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	78
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.