25 February 2016
EMA/245070/2016
Procedure Management and Committees Support Division

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

Hexacima Hexaxim Hexyon

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

Procedure no: EMEA/H/C/002702/P46/014

Procedure no: EMEA/H/W/002495/P46/015

Procedure no: EMEA/H/C/002796/P46/013

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

On 23 July 2015, the MAH submitted the final clinical study report of paediatric study A3L33 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 revealed no new information regarding seroconversion/vaccine response or the safety profile of Hexaxim™/Hexacima™/Hexyon™ that is not yet already included in the CCDS. Therefore, no modification is foreseen for CCDS or other related documents, including the SmPC or Package leaflet.

To simplify matters, this report mentions just Hexaxim as study vaccine. However, the information equally applies to Hexacima and Hexyon.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that A3L33 is a standalone study.

Study A3L33 was designed as a phase 3, open-label, multicentre study to assess the immunogenicity and safety of Hexaxim given at 6, 10 and 14 weeks of age in infants for the purpose of marketing authorization application in India.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation of Hexaxim was used.

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 to 24 months of age against diphtheria (D), tetanus (T), pertussis, HepB, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

The MAH submitted the final report for:

A3L33: 'Immunogenicity and Safety of Sanofi Pasteur's DTaP-IPV-HB-PRP-T Combined Vaccine Given at 6, 10 and 14 Weeks of Age in Infants from India Who Previously Received a Dose of Hepatitis B Vaccine at Birth.'

Note: The infants primed with the study vaccine were to be administered a booster dose during their second year of life (at 15-18 months of age) using any commercially available standalone or combined DTaP-polio-Hib vaccine(s). The booster vaccination was not given as part of this study.

2.3.2. Clinical study

Description

This open-label multicenter study was designed to assess the safety and immunogenicity of Hexaxim given at 6, 10 and 14 weeks of age in infants in order to meet the regulatory requirements of Drug Controller General, India, for registration of Hexaxim in India.

Methods

Objectives

a) Immunogenicity:

- Primary - To evaluate the immunogenicity of the study vaccine in terms of seroprotection (D, T, poliovirus types 1, 2 and 3, Hib polysaccharide [PRP], Hep B antigens) and vaccine response for pertussis antigens (PT and FHA) 1 month after the third dose.

- Secondary - To further describe the immunogenicity of the study vaccine, before the 1st dose and 1 month after the 3rd dose.

b) Safety:

- Secondary only - To describe the safety after each and any dose of the study vaccine.

Study design

The study was a phase III, open-label study implemented in 2 centres in India.

Trial period: 19 Feb 2014 (FVFS) to 14 Oct 2014 (LVLS).

177 infants aged 6 weeks (up to 8 weeks) were enrolled. The subjects had received a documented dose of any commercially available oral poliovirus vaccine (OPV) and recombinant Hep B monovalent vaccine at birth according to the National Immunization Program (NIP) in India.

Infants were to receive Sanofi Pasteur's DTaP-IPV-HB-PRP-T combined vaccine (study vaccine, Hexaxim) at 6, 10 and 14 weeks of age.

There were 4 visits (V) scheduled with vaccinations on Day (D) 0 (=V01), D30 (=V02) and D60 (=V03), and blood samplings on D0 and D90 (=V04; i.e., 30 days [up to 42 days] after the third vaccination).

Parents/legally acceptable representatives were to record information about solicited reactions and unsolicited AEs in a DC after each vaccination, from D0 to D7 for solicited reactions and from D0 to D30 for non-serious unsolicited AEs. SAEs were collected throughout the study.

The expected participation of each subject in the study was approximately 3 months.

Table 1 Study Procedures

Visit/Contact	**V01**	**Phone Calls***	**Home Visit**	**V02**	**Phone Calls***	**Home Visit**	**V03**	**Phone Calls***	**Home Visit**	**V04**
Trial timelines (days)	**D0**	**D1 D2 D3**	**D8**	**D30**	**D31 D32 D33**	**D38**	**D60**	**D61 D62 D63**	**D68**	**D90**
Visit Intervals	**Inclusion**	V01 +1 day +2 days +3 days	V01 + 8 days	**V01 +30-42 days**	V02 +1 day +2 days +3 days	V02 + 8 days	**V02 +30-42 days**	V03 +1 day +2 days +3 days	V03 + 8 days	**V03 +30-42 days**
Approximate Age of Subject (weeks)	**6**			**10**			**14**			**18**
Informed consent signed	✓									
Inclusion/exclusion criteria	✓									
Collection of demographic data	✓									
Medical history (subject and family)	✓									
Physical examination	✓			✓			✓			✓
Allocation of subject number	✓									
Blood sampling	BL-1[†]									BL-2[‡]
Contraindications to vaccination				✓			✓			✓
Vaccination *with DTaP-IPV-HB-PRP-T* *combined vaccine*	Vac1			Vac2			Vac3			
Immediate surveillance (30 min)	✓			✓			✓			
DC provided[§]	DC1			DC2			DC3			
DC collected				DC1			DC2			DC3

Visit/Contact	**V01**	**Phone Calls***	**Home Visit**	**V02**	**Phone Calls***	**Home Visit**	**V03**	**Phone Calls***	**Home Visit**	**V04**
Trial timelines (days)	**D0**	**D1 D2 D3**	**D8**	**D30**	**D31 D32 D33**	**D38**	**D60**	**D61 D62 D63**	**D68**	**D90**
Visit Intervals	**Inclusion**	V01 +1 day +2 days +3 days	V01 + 8 days	**V01 +30-42 days**	V02 +1 day +2 days +3 days	V02 + 8 days	**V02 +30-42 days**	V03 +1 day +2 days +3 days	V03 + 8 days	**V03 +30-42 days**
Approximate Age of Subject (weeks)	**6**			**10**			**14**			**18**
Phone call to subject's parents/legally acceptable representatives*		✓			✓			✓		
Collection of solicited injection site & systemic reactions	✓		✓	✓		✓	✓		✓	✓
Collection of unsolicited adverse events	✓		✓	✓		✓	✓		✓	✓
Collection of reportable concomitant	✓			✓			✓			✓
Trial termination record										✓
Collection of SAEs	Anytime throughout the study									

Source: Table 3.1 of A3L33 CSR

* Phone calls were to be given on D1, D2 and D3 after each vaccination, to remind subject's parents/legally acceptable representatives to fill out solicited injection site and systemic reactions from D0 to D7 post-vaccination in the DC provided. Trial personnel asked parents/legally acceptable representatives whether the subject experienced any SAEs not yet reported. The home visit on D8 was used to collect D0–D8 safety data

† Blood sample of approximately 3 mL performed before vaccination

‡ Blood sample of approximately 4 mL performed at this visit

§ The DC provided at a given visit was collected at the beginning of the next visit and a new DC was provided at the end of the visit.

Concomitant Vaccination(s):

If the subject's parents/legally acceptable representatives agreed and the Investigator/family doctor deemed it necessary, other vaccines licensed in India might have been given during the study, except those containing the same antigens as the study vaccine. However, concomitant vaccines were not to be administered within the period from 8 days before to 8 days after each study vaccine administration.

According to the immunization program in India, OPV is given at birth and later in infants and children during the National Immunization Days (NIDs). This implied that subjects could have received OPV during the course of the study while they already received IPV from the study vaccine. Subjects who received OPV during the study should receive subsequent study vaccine injections as scheduled. However, no NIDs have been conducted during the course of the study; thus, not any subject received OPV as part of an NID.

Study population / sample size

Infants,

- aged between 42-56 days (6 to 8 weeks), born at full term (≥ 37 gestational weeks) and with a birth weight ≥ 2.5 kg,
- born to known HBsAg seronegative mother (with documented laboratory result during last trimester of pregnancy),
- who had received 1 documented dose of Hep B vaccine and OPV at birth as per national recommendations

were included.

Usual exclusion criteria were applied, e.g., receipt of any vaccine (except BCG) in the 4 weeks before 1st study vaccination or planned vaccination from 8 days before to 8 days after each study vaccination, previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis, Hep B, and/ or Hib (except Hep B and OPV at birth).

The number of subjects was designed to provide supportive immunogenicity and safety data of the study vaccine when administered as a primary vaccination in infants with previous hepatitis B and OPV vaccination at birth.

The sample size was arbitrarily chosen to 150 evaluable subjects. Assuming an attrition rate of approximately 15%, a total of 177 subjects were to be included in the study.

Assuming seroprotection/seroconversion rates of 94% or more for each vaccine antigen, a sample size of 150 evaluable subjects ensured a 95% confidence interval with a range of no more than 8.3% (using the exact binomial method) for all antibody responses.

In terms of safety, the planned sample size of 150 evaluable subjects allowed, with 95% probability, the observation of any given AE occurring with a true frequency of 2% or more, using the rule of threes.

Treatments

Subjects received 3 doses of Hexaxim on D0, D30 and D60.

Batch No.: S4370 (non-commercial lot)

Route: IM injection into the anterolateral aspect of the right thigh

Outcomes/ endpoints

a) Immunogenicity (primary):

One month after the 3rd vaccine dose (D90, at approximately 18 weeks of age):

- Anti-D antibody (Ab) concentrations ≥ 0.01 International Units (IU)/mL
- Anti-T Ab concentrations ≥ 0.01 IU/mL
- Anti-PRP Ab concentrations ≥ 0.15 µg/mL
- Anti-poliovirus 1, 2 and 3 Ab titers ≥ 8 (1/dilution [dil])
- Anti-PT and anti-FHA Ab concentrations in ELISA units (EU)/mL ≥ 4 x Lower Limit of Quantification (LLOQ) if prevaccination concentration was < 4 x LLOQ or ≥ pre-vaccination level if prevaccination concentration was ≥ 4 x LLOQ (Remark: LLOQ = 2 EU/ml)
- Anti-Hep B Ab concentrations ≥ 10 mIU/mL

b) Immunogenicity (secondary):

At baseline (D0), before the 1st dose:

- Anti-D Ab concentrations ≥ 0.01 and 0.1 IU/mL
- Anti-Hep B Ab concentrations ≥10 mIU/mL
- Pertussis (PT, FHA) Ab concentrations ≥ LLOQ
- Individual D, Hep B, PT and FHA Ab concentrations/titers

One month after the 3rd vaccine dose (D90, at approximately 18 weeks of age):

- Anti-D Ab concentrations ≥ 0.1 and 1.0 IU/mL
- Anti-T Ab concentrations ≥ 0.1 and 1.0 IU/mL
- Anti-PRP Ab concentrations ≥ 1.0 µg/mL
- Anti-Hep B Ab concentrations ≥ 100 mIU/mL
- Individual Ab concentrations/titers: all antigens
- ≥ 4-fold and ≥ 2-fold increase in anti-PT and anti-FHA Ab concentrations (EU/mL) from pre-Dose 1 (V01) to 1 month post-Dose 3 (V04)
- Anti-PT and anti-FHA Ab concentrations ≥ 5 EU/mL, ≥ 10 EU/mL and ≥ 25 EU/mL
- Individual post-/pre-primary vaccination Ab concentration (EU/mL) ratios (for D, HepB, PT and FHA)

c) Safety (secondary):

- Occurrence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each and any vaccination(s) (=immediate post-vaccination surveillance period)
- Occurrence of solicited (prelisted in the subject's diary card [DC] and electronic Case Report Form [CRF]) injection site and systemic reactions occurring through 7 days following each and any vaccination
- Occurrence of unsolicited AEs through 30 days following each and any vaccination
- Occurrence of serious adverse events (SAEs) throughout the trial (V01 to V04)

The definitions of AEs and SAEs, of adverse reactions (AR) and unexpected adverse reactions (UAR) and of solicited and unsolicited AEs /ARs were according to ICH E2A and cover essential time periods. For convenience and comparability, digital thermometers and flexible rulers were handed out along with the Diary Cards. The preferred route for temperature measurement was axillary (at least once per day, preferred in the evening time).

The following Adverse Events of Special Interest (AESIs) were considered by the Sponsor to be relevant for the monitoring of the safety profile of Hexaxim: Extensive limb swelling (ELS), hypotonic hyporesponsive episodes (HHE) and convulsions (whether febrile or not), anaphylactic reactions, apnea, severe neurological conditions (all defined as important identified or potential risks), in addition to sudden infant death syndrome (SIDS), sudden unexpected death (SUD) (defined as other AESIs) and apparent life-threatening events (ALTEs).

Convulsions, HHE, anaphylactic reactions, severe neurological conditions, ALTEs and fatal outcomes were by definition to be considered as SAEs.

Assays

All immunological analyses were performed at the Sponsor's Global Clinical Immunology (GCI) laboratory (Swiftwater, Pennsylvania, USA).

Table 2 Immunoassays Applied in the Study

Endpoint	Assay	Reference serum
Anti-D	Micrometabolic inhibition test (MIT, using Vero cells)	WHO Int. Standard for D-antitoxin
Anti-T	ELISA	WHO human ref. standard lot TE3
Anti-PT	ELISA	Reference standard serum
Anti-FHA	ELISA	Reference standard serum
Anti-Polio	Micrometabolic inhibition test (MIT, using Vero cells)	-
Anti-HepB	VITROS ECi/ECiQ enhanced chemiluminescence detection	Comparison to calibrator previously calibrated to the WHO 1st Int. Reference Preparation for Antibody to HBsAg
Anti-PRP	RIA	CBER reference standard Lot 1983

Table 3 Correlates and Surrogates of Protection Applied

Antigen	Antibody (Ab) Titer as Level of Protection	Assessment
iphtheria	≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term)	Established correlate
etanus	≥ 0.01 IU/mL (short-term) ≥ 0.1 IU/mL (long-term)	Established correlate
olio 1, 2, 3	≥ 8 (1/dil)	Established correlate
RP-T	≥ 0.15 µg/mL (short-term) ≥ 1 µg/mL (long-term)	Established correlate
epatitis B	≥ 10 IU/mL	Established correlate
T, FHA (Pertussis)	**Vaccine Response:** If pre-vaccination antibody concentration was <4xLLOQ, then the post-vaccination antibody concentration was to be ≥4xLLOQ; If pre-vaccination antibody concentration was ≥4xLLOQ, then the post-vaccination antibody concentration was to be ≥pre-immunisation levels. **Remark: LLOQ = 2 EU/ml, i.e., 4 x LLOQ = 8 EU/mL for PT and FHA**	Accepted surrogate

CHMP comment:

Established correlates or accepted surrogates of protection were applied to calculate seroprotection rates (D, T, IPV, Hep B, PRP) and vaccine response rates (PT, FHA). The serological assays were the same as those used in previous studies with Hexaxim/ Hexacima/ Hexyon.

Furthermore, the safety observations were in accordance to those applied to previous vaccine studies conducted in the EU.

Statistical Methods

All analyses were descriptive; no hypotheses were tested.

Primary endpoints were described with 95% confidence intervals (CI) using the exact binomial method (Clopper-Pearson method) for single proportions.

Secondary endpoints were described with 95% CI

- Using the exact binomial method (Clopper-Pearson method) for single proportions and
- Using the normal approximation of the Log10 concentrations/titers, followed by a back transformation for geometric mean concentrations (GMCs)/ geometric mean titers (GMTs).

The immunogenicity analyses were performed on the Per-Protocol (PP) analysis set and on the full analysis set (FAS). The latter comprised the PP analysis set plus subjects representing with at least one relevant protocol deviation, e.g., incomplete vaccination schedule or vaccination outside the protocol-specified time window, missing blood sample. Thus, all subjects who had received at least one vaccine dose were included in the FAS.

Immunogenicity criteria were described for all valid serological results from sera obtained before the 1st dose and 1 month after the 3rd dose. Reverse Cumulative Distribution Curves (RCDCs) were constructed for all antigens.

Safety was described for all subjects, after each and any vaccine dose (percentage of subjects with a given symptom plus 95% CI). The safety analyses were performed on the safety analysis set (SafAS) which was defined for each dose.

Protocol amendments: none

Results

Recruitment / Number analysed

All subjects (177 infants) planned to be included were vaccinated at V01. Blood samples were taken from each of these subjects at V01.

Out of the 177 subjects included in the FAS, 156 subjects were included in the PP analysis set. Among the 21 subjects excluded from the PP analysis set (**Table 4**),

- 13 subjects did not provide the 2nd blood sample or did not provide it in the proper time window,
- 6 subjects did not receive a vaccine dose in the proper time window,
- 5 subjects (2.8%) did not complete the vaccination schedule and
- for 4 subjects (2.3%), the administration of vaccine was not done as per protocol. In the source protocol this deviation was described as:

'The subject received a vaccine unacceptable for use.'/ 'The subject received a dose which had a CCB. The subject should be excluded from the per-protocol set […]' (Appendix 16.2, A3L33)

CHMP comment:
The sponsor is asked to explain the abbreviated term 'CCB' (not included in list of abbreviations).

Furthermore, it should be clarified whether this vaccine administration might represent a wrong medication/ vaccination. In this case, there would be a discrepancy between CSR data (no subject with 'prohibited therapy/ medication/ vaccine') and Appendix 16.2 (4 subjects 'received a vaccine unacceptable for use').

Out of the 177 subjects present at V01, 168 subjects (94.9%) completed the study. Among the

9 subjects with early termination, 7 subjects were lost to follow-up and 2 subjects discontinued due to an SAE:

- One subject (003-00072) experienced bronchopneumonia that appeared after the second injection. The event lasted 23 days and was considered by the Investigator as not related to vaccination. The subject recovered but the Investigator decided to withdraw the subject from the study for safety concern.

- One subject (003-00087) died after the second injection. The death was considered by the Investigator as not related to the vaccination.

Detailed information on SAEs is presented in the Safety section below.

Table 4 Immunogenicity Analysis Sets

	All (N =177)
	n (%)
Subjects with data in CRF	177 (100.0)
With data in CRF but did not receive any vaccination	0 (0.0)
Full Analysis Set	177 (100.0)
Subjects excluded from the Per-Protocol Analysis Set	21 (11.9)
Violation type:	
Subject did not meet all protocol-specified inclusion criteria or met at least one exclusion criterion	0 (0.0)
Subject did not complete the vaccination schedule	5 (2.8)
Preparation and / or administration of vaccine was not done as per protocol	4 (2.3)
Subject did not receive vaccine in the proper time window	6 (3.4)
Baseline serology sample was not collected in the protocol-specified time window or the serology sample was not drawn	0 (0.0)
Subject did not provide the serology sample at Visit 4 in the proper time window or a serology sample at Visit 4 was not drawn	13 (7.3)
Subject received a protocol-prohibited therapy/medication/vaccine	0 (0.0)
Subject's serology sample at baseline did not produce a valid test result for PT or FHA	0 (0.0)
Subject's serology sample at Visit 4 did not produce a valid test result	0 (0.0)
Per-Protocol Analysis Set	156 (88.1)

N: number of subjects analyzed according to data present in CRF

n: number of subjects fulfilling the item listed

Source: Table 4.3 CSR A3L33

Table 5 Safety Analysis Sets

	All (N =177)
	n (%)
Safety Analysis Set	177 (100.0)
Safety Analysis Set after injection at **V01**	177 (100.0)
Solicited injection site and systemic safety assessed	174 (98.3)
Safety Analysis Set after injection at **V02**	174 (98.3)
Solicited injection site and systemic safety assessed	174 (98.3)
Safety Analysis Set after injection at **V03**	172 (97.2)
Solicited injection site and systemic safety assessed	168 (94.9)

Source: reproduced from Table 4.5 CSR A3L33

Demography

Among the subjects with data in their CRF, there were 99 males (55.9%) and 78 females (44.1%). The male/female ratio was 1.27. The mean age of the subjects at enrollment was 6.9 weeks (SD 0.6), with an age range between 6.1 and 8.1 weeks. The mean weight of the subjects was 4.6 kg (SD 0.6), with a weight range between 2.5 and 6.4 kg.

Baseline demographics were the same in the FAS and SafAS, however, they were somewhat different for the PP analysis set which showed a further increased sex ratio of 1.36 (see CSR table 9.15).

No data were presented with regard to ethnic origin of the subjects.

Immunogenicity Results

One month after the 3rd dose of Hexaxim, at least 99% of subjects met the (short-term) seroprotection thresholds defined for the various vaccine antigens and at least 93% met the vaccine response criteria for pertussis (at least 4 x LLOQ = 8 EU/mL and minimum baseline; **Table 6**).

Table 6 Summary of Seroprotection and Vaccine Response Rates at 1 month post-Dose 3 – PP Analysis Set (Primary Endpoints)

		All	
		%	**95% CI**
Anti-D	≥ 0.01 IU/mL	99.3	95.9; 100
Anti-T	≥ 0.01 IU/mL	100.0	97.3; 100
Anti-PT (EU/mL)	Vaccine response *	93.8	88.6; 97.1
Anti-FHA (EU/mL)	Vaccine response *	99.3	96.3; 100
Anti- Polio 1	≥ 8 (1/dil)	100.0	97.5; 100
Anti- Polio 2	≥ 8 (1/dil)	100.0	97.5; 100
Anti- Polio 3	≥ 8 (1/dil)	100.0	97.5; 100
Anti-Hep B	≥ 10 mIU/mL	100.0	97.6; 100
Anti-PRP	≥ 0.15 µg/mL	100.0	97.7; 100

* Vaccine response was defined as % of subjects with post-Dose 3 anti-PT or anti-FHA Ab concentrations ≥ 4 x LLOQ if pre-vaccination concentration was < 4 x LLOQ or ≥ pre-vaccination levels if pre-vaccination concentrations were ≥ 4 x LLOQ

Source: Synopsis, CSR A3L33

Regarding diphtheria, following the 3rd Hexaxim dose 99% of subjects showed short-term protection levels of ≥ 0.01 IU/mL. About 50 % reached or exceeded the long-term protection level of 0.1 IU/mL (**Table 7**).

All subjects reached anti-tetanus Ab concentrations of at least 0.1 IU/mL indicating long-term protection. Regarding pertussis, 93% of subjects showed a vaccine response (≥ 8 EU/mL but minimum baseline) regarding anti-PT Ab levels and 99% regarding anti-FHA Ab levels. 88 and 90% of subjects, respectively, showed a 4-fold increase in anti-PT and anti-FHA Ab concentrations relative to baseline at 1 month-post dose 3. All subjects reached anti-PRP levels of ≥ 0.15 µg/mL indicating short-term protection and approximately 94% reached the long-term threshold of ≥ 1 µg/mL.

All subjects reached protective Ab titers against polio type 1, 2, and 3 of ≥ 8 (1/dil). Further, all subjects showed seroprotection against Hep B with Ab levels of ≥ 10 mIU/mL, and even 99% reached

the more conservative anti-Hep B threshold of ≥ 100 mIU/mL following the 3-dose primary vaccination with Hexaxim.

Relative to baseline, the 3-dose primary vaccination with Hexaxim resulted in a 5.9-fold increase in anti-D Ab levels. Anti-PT levels increased 51-fold and anti-FHA levels 37-fold. Furthermore, a 686-fold increase in anti-Hep B levels from baseline to post-dose 3 was observed.

Very similar results were observed for the FAS (data not presented here).

In summary, following vaccination of infants with 3 doses of Hexaxim given at 6, 10 and 14 weeks of age high and satisfactory seroprotection and vaccine response rates, respectively, were achieved.

CHMP comment:

The Ab levels generally were in the range or even higher than those found in previous studies with Hexaxim, except for PT. Vaccine response rates for PT were lower in the current study (93.8%) compared to those in previous studies as summarised in the SmPC (99-100% for both the 2-dose and 3-dose vaccination schemes). Since the reverse cumulative distribution curve (RCDC) for PT and Table 9.22 of A3L33 CSR show Ab levels of at least 25 EU/mL for all subjects (i.e. 100% with ≥ 8 EU/mL = 4xLLOQ) the observed vaccine response rate for PT would indicate that >6% of subjects showed protective levels at baseline (i.e., ≥ 4 x LLOQ / ≥8 EU/mL) combined with an (unexpected) decrease in Ab levels from baseline to post-dose 3.

The applicant is asked to provide data (PT and FHA) on subsets of subjects experiencing a decrease in aP Ab levels during the course of the study.

Following the 3-dose primary immunization, almost all subjects showed short-term seroprotection against diphtheria (≥ 0.01 IU/mL), and all subjects showed long-term seroprotection against tetanus (≥ 0.1 IU/mL) and against polio type 1, 2, and 3 (≥ 8 [1/dil]).

Seroprotection rates against Hep B and polio are higher than those of previous studies with Hexaxim. This could be expected as a consequence of the additional Hep B and OPV vaccine doses at birth. The SmPC already mention the higher Hep B seroprotection rates in infants who had received a Hep B dose at birth.

Finally, all subjects showed protection against Hib (PRP) at the short-term threshold of 0.15 µg/mL and even 94% were long-term protected at ≥ 1 µg/mL.

Table 7 Summary of Seroprotection/Seroconversion and Vaccine Response Rates at Baseline and 1 Month Post-Dose 3 – PP Analysis Set

			All (N=156)		
			n/M	%	(95% CI)
Anti-D (IU/mL)	**Pre-Dose 1 (V01)**	**≥ 0.01 IU/mL**	102/152	67.1	(59.0; 74.5)
		≥ 0.1 IU/mL	24/152	15.8	(10.4; 22.6)
	Post-Dose 3 (V04)	**≥ 0.01 IU/mL**	134/135	99.3	(95.9; 100)
		≥ 0.1 IU/mL	67/135	49.6	(40.9; 58.4)
		≥ 1.0 IU/mL	7/135	5.2	(2.11; 10.4)
Anti-T (IU/mL)	**Post-Dose 3 (V04)**	**≥ 0.01 IU/mL**	134/134	100.0	(97.3; 100)
		≥ 0.1 IU/mL	134/134	100.0	(97.3; 100)
		≥ 1.0 IU/mL	113/134	84.3	(77.0; 90.0)
Anti-PT (EU/mL)	**Pre-Dose 1 (V01)**	**≥ 2 EU/mL (LLOQ)**	88/147	59.9	(51.5; 67.9)
	Vaccine response*		137/146	93.8	(88.6; 97.1)
	≥ 4-fold increase		129/146	88.4	(82.0; 93.1)
Anti-FHA (EU/mL)	**Pre-Dose 1 (V01)**	**≥ 2 EU/mL (LLOQ)**	134/151	88.7	(82.6; 93.3)
	Vaccine response*		146/147	99.3	(96.3; 100)
	≥ 4-fold increase		133/147	90.5	(84.5; 94.7)
Anti-Polio 1 (1/dil)	**Post-Dose 3 (V04)**	**≥ 8 (1/dil)**	145/145	100.0	(97.5; 100)
Anti-Polio 2 (1/dil)	**Post-Dose 3 (V04)**	**≥ 8 (1/dil)**	146/146	100.0	(97.5; 100)
Anti-Polio 3 (1/dil)	**Post-Dose 3 (V04)**	**≥ 8 (1/dil)**	144/144	100.0	(97.5; 100)
Anti-Hep B (mIU/mL)	**Pre-Dose 1 (V01)**	**≥ 10 mIU/mL**	20/152	13.2	(8.23; 19.6)
	Post-Dose 3 (V04)	**≥ 10 mIU/mL**	152/152	100.0	(97.6; 100)
		≥ 100 mIU/mL	151/152	99.3	(96.4; 100)
Anti-PRP (µg/mL)	**Post-Dose 3 (V04)**	**≥ 0.15 µg/mL**	156/156	100.0	(97.7; 100)
		≥ 1.0 µg/mL	146/156	93.6	(88.5; 96.9)

N: number of subjects analyzed in the PP analysis set

n: number of subjects experiencing the endpoint listed in the first 3 columns

M: number of subjects with available data for the relevant endpoint

* Vaccine response was defined as % of subjects with post-Dose 3 anti-PT or anti-FHA Ab concentrations ≥ 4 x LLOQ if pre-vaccination concentration was < 4 x LLOQ or ≥ pre-vaccination levels if pre-vaccination concentrations were ≥ 4 x LLOQ

Source: Table 6.1, CSR A3L33

Table 8 Summary of Geometric Mean Concentrations/Titers at Baseline and 1 Month Post-3rd Dose – PP Analysis Set

		All (N=156)		
		M	GM	(95% CI)
Anti-D (IU/mL)	**Pre-Dose 1 (V01)**	152	0.019	(0.015; 0.025)
	Post-Dose 3 (V04)	135	0.120	(0.099; 0.146)
	GMTR (V04/V01)	131	5.85	(3.93; 8.72)
Anti-T (IU/mL)	**Post-Dose 3 (V04)**	134	1.95	(1.75; 2.17)
Anti-PT (EU/mL)	**Pre-Dose 1 (V01)**	147	3.84	(3.00; 4.91)
	Post-Dose 3 (V04)	155	191	(173; 210)
	GMTR (V04/V01)	146	50.7	(37.3; 69.0)
Anti-FHA (EU/mL)	**Pre-Dose 1 (V01)**	151	6.17	(5.10; 7.48)
	Post-Dose 3 (V04)	152	226	(208; 247)
	GMTR (V04/V01)	147	36.6	(28.6; 46.8)
Anti-Polio 1 (1/dil)	**Post-Dose 3 (V04)**	145	1124	(861; 1468)
Anti-Polio 2 (1/dil)	**Post-Dose 3 (V04)**	146	1401	(1108; 1771)
Anti-Polio 3 (1/dil)	**Post-Dose 3 (V04)**	144	2019	(1672; 2437)
Anti-Hep B (mIU/mL)	**Pre-Dose 1 (V01)**	152	3.78	(3.23; 4.43)
	Post-Dose 3 (V04)	152	2491	(2073; 2995)
	GMTR (V04/V01)	149	686	(542; 870)
Anti-PRP (µg/mL)	**Post-Dose 3 (V04)**	156	7.86	(6.35; 9.73)

N: number of subjects analyzed in the PP analysis set

M: number of subjects with available data for the relevant endpoint

GM: geometric mean; GMTR: geometric mean titer ratio

Source: Table 5.2, CSR A3L33

Safety Results (Secondary Objective)

None of the subjects experienced any immediate unsolicited AE in the 30 min after any vaccine injection.

Within 7 days after any vaccine injection, 37.9% of subjects experienced at least one solicited injection site reaction. Grade 3 solicited injection site reactions were reported for 2.9% of subjects. The most frequently reported injection site reaction was tenderness (30.5% of subjects)

Within 7 days after any vaccine injection, 54.6% of subjects experienced at least 1 solicited systemic reaction. Grade 3 solicited systemic reactions were reported for 2.3% of subjects. The most frequently reported systemic reaction was irritability (36.2% of subjects), followed by abnormal crying (24% of subjects). Fever was reported for 19.0% of subjects. No Grade 3 fever (>39.5°C) was reported.

The incidences of solicited reactions and Grade 3 solicited reactions decreased with successive doses. After the third vaccine injection no Grade 3 solicited reaction was reported.

Within 30 days after any vaccine injection, 60 unsolicited AEs were reported for 20.3% of subjects. The most frequently reported AE preferred term (PT) was upper respiratory tract infection (24 AEs reported for 11.9% of subjects).

A total of 4 SAEs (including 1 death and 1 case of infantile epilepsy) were reported from 3 subjects during the trial. None of these SAEs were considered by the Investigator to be related to the study vaccine (see below).

A total of 2 subjects (1.1%) experienced an SAE leading to discontinuation of the study (bronchopneumonia and death). None of them were considered by the Investigator to be related to the study vaccine.

Adverse events of special interest (AESIs) were reported for 1 subject who experienced several episodes of convulsion. The time to onset of the convulsion episodes (25-26 days) was not suggestive of a relationship with the study vaccine. The Investigator and the Sponsor assessed this event as not related to study vaccine or study procedure.

In summary, Hexaxim was well tolerated in infants who had received a first dose of Hep B and oral poliovirus vaccines at birth.

CHMP comment:

Overall, the incidences of various solicited systemic reactions were in the range of those mentioned in the SmPC, except for the AR 'crying abnormal' with a higher frequency (24% of subjects vs. <10% in the SmPC) and erythema with a lower frequency (8% vs. >10% in SmPC). Since the incidences reported in the SmPC result from a pooled analysis from several trials, these differences are considered normal inter-trial variations.

In conclusion, Hexaxim was well tolerated by study subjects. Study data fit to the safety profile of Hexaxim as summarized in the SmPC.

Shortened narratives regarding SAEs and AESIs:

(1) Subject 003-00087, female; **severe sepsis with hypovolemic shock** accompanied with viral lower respiratory tract infection (LRTI) at 2 MoA and **death** at 3 MoA**:**

Hospitalization (paediatric ICU) at 26 days-post 1st dose because of lethargy, dehydration, deep and rapid breathing, tachycardia. Subject was diagnosed severe sepsis with hypovolemic shock and viral LRTI. The infant fully recovered upon treatment and was discharged after 11 d. The subject continued in the trial. A social worker confirmed the subject's good condition 8 d after 2nd vaccination.

At 27 d post-2nd dose the subject experienced hiccough during spoon top milk feeding and then did not respond. A physician confirmed the subject's death. No autopsy was performed.

(2) Subject 003-00072, male**, bronchopneumonia** at 3 MoA**:**

The subject developed mild fever, cough and coryza 22 d after the 2nd vaccination. The subject was admitted to hospital (first paediatric ward, then paediatric ICU) and diagnosed respiratory distress and bronchopneumonia. The subject finally recovered after prolonged antibiotics therapy and was discharged after 25 days of inpatient hospitalisation. The subject was discontinued from the trial due to safety concern.

Subject 003-00081, female**, infantile epilepsy** at 4 MoA**:**

26 days after 3rd vaccine dose the subject with a family history of convulsions experienced a total of 3 epileptic episodes both lasting a few minutes. She was admitted to the hospital with a diagnosis of infantile epilepsy. She recovered upon antiepileptics therapy, no further episodes of seizure were noted. She was discharged 6 d after admission and continued in the trial.

CHMP comment:

Because of the long delay (≥ 3 weeks) between vaccination and disease onset, the CHMP agrees that there is no causal relationship between the SAEs of sepsis or bronchopneumonia, respectively, and the study vaccine.

The sudden death of one subject is still unclear since no autopsy was performed but might result from suffocation in consequence of swallowing up food. - No relationship to vaccination is being seen.

Further, there is no indication that the AESI/ SAE of afebrile seizures in one subject might be related to vaccination since the subject had a family history of convulsions and because of the 1 month-gap between last vaccine dose and disease onset.

In summary, the CHMP concurs with the judgement of the Investigator(s) that the observed SAEs / AESIs were not related to study vaccination.

Table 9: Solicited Reactions Within 7 Days After Any Vaccine Injection – SafAS

	All (N=177)		
Subjects experiencing at least one:	n/M	%	(95% CI)
Solicited reaction	111/174	63.8	(56.2; 70.9)
Injection site reaction	66/174	37.9	(30.7; 45.6)
Tenderness	53/174	30.5	(23.7; 37.9)
Erythema	13/174	7.5	(4.0; 12.4)
Swelling	26/174	14.9	(10.0; 21.1)
Systemic reaction	95/174	54.6	(46.9; 62.1)
Fever	33/174	19.0	(13.4; 25.6)
Vomiting	26/174	14.9	(10.0; 21.1)
Crying abnormal	42/174	24.1	(18.0; 31.2)
Drowsiness	23/174	13.2	(8.6; 19.2)
Appetite lost	19/174	10.9	(6.7; 16.5)
Irritability	63/174	36.2	(29.1; 43.8)

N: number of subjects analyzed in the SafAS

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

Source: Table 6.2, CSR A3L33

Table 10: Unsolicited AEs Within 30 Days After Any Vaccine Injection, by System Organ Class and Preferred Term – SafAS

	All (N=177)			
Subjects experiencing at least one:	n	%	(95% CI)	n AEs
Unsolicited AE	36	20.3	(14.7; 27.0)	60
Ear and labyrinth disorders	1	0.6	(0.0; 3.1)	1
Cerumen impaction	1	0.6	(0.0; 3.1)	1
Gastrointestinal disorders	11	6.2	(3.1; 10.8)	11
Diarrhea	9	5.1	(2.4; 9.4)	9
Infantile colic	1	0.6	(0.0; 3.1)	1
Stomatitis	1	0.6	(0.0; 3.1)	1
General disorders and administration site conditions	5	2.8	(0.9; 6.5)	7
Death	1	0.6	(0.0; 3.1)	1
Irritability	1	0.6	(0.0; 3.1)	1
Pyrexia	5	2.8	(0.9; 6.5)	5
Infections and infestations	29	16.4	(11.3; 22.7)	36
Bronchiolitis	1	0.6	(0.0; 3.1)	1
Bronchopneumonia	1	0.6	(0.0; 3.1)	1
Gastroenteritis	4	2.3	(0.6; 5.7)	4
Lower respiratory tract infection viral	1	0.6	(0.0; 3.1)	1
Oral candidiasis	1	0.6	(0.0; 3.1)	1
Rhinitis	2	1.1	(0.1; 4.0)	2
Septic shock	1	0.6	(0.0; 3.1)	1
Upper respiratory tract infection	21	11.9	(7.5; 17.6)	24
Varicella	1	0.6	(0.0; 3.1)	1
Metabolism and nutrition disorders	1	0.6	(0.0; 3.1)	1
Decreased appetite	1	0.6	(0.0; 3.1)	1
Nervous system disorders	1	0.6	(0.0; 3.1)	1
Epilepsy	1	0.6	(0.0; 3.1)	1
Skin and subcutaneous tissue disorders	3	1.7	(0.4; 4.9)	3
Dermatitis atopic	1	0.6	(0.0; 3.1)	1
Heat rash	1	0.6	(0.0; 3.1)	1
Pityriasis alba	1	0.6	(0.0; 3.1)	1

N: number of subjects analyzed in the SafAS

n: number of subjects experiencing the endpoint listed in the first column

nAE: number of AEs

Source: Table 6.12, CSR A3L33

2.3.3. Discussion on clinical aspects

Hexaxim was highly immunogenic in infants who received a 3-dose primary vaccination at 6, 10, and 14 weeks of age and who had obtained a first dose of recombinant Hep B and oral poliovirus vaccines at birth. One month after the 3rd Hexaxim dose, most of the subjects reached the pre-defined short-term seroprotective Ab levels against D, T, poliovirus types 1, 2 and 3, PRP and HepB. At least 94% of the subjects even reached long-term seroprotection levels against these vaccine antigens except for diphtheria (50% protected at $\geq$ 1.0 IU/mL).

At least 94% of the subjects showed a vaccine response to PT and FHA antigens 1 month after the 3rd dose.

The immunogenicity results were consistent with those obtained in previous trials with Hexaxim/ Hexacima/ Hexyon.

Hexaxim was well tolerated in infants. No new safety signals emerged.

3. CHMP overall conclusion and recommendation

Following vaccination with 3 doses of Hexaxim given at 6, 10, and 14 weeks of age, high and satisfactory seroprotection/seroconversion and vaccine response rates, respectively, were achieved in Indian infants who previously had received a recombinant monovalent Hep B and an OPV vaccine dose at birth.

At one month post-dose 3 all subjects were seroprotected against T, poliovirus types 1, 2, and 3, Hep B, and PRP antigens at the pre-defined short-term thresholds. 99% of subjects (all but 1) were protected against diphtheria at 0.01 IU/mL. At least 94% of subjects were even protected against T, Hep B and PRP at long-term protection levels. Additionally, 94% and 99% of subjects showed an anti-PT and anti-FHA vaccine response, respectively. Overall, the results were consistent with what has been observed outside India.

However, the results obtained for PT vaccine response were somewhat lower compared to those in previous studies. These were related to the relatively high Ab levels at pre-vaccination time point that resulted from passively transmitted maternal Abs and declined over time. Since satisfactory anti-PT Ab levels were achieved at post-primary dose 3, this (lower) anti-PT vaccine response does not provide any concern.

The study vaccine was well tolerated, no new safety signals have arisen. The SAEs and AESIs seen were all unrelated to study vaccination.

There is no need to update the product information including SmPC and PiL.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Based on the data submitted, the MAH should provide description of the additional clarifications requested as part of this procedure (see section below).

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- The sponsor is asked to explain the abbreviated term 'CCB' (not included in list of abbreviations). Furthermore, it should be clarified whether the wrong vaccine administration ('the administration of vaccine was not done as per protocol) might represent a wrong medication/ vaccination.
In this case, there would be a discrepancy between CSR data (no subject with 'prohibited therapy/ medication/ vaccine') and Appendix 16.2 (4 subjects 'received a vaccine unacceptable for use').

- Vaccine response rates for PT were lower in the current study (93.8%) compared to those in previous studies as summarised in the SmPC (99-100% for both the 2-dose and 3-dose vaccination schemes). Since the reverse cumulative distribution curve (RCDC) for PT and Table 9.22 of A3L33 CSR show Ab levels of at least 25 EU/mL for all subjects (i.e. 100% with ≥8 EU/mL = 4xLLOQ) the observed vaccine response rate for PT would indicate that >6% of subjects showed protective levels at baseline (i.e., ≥ 4 x LLOQ / ≥8 EU/mL) combined with an (unexpected) decrease in Ab levels from baseline to post-dose 3.
The applicant is asked to provide data (PT and FHA) on subsets of subjects experiencing a decrease in aP Ab levels during the course of the study.

The timetable is a 30 day response timetable without clock stop.

5. MAH responses to Request for supplementary information

Question 1

The sponsor is asked to explain the abbreviated term 'CCB' (not included in list of abbreviations).

Furthermore, it should be clarified whether the wrong vaccine administration ('the administration of vaccine was not done as per protocol) might represent a wrong medication/ vaccination.

In this case, there would be a discrepancy between CSR data (no subject with 'prohibited therapy/ medication/ vaccine') and Appendix 16.2 (4 subjects 'received a vaccine unacceptable for use').

Response

The CCB abbreviation means 'Cold Chain Break'.

During the trial, four subjects did receive an injection of the investigational product having been exposed to too high storage temperature (>8°C). These events were discovered by the investigators after the vaccines have been effectively injected, and consequently, these events have been consigned in the individual CRFs and later denominated/classified as 'subject received a vaccine unacceptable for use' by sponsor monitors and data management team. These events do not really represent 'wrong medication/vaccination' events. As with all similar types of events, these subjects have not been considered in the PP population but were, obviously, considered in the ITT population.

CHMP comment:

The MAH provided an explanation for the discrepancy between 'wrong vaccine administration' and 'wrong medication/ vaccination'. Four subjects were vaccinated using a vaccine suspension that had been stored at too high storage temperatures. These subjects were excluded from the PP analysis set. This is acknowledged.

Question 2

Vaccine response rates for PT were lower in the current study (93.8%) compared to those in previous studies as summarised in the SmPC (99-100% for both the 2-dose and 3-dose vaccination schemes). Since the reverse cumulative distribution curve (RCDC) for PT and Table 9.22 of A3L33 CSR show Ab levels of at least 25 EU/mL for all subjects (i.e. 100% with ≥8 EU/mL = 4xLLOQ) the observed vaccine response rate for PT would indicate that >6% of subjects showed protective levels at baseline (i.e., ≥ 4 x LLOQ / ≥8 EU/mL) combined with an (unexpected) decrease in Ab levels from baseline to post-dose 3.
The applicant is asked to provide data (PT and FHA) on subsets of subjects experiencing a decrease in aP Ab levels during the course of the study.

Response

The MAH do not fully concur with reviewer's conclusion that vaccine response rates for PT were lower in the current study (93.8%) compared to those observed in previous studies as summarized in the SmPC (98.4-100% for both the 2-dose and 3-dose vaccination schemes). The only trial previously conducted with this product and which used the exact same infant 3-dose primary series regimen has been trial A3L15 from which results have been used to feed some of the data presented in the SmPC immunogenicity Table 1; column 3 (anti-PT Ab VR rate of 100%). Due to the known lower overall immunogenicity of the 6-10-14 week infant regimen, we consider that the historical observation of a 100% VR rate in the A3L15 trial might in fact not represent the true performance of the product when

used in such regimen. Trial A3L33 has provided another perspective of the immune performance of this vaccine when used with the EPI regimen, and due to inter-trial variability results have been different. The reality is probably in the middle.

In addition, it should be remembered that the definition of the Vaccine Response rate (VRR) used to describe responses[1] is not taking in consideration the expected decline of the maternally derived Abs that might be present on some of the pre-primary series samples and that will decline over time between the pre-primary series time point and the post-primary series time point (following generally a 3-week half-life period). The use of a VRR based on this method of calculation would have certainly provided higher values. In fact, the use of this adjusted VRR should be applied particularly for antigens when it is expected high prevalence of maternally transmitted antibodies.

We have extracted from the A3L33 trial database the subjects who have not presented an increase of anti-PT and/or of anti-FHA during the course of the study (either they have maintained equal levels or have presented lower levels). This analysis identified 10 subjects (out of 156) for anti-PT Abs and 1 subject for anti-FHA Abs. No subject presented with an absence of responses against the two pertussis antigens.

The antibody levels against PT in these 10 subjects are listed below:

Subject #	Pre (EU/mL)	Post (EU/mL)
002-00045	71	50
002-00060	258	73
002-00062	121	76
002-00075	195	72
003-00050	361	110
003-00051	180	90
003-00057	131	86
003-00063	178	94
003-00065	81	51
003-00067	103	37

Their Ab levels at pre-dose 1 time point (6 weeks of age) were high and originated from passively-transmitted maternal antibodies. Despite this, their individual post-dose 3 Ab levels (18 weeks of age) were high and not fundamentally different from the Ab levels achieved in their ‘sero-negative at enrollment’ counterparts.

The antibody levels against FHA in the subject identified was 71 EU/mL and 46 EU/mL before and after vaccination, respectively. Again, the same conclusion could be drawn.

[1] Vaccine response was defined as % of subjects with post-Dose 3 anti-PT or anti-FHA Ab concentrations ≥ 4 x LLOQ (8 EU/mL) when pre-vaccination concentration was < 4 x LLOQ or ≥ pre-vaccination anti-PT or anti-FHA concentrations if pre-vaccination concentrations were ≥ 4 x LLOQ

In conclusion, the MAH considers that it is not true that the 'response rates' for PT were lower in the current study. This conclusion is driven by the mode of calculation of the 'response rates' used in these studies. A criteria taking into consideration the expected decline of the maternally derived Abs would provide higher 'response rates' values. Finally, as Ab against PT and against FHA are not correlates of protection but can only be seen as a surrogate of protection, the full interpretation of these observations remains unclear.

CHMP comment:

The subjects that presented with a decline in Ab levels from pre-dose 1 to post-primary dose 3 had indeed very high Ab levels at baseline that resulted from passively transmitted maternal Abs. Every subject showed satisfactory anti-PT and anti-FHA Ab levels following the 3-dose primary vaccination.

The MAH's explanation is acknowledged.