjects in 2-4-6 group showed vaccine response to anti-PT antibodies.
- The vaccine response against anti-FHA antibodies was reported for 97% of subjects in 6-10-14 group and 98% of subjects in 2-4-6 group, respectively.
- The vaccine response against anti-PRN antibody was reported for 99% of subjects in both 6-10-14 group and 2-4-6 group.

Table 5. Seropositivity rates and geometric mean concentrations (GMCs) for anti-PT, anti-FHA and anti-PRN by groups before first dose of vaccination and one month after third dose of vaccination (ATP cohort for immunogenicity)

				≥ 5 EU/ml				GMC		
						95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti-PT	6-10-14 group	Pre-Pri	105	44	41.9	32.3	51.9	5.0	4.2	6.0
		Post-Pri	105	105	100	96.5	100	107.3	96.6	119.1
	2-4-6 group	Pre-Pri	104	37	35.6	26.4	45.6	4.6	3.8	5.6
		Post-Pri	106	106	100	96.6	100	108.2	97.4	120.2
Anti-FHA	6-10-14 group	Pre-Pri	101	89	88.1	80.2	93.7	18.7	15.0	23.3
		Post-Pri	105	105	100	96.5	100	293.7	259.4	332.6
	2-4-6 group	Pre-Pri	102	90	88.2	80.4	93.8	20.1	16.1	25.2
		Post-Pri	106	106	100	96.6	100	369.3	335.5	406.5
Anti-PRN	6-10-14 group	Pre-Pri	105	19	18.1	11.3	26.8	3.4	2.9	3.9
		Post-Pri	105	105	100	96.5	100	224.4	194.2	259.3
	2-4-6 group	Pre-Pri	104	15	14.4	8.3	22.7	3.2	2.8	3.7
		Post-Pri	106	106	100	96.6	100	243.6	213.2	278.4

6-10-14 group = Subjects in this group received *Infanrix hexa* at 6-10-14 weeks of age
2-4-6 group = Subjects in this group received *Infanrix hexa* at 2-4-6 months of age
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Pre-Pri = Blood sample collected before the first dose of the primary vaccination course
Post-Pri = Blood sample collected one month after the third dose of the primary vaccination course

Seropositivity rates and geometric mean concentrations (GMCs) for anti-PT, anti-FHA and anti-PRN by groups before first dose of vaccination and one month after third dose of vaccination are given below:

- Before first dose of vaccination the seropositivity rates for **anti-PT** antibody was reported for 41.9% of subjects and 35.6% of subjects in 6-10-14 group and 2-4-6 group respectively. One month after the third dose of vaccination all subjects in both the groups were reported to be seropositive against anti-PT antibody. The GMC values ranged between 5.0 EU/ml and 4.6 EU/ml before first dose of vaccination and between 107.3 EU/ml and 108.2 EU/ml one month after the third dose of vaccination across two groups.
- Before first dose of vaccination the seropositivity rates for **anti-FHA** was reported for 88.1% of subjects and 88.2% of subjects in 6-10-14 group and 2-4-6 group respectively. One month after the third dose of vaccination all subjects reported to be seropositive against anti-FHA antibody in both the groups. The GMC value ranged between 18.7 EU/ml and 20.1 EU/ml before first dose of vaccination and one month after the third dose vaccination across two groups.
- Before first dose of vaccination the seropositivity rates for **anti-PRN** was reported for 18.1% of subjects and 14.4% of subjects in 6-10-14 group and 2-4-6 group respectively. One month after third dose of vaccination all subjects reported to be seropositive against anti-PRN antibody in both the groups. The GMC value ranged between 3.4 EU/ml and 3.2 EU/ml before first dose of vaccination and one month after the third dose of vaccination across two groups.
- The levels of pertussis antibodies observed at the pre-vaccination time-point are probably due to the natural exposure to the disease or maternal transfer of antibodies against pertussis.

Conclusion

Although no formal comparison was made between the two groups, the immunogenicity and safety results are comparable between the 6-10-12 weeks and 2-4-6 months schedule.

The results of the 2-4-6 months schedule were also comparable with study DTPa-HBV-IPV-070, an open clinical study conducted in Spain in 2000-2001 to assess the immunogenicity and safety of Infanrix hexa as a primary vaccination course to pre-term infants (< 37 weeks) at 2, 4 and 6 months of age in comparison with infants born after normal gestation period (≥ 37 weeks), see table below:

Table 2: Seroprotection or seropositivity rates one month after the full vaccination course (ATP immunogenicity cohort) are tabulated below:

Endpoints	Pre-term Group (N = 93)				Full-term Group (N = 89)			
	%	GMT/GMC	LL	UL	%	GMT/GMC	LL	UL
Anti-PRP (≥ 0.15 µg/ml)	92.5	2.241	1.655	3.035	97.8	4.247	3.201	5.634
Anti-PRP (≥ 1 µg/ml)	76.3	-	-	-	86.5	-	-	-
Anti-HBs (≥ 10 mIU/ml)	93.4	634.1	433.8	927.0	95.2	867.1	576.6	1303.9
Anti-diphtheria (≥ 0.1 IU/ml)	100.0	3.661	3.064	4.376	100.0	5.441	4.547	6.511
Anti-tetanus (≥ 0.1 IU/ml)	100.0	2.461	2.112	2.868	100.0	2.303	1.963	2.702
Anti-poliovirus type 1 (≥ 8)	100.0	424.1	308.7	582.7	100.0	773.7	577.3	1037.0
Anti-poliovirus type 2 (≥ 8)	100.0	450.1	319.8	633.6	100.0	614.4	449.8	839.2
Anti-poliovirus type 3 (≥ 8)	100.0	468.2	312.0	702.8	100.0	1208.1	930.9	1567.9
Anti-PT (≥ 5 EL.U/ml)	100.0	61.3	53.1	70.8	100.0	60.4	53.8	67.8
Anti-FHA (≥ 5 EL.U/ml)	100.0	239.5	205.8	278.6	100.0	252.8	226.2	282.5
Anti-PRN (≥ 5 EL.U/ml)	100.0	155.3	131.3	183.7	100.0	200.3	167.5	239.5

Pre-term infants: gestation period < 37 weeks; Full-term infants: gestation period ≥ 37 weeks; Both groups received DTPa-HBV-IPV/Hib; N: Number of subjects with available results
%: percentage of subjects with antibody concentration/titers ≥ specified assay cut-off
L.L, UL: Lower and upper limits of 95% confidence interval

Although no formal comparison was made between the two studies, seroprotection/seropositivity rates and GMT/GMC were higher in the present study compared to immunogenicity data obtained in Spain in the 2-4-6 month schedule (study DTPa-HBV-IPV-070) with overlapping or superior 95%CI, except for the diphteria component.

The antibody levels of the diphteria component in the present study were somewhat lower compared to the data obtained in full-term babies in study DTPa-HBV-IPV-070: GMC of 2.334 (95%CI: 2.049; 2.659) and 3.726 (95%CI: 3.260; 4.258) in the 6-10-14 weeks and 2-4-6 months schedule, resp.

In conclusion, one month post-dose3,

- All subjects in both groups were seroprotected against diphtheria and tetanus antigens.
- All subjects in 6-10-14 group and 99% of subjects in 2-4-6 group were seroprotected against hepatitis B.
- All the subjects in both the groups were seroprotected against poliovirus types 1 and 2. All subjects in 2-4-6 group and 98.6% of subjects in 6-10-14 group were seroprotected against poliovirus type 3.
- All except one subject in each group were seroprotected against PRP antigen .
- The vaccine response to anti-PRN antibodies was reported in 99% of the subjects in both groups.
- All subjects in 6-10-14 group and 99% of subjects in 2-4-6 group showed vaccine response to anti-PT antibodies. Similarly, 97% of subjects in 6-10-14 group and 98% of subjects in 2-4-6 group showed vaccine response to anti-FHA antibodies.

CHMP comment

The generated immunogenicity data are consistent with previous data of Infanrix hexa as priming vaccine for DTPa-IPV-Hib and booster vaccine for HepB.

Safety results

- *Solicited local and general adverse events*

During the 4-day follow-up period, **pain** was the most frequently reported solicited local symptom, reported for 25.2% of subjects in 6-10-14 group and 13.4% of subjects in 2-4-6 group. Pain was also the most frequently reported Grade 3 solicited local symptom, reported for 1.8% and 0.9% of subjects in 6-10-14 and 2-4-6 groups, respectively. Grade 2 for Pain means moderate pain, i.e. the subject cries/protests on touch. Grade 3 For Pain means severe pain, i.e. the subjects cries when limb is moved/spontaneously painful.

Fever was the most frequently reported solicited general symptom, reported for 15.3% and 15.2% of subjects in 6-10-14 and 2-4-6 group. It was also the most frequently reported Grade 3 solicited general symptom in 0.9% of subjects in 2-4-6 group. None of subjects in 6-10-14 group reported fever of Grade 3 intensity. None of the subjects in 6-10-14 group and 0.9% of the subjects in 2-4-6 group reported solicited general symptoms related to vaccination.

- *Unsolicited Adverse Events (AEs)*

During the 31 day (Day 0-30) post vaccination period:

- At least one unsolicited symptom was reported for 35.7% and 22.3% of subjects in 6-10-14 and 2-4-6 group, respectively.
- The most frequently reported unsolicited symptom was upper respiratory tract infection reported for 16.1% and 9.8% of subjects in 6-10-14 and 2-4-6 group,
- respectively.
- None of the subjects reported Grade 3 unsolicited symptoms. None of the unsolicited symptoms were assessed by the investigator to be causally related to vaccination.

- *SAEs*

No fatal events were reported in this study.

Overall five subjects reported at least one symptom in occurrence of SAEs in both the groups (two subjects in 6-10-14 group and three subjects in 2-4-6 group). Bronchiolitis and pneumonia were reported for two subjects each in 6-10-14 group and one subject in 2-4-6 group. Lower respiratory tract infection was reported for two subjects in 2-4-6 group.

All the SAEs resolved during the study period.

No AEs leading to premature discontinuation of the study vaccine and/or study were reported.

In conclusion, during the 31 day (Day 0-30) post vaccination period, at least one unsolicited symptom was reported for 35.7% of subjects in 6-10-14 group and 22.3% of subjects in 2-4-6 group. A total of five subjects (two subjects in 6-10-14 group and three subjects in 2-4-6 group) reported SAEs during the study period. None of the SAEs were causally related to the vaccine in both the groups and resolved during the study period. None of the subjects were withdrawn the study due to a SAE.

CHMP comment

The generated safety data are consistent with previous data on Infanrix hexa.

1.3.3. Discussion on clinical aspects

A limitation of the current study is the potential bias due to the open-label design.

The study investigated the immunogenicity and safety of Infanrix hexa in 224 healthy infants in India who were vaccinated at birth with BCG and HepB vaccine, in two schedules, the standard of care schedule of 6-10-14 weeks (EPI schedule) and the 2-4-6 months schedule adopted by countries such as Australia, Canada and the United States, as well as neighboring countries such as Thailand and Sri Lanka.

One month post primary vaccination, the seroprotection status for diphtheria, tetanus, polio, hepatitis B and Hib antigens ranged from 98.6% to 100% in the two study groups. The vaccine response to the pertussis antigens ranged from 97% to 100% in the two study groups.

The vaccine was considered to be safe and generally well-tolerated. SAEs (pneumonia and bronchiolitis) were reported for two subjects in 6-10-14 group and pneumonia and lower respiratory tract infection were reported for three subjects in 2-4-6 group during the study period. All SAEs were resolved by the end of the study. None of the SAEs were considered by the investigator as causally related. Fever was the most frequently reported solicited general symptom reported for 15.3% and 15.2% of subjects in 6-10-14 and 2-4-6 group. Fever was also the most frequently reported Grade 3 solicited general symptom, reported for 0.9% of subjects in both the groups. Only one subject from 2-4-6 group showed temperature >39.0°C.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The article 46 paediatric submission is considered fulfilled, and no further regulatory action is needed. The provided data do not cause concern regarding efficacy or safety of Infanrix hexa.

The benefit/risk balance of Infanrix hexa therefore remains positive.

Recommendation

☒ Fulfilled:

No regulatory action required.