Application Type	Supplement
STN	125347/231
CBER Received Date	March 15, 2015
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Division / Office	DVRPA/OVRR
Committee Chair	Joseph Temenak, Ph.D.
Clinical Reviewer(s)	Ralph LeBlanc, MD, Ph.D.
Project Manager	Ramachandra Naik, Ph.D. David Staten, Ph.D.
Priority Review	NO
Reviewer Name(s)	Ghideon Solomon, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lihan Yan, Ph.D. Team Leader, Bacterial and allergenic team, VEB/DB/OBE
	Dale Horne, Dr.PH, Chief, Vaccine Evaluation Branch, DB/OBE
Applicant	GlaxoSmithKline (GSK) Biologicals SA
Established Name	Hiberix, Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
(Proposed) Trade Name	Hiberix®
Formulation(s), including Adjuvants, etc	Per dose: 10mcg of purified capsular polysaccharide of Hib covalently bound to approximately (b) (4) mcg of tetanus toxoid 12.6 mg of lactose as stabilizer
Dosage Form(s) and Route(s) of Administration	0.5mL/dose (clear colorless liquid) given intramuscularly into the right thigh of subjects
Indication(s) and Intended Population(s)	Active immunization for the prevention of disease caused by Haemophilus influenza type b in healthy infants at 2, 4, 6 and 15-18 months of age.

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GLOSSARY

AE	Adverse event
ANOVA	Analysis of Variance
Anti-D	Anti-diphtheria
Anti-T	Anti-tetanus
ATP	According-To-Protocol
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
DTaP	Diphtheria, Tetanus, acellular Pertussis
DTwP	Whole-cell Diphtheria and Tetanus toxoids and Pertussis
eCRF	electronic Case Report Form
(b) (4)	
(b) (4)	units per milliliter
ER	Emergency Room
ESFU	Extended Safety Follow-Up
FHA	Filamentous Hemagglutinin
GMC/T	Geometric Mean Concentration/ Titer
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
Hib	*Haemophilus influenzae* type b
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IPV	Inactivated Poliovirus Vaccine
IRB	Institutional Review Board
IU/mL	International units per milliliter
LAR	Legally AccepTable Representative
MedDRA	Medical Dictionary for Regulatory Activities
Prim-TVC	Primary Total Vaccinated Cohort
PRN	Pertactin
PRP	Polyribosylribitol Phosphate
PT	Pertussis Toxoid
RDE	Remote Data Entry
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBIR	Simply the Best Internet Randomization (internet-based randomization system)
SCID	Severe Combined Immunodeficiency Disease
TVC	Total Vaccinated Cohort
URTI	Upper respiratory tract infection

1. Executive Summary

Hib-097 was a Phase III, randomized, multicenter study that was double blind for the immunogenicity and consistency evaluation of three lots of GSK Biologicals' *Haemophilus influenza* type b (Hib) conjugate vaccine and single blind and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Hib vaccine 208108 compared to the monovalent Hib vaccine *ActHIB. The trial was* open label for comparison with the combined DTaP-IPV-Hib vaccine *Pentacel* when administered to healthy infants at 2, 4, 6, and 15-18 months of age with recommended co-administrations at separate sites.

This partially double-blind study (double-blind for the 3 *Hiberix* lots and single blind vs. the comparator *ActHIB* and open label vs. the comparator *Pentacel*) comprising a primary and a booster vaccination epoch was intended to evaluate safety and to demonstrate lot-to-lot consistency of three different lots of *Hiberix*. The study also provided a comparison to the licensed monovalent Hib vaccine *ActHIB* as well as the licensed combination product *Pentacel* in infants in the US at 2, 4, 6, and 15-18 months of age. Relevant vaccines (i.e., *Pediarix, Prevnar13, Rotarix* for the subjects receiving *Hiberix* and *ActHIB* or *Engerix-B, Prevnar13* and *Rotarix* for the subjects receiving *Pentacel* during the primary epoch, and *Infanrix* for the subjects receiving *Hiberix* and *ActHIB* during the booster epoch) that are recommended for children in the US during the first and second years of life were administered concomitantly with the Hib vaccines.

The first and second primary hypotheses of the study with respect to lot-to-lot consistency between the three *Hiberix* lots and non-inferiority of *Hiberix* compared to *ActHIB* in terms of anti-PRP antibody concentrations ≥ 1.0 μg/mL, were statistically not met. Therefore, a formal statistical conclusion for the remaining objectives is not technically allowed according to the sequential nature of the statistical testing.

However, the pre-defined statistical criteria for non-inferiority for anti-PRP antibody concentrations ≥ 0.15μg/mL one month after primary vaccination were satisfied. In addition, pre-defined statistical criteria for non-inferiority for the co-administered diphtheria, tetanus, pertussis, polio, and *S.pneumonia* antigens were satisfied, and no immune interference with these co-administered antigens was observed.

Based on the totality of the evidence, I defer to the medical officers to determine whether the overall results support approval despite certain pre-specified statistical criteria not being met.

2. Clinical and Regulatory Background

GlaxoSmithKline Biologicals' (GSK) Biologics License Application for Hiberix® [*Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate)] BLA 125347 was approved August 19, 2009 under accelerated approval regulations.

Following licensure of *Hiberix* in the US, GSK committed to conduct a comparative safety and immunogenicity clinical trial of primary and booster immunization with *Hiberix* relative to US licensed control vaccines to further verify and describe the clinical benefits of *Hiberix* in accordance with accelerated approval of biological products regulations (21 CFR 601, 40-46) and to evaluate *Hiberix* for use in subjects ages 6 weeks to 14 months in accordance with Pediatric Research Equity Act (PREA) requirements (21 USC 355c).

Study 112957, Hib-097, entitled "A Phase III, randomized, multicenter study, double-blind for the immunogenicity and consistency evaluation of 3 lots of GSK Biologicals' *Haemophilus influenzae* type b (Hib) conjugate vaccine and single blind and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Hib vaccine 208108 compared to the monovalent Hib vaccine *ActHIB* and open for comparison with the combined DTPa-IPV-Hib vaccine *Pentacel* when administered to healthy infants at 2, 4, 6 and 15-18 months of age with recommended co-administrations at separate sites."
The purpose of this supplemental Biologics License Application (sBLA) is to apply for licensure of *Hiberix* for use in children 6 weeks to 14 months of age.

While study HIB-097 evaluated *Hiberix* administered at 2, 4, 6, and 15 to 18 months, the submitted clinical study report and clinical overview focus on the primary vaccination course, based upon agreements made with the FDA during the March 14, 2014 Type B pre-sBLA meeting to limit the present supplement to the application for licensure of *Hiberix* for use in children 6 weeks to 14 months of age. Hence, the statistical review memo is also based on the submitted data and report for application for licensure of Hiberix for use in children 6 weeks to 14 months of age.

2.1 Disease or Health-Related Condition(s) Studied

The Advisory Committee on Immunization Practices, United States (ACIP) recommends routine administration of a conjugate Hib vaccine series beginning at age 2 months. The first dose can be administered as early as age 6 weeks. A booster dose (dose 3 or 4 depending on vaccine used in the primary series) is recommended at age 12 through 15 months and at least 8 weeks after the most recent Hib vaccination.

Hiberix is presently indicated for active immunization as a booster dose for the prevention of invasive disease caused by *Haemophilus influenza* type b. *Hiberix* is approved for use in children 15 months through 4 years of age (prior to fifth birthday).
The purpose of this supplemental BLA is to apply for licensure of *Hiberix* for use in children 6 weeks to 14 months of age, and the proposed indication and usage is as follows:

> *Hiberix* is indicated for active immunization for the prevention of invasive disease caused by *Haemophilus influenza* type b. *Hiberix* is approved for use in children 6 weeks through 4 years of age (prior to fifth birthday).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Study HIB-097 was initiated on June 18, 2010 and completed on July 17, 2013 and was conducted under U.S. IND 14151 at 67 sites in the U.S. The protocol and other study plans have been reviewed by the FDA under this IND.

On March 14, 2014 a Type B pre-sBLA meeting was conducted and an agreement was reached between the applicant and the FDA to submit the application in two separate supplements. The first supplement will focus on the primary vaccination course and licensure of *Hiberix* for use in children 6 weeks to 14 months of age, and the second supplement will be for a booster vaccination course.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

Data sources including all materials reviewed (applicant's study reports, data sets analyzed, and literature referenced) were provided electronically and are available in the EDR on the following link:

(b) (4)

5.1 Review Strategy

The sBLA is based on safety and immunogenicity data from the clinical trial HIB-097. Section 6 of this review discusses all the relevant statistical information of the study that reflects the indication sought by the applicant. This study provides safety and immunogenicity data to support licensure of *Hiberix* for use in children 6 weeks to 14 months of age.

5.2 BLA/IND Documents that Serve as the Basis for the Statistical Review

Table 1 summarizes study HIB-097 that served as a basis for the statistical review and licensure of the product for the sought indication.

Table 1: Overview of study HIB-097

Study ID	Country	Study design	Population (age) schedule of vaccination	Study group	Number of subjects ATP	Number of subjects TVC
HIB-097	USA	Phase III, partially double-blinded (immunogenicity and lots consistency), single-blinded (safety and immunogenicity of *Hiberix* compared to *ActHIB*) and open (comparison of *Hiberix* with P*entacel*), randomized, controlled.	Infants (6-12 weeks) Primary vaccination: 3 doses: 2, 4, 6 months † Booster vaccination: 1 dose: 15-18 months	<u>Primary Vaccination:</u> Hiberix A (*Hiberix* Lot A + *Pediarix* + *Prevnar13* +*Rotarix*)	529	987
				Hiberix B (*Hiberix* Lot B + *Pediarix* + *Prevnar13* +*Rotarix*)	537	982
				Hiberix C (*Hiberix* Lot C + *Pediarix* + *Prevnar13* +*Rotarix*)	526	994
				Pooled Hiberix (*Hiberix* + *Pediarix* + *Prevnar13* +*Rotarix*)	1592	2963
				ActHIB (*ActHIB* + *Pediarix* + *Prevnar13* + *Rotarix*)	275	520
				Pentacel (*Pentacel* + *Prevnar13* + *Engerix-B* +*Rotarix*)	253	520
				<u>Booster Vaccination:</u> *Hiberix* + *Infanrix*	336	2337
				ActHIB + *Infanrix*	236	435
				Pentacel	186	400

† *Rotarix* at 2 and 4 months. If a dose of hepatitis B virus (HBV) vaccine was received at birth, *Engerix-B* was administered at 2 and 6 months
ATP=According-To-Protocol, TVC=Total Vaccinated Cohort
Source: Reviewer's Table based submitted files.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS: STUDY HIB-097

6.1 Study Objectives

6.1.1 Primary Objectives

The co-primary objectives were assessed sequentially. A co-primary objective was only met if the statistical criteria for a particular objective, as well as those for all previous objectives were met:

1. To demonstrate lot-to-lot consistency of 3 manufacturing lots of Hiberix co-administered with Pediarix, Prevnar13, and Rotarix following 3 primary vaccine doses in terms of immune response to PRP.

Criteria for lot-to-lot consistency (1 month after last dose of primary vaccination):

- Lot-to-lot consistency was evaluated by each pair-wise ratio of geometric mean concentration (GMC) values for anti-PRP obtained for the 3 lots of Hiberix (Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP). The criterion for lot-to-lot consistency was that the two-sided 95% confidence limits on the anti-PRP GMC ratio between lots were within the [0.67, 1.5] interval for all 3 pair-wise comparisons.

2. To demonstrate non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13, and Rotarix, following 3 primary vaccine doses in terms of anti-PRP antibody concentration ≥1.0 μg/mL.

   Criterion for non-inferiority (1 month after last dose of primary vaccination):

   - Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP minus Subcohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥ 1.0 μg/mL was ≥-10%.

3. To demonstrate non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13, and Rotarix, following 3 primary vaccine doses in terms of anti-PRP antibody concentrations ≥0.15 μg/mL.

   Criterion for non-inferiority (1 month after last dose of primary vaccination):

   - Lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP minus Subcohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 g/mL was ≥-5%.

4. To demonstrate non-inferiority of Pediarix co-administered with Hiberix, Prevnar13, and Rotarix to Pediarix co-administered with ActHIB, Prevnar13, and Rotarix, following 3 primary vaccine doses in terms of immune response to diphtheria, tetanus, pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and poliovirus types 1, 2, and 3.

   Criteria for non-inferiority (1 month after last dose of primary vaccination):

   - Lower limit of the standardized asymptotic 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) of anti-diphtheria and anti-tetanus antibodies was ≥ -10%, and
   - Lower limit of the 97.5% CIs on the GMC ratios (Subset Pertussis Co-Ad divided by Sub-cohort ActHIB) for antibodies to each of the pertussis antigens (PT, FHA and PRN) was ≥0.67, and

   - Lower limit of the standardized asymptotic 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) in the percentages of

subjects with seroprotective titers (≥8) of antibodies to each of the poliovirus antigens was ≥ -5%.

5. To demonstrate acceptability of the immune response of Pediarix when co-administered with Hiberix, Prevnar13, and Rotarix, following 3 primary vaccine doses in terms of immune response to poliovirus types 1, 2, and 3.

   Criteria for acceptability (1 month after last dose of primary vaccination):
   - Lower limit of the standardized asymptotic 97.5% CIs on the percentage of subjects (Subset Hiberix Co-Ad) with seroprotective titers (≥8) of antibodies to each of the poliovirus antigens was ≥90%.

6. To demonstrate non-inferiority of a 3-dose primary vaccination course of Prevnar13 co-administered with Hiberix, Rotarix, and Pediarix compared to that of Prevnar13 co-administered with ActHIB, Rotarix, and Pediarix in terms of S.pneumoniae GMCs.

   Criteria for evaluation (1 month after last dose of primary vaccination):
   - Lower limits of the two-sided 97.5% CIs on the GMC ratio (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumoniae serotype (1 [anti-1], 3 [anti-3], 4 [anti-4], 5 [anti-5], 6A [anti-6A], 6B [anti-6B], 7F [anti-7F], 9V [anti-9V], 14 [anti-14], 18C [anti-18C], 19A [anti-19A], 19F [anti-19F], and 23F [anti-23F]) were ≥ 0.5.

7. To rule out a 10% decrease in seroresponse to PT, FHA, and PRN in subjects who received Pediarix co-administered with Hiberix, Prevnar13, and Rotarix compared to subjects who received Pediarix co-administered with ActHIB, Prevnar13, and Rotarix, following 3 primary vaccine doses where seroresponse is defined as the percentage of subjects showing an antibody concentration above a threshold that leads to 95% seroresponse in the control group.

   Criteria for evaluation (1 month after last dose of primary vaccination):
   - P-value on the difference in seroresponse between groups was <1.25% for each PT, FHA, and PRN antigen (p-value was computed by integrating on the p-value for the null hypothesis that the seroresponse rate in the Subset Pertussis Co-Ad was <85% and the a-posteriori probability of the cut-off in the Sub-cohort ActHIB).

6.1.2 Secondary objectives

6.1.2.1 Descriptive immunogenicity objectives

- To evaluate immunogenicity of 3 manufacturing lots of Hiberix following 3 primary vaccine doses in terms of the percentage of subjects with anti-PRP concentrations ≥0.15 μg/mL and ≥1.0 μg/mL and in terms of anti-PRP GMCs.

- To evaluate immunogenicity of a 3-dose primary vaccination course of Hiberix co-administered with Prevnar13, Rotarix, and Pediarix, that of ActHIB, co-administered with Prevnar13, Rotarix and Pediarix and that of Pentacel co-administered with Prevnar13, Rotarix and Engerix-B in terms of anti-PRP concentrations ≥0.15 μg/mL, ≥1.0 μg/mL, and in terms of anti-PRP GMCs (except for the evaluations specified in the primary objectives).
- To evaluate the immunogenicity of a 3-dose primary vaccination course of Pediarix co-administered with Hiberix, Rotarix, and Prevnar13, that of Pediarix co-administered with ActHIB, Rotarix, and Prevnar13 and that of Pentacel co-administered with Prevnar13, Rotarix, and Engerix-B with respect to diphtheria, tetanus, PT, FHA, PRN, hepatitis B, and poliovirus types 1, 2, and 3 (except for the evaluations specified in the primary objectives).
- To evaluate the immunogenicity of a 3-dose primary vaccination course of Prevnar13 co-administered with Hiberix, Rotarix, and Pediarix, of Prevnar13 co-administered with ActHIB, Rotarix, and Pediarix and of Prevnar13 co-administered with Pentacel, Rotarix, and Engerix-B in terms of S.pneumoniae GMCs and antibody concentrations ≥0.05μg/mL, ≥0.2 μg/mL, ≥1.0 μg/mL (except for the evaluations specified in the primary objectives).

6.1.2.2 Exploratory immunogenicity objectives

- To compare immunogenicity of *Hiberix* co-administered with *Pediarix, Prevnar13,* and *Rotarix* to *Pentacel* co-administered with *Prevnar13, Rotarix,* and *Engerix-B,* following 3 primary vaccine doses in terms of GMCs and anti-PRP concentrations ≥0.15 μg/mL and ≥1.0 μg/mL.
- To compare immunogenicity of *Prevnar13* co-administered with *Hiberix, Pediarix* and *Rotarix* to *Prevnar13* co-administered with *ActHIB, Pediarix* and *Rotarix,* following 3 primary vaccine doses in terms of immune response to 13 *S. pneumoniae* serotypes (≥0.2 μg/mL and ≥1.0 μg/mL as measured by (b) (4)).
- To compare seroresponse to PT, FHA, and PRN in subjects receiving *Pediarix* co-administered with *Hiberix, Prevnar13,* and *Rotarix* compared to subjects who received *Pediarix* co-administered with *ActHIB, Prevnar13,* and *Rotarix,* following 3 primary vaccine doses, where seroresponse is defined as the percentage of subjects showing an antibody concentration above a threshold that leads to 90% seroresponse in the control group.

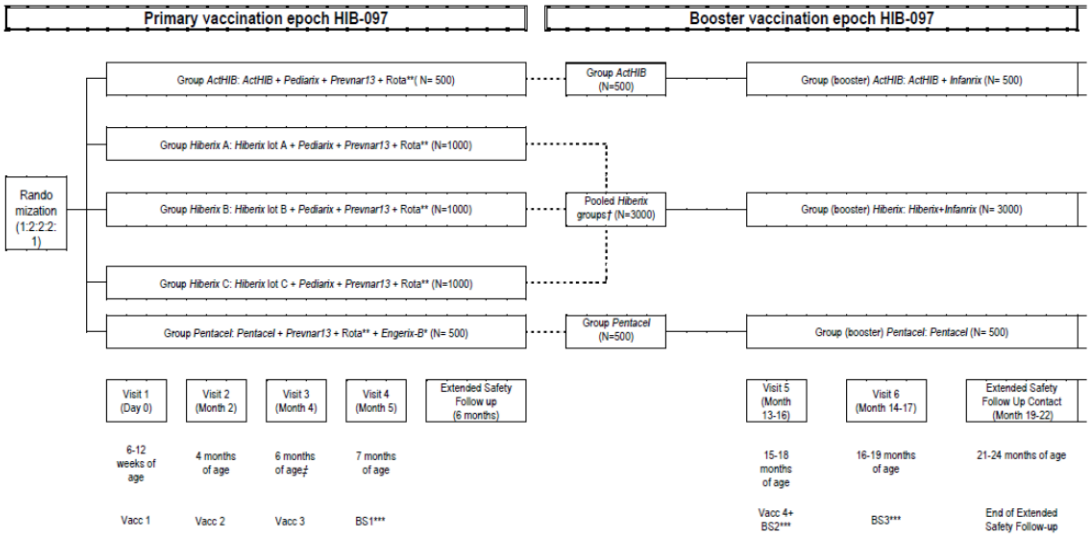
6.1.2.3 Safety Secondary Objectives

To evaluate safety and reactogenicity of a 3-dose primary vaccination course of *Hiberix* co-administered with *Pediarix, Rotarix,* and *Prevnar13* , that of *ActHIB* co-administered with *Pediarix, Rotarix,* and *Prevnar13,* and that of *Pentacel* co-administered with *Prevnar13, Rotarix,* and *Engerix-B.*

6.2 Overall Trial Design

Figure 1 below presents a general overview of study HIB-097 (both the primary vaccination epoch and booster epoch). The booster phase of the study will be submitted in a separate subsequent sBLA.

Fig. 1: General overview of the study design



* *Engerix-B* was not to be given at Month 2 (4 months of age) if a birth dose of Hepatitis B vaccine was administered to the subject
** Rota stands for *Rotarix*. *Rotarix* was administered only at Day 0 and Month 2; The dotted line refers to the period between the primary vaccination epoch and the booster vaccination epoch
† Group *Hiberix* A + Group *Hiberix* B + Group *Hiberix* C (primary vaccination epoch)
‡ Visit 3 was to be conducted at least 8 weeks after visit 2, with subjects at least 24 weeks of age, in order to comply with US recommendations on hepatitis B dosing
***A blood sample was to be taken at Visit 4 from all subjects included in the Sub-cohorts *Hiberix* A-PRP, B-PRP and C-PRP, Sub-cohorts *ActHIB* and *Pentacel*. At Visit 5 and Visit 6, a blood sample was to be taken from all subjects included in the Sub-cohorts (booster) *ActHIB* and (booster) *Pentacel* and from subjects included in the Sub-cohort (booster) *Hiberix*.
BS: blood sample; Vacc: vaccination
Source: Adapted from - BLA 125347/231; Clinical Study Report 112957 (HIB-097), p.78

Figure 1 above summarizes the general study design depicting the randomization scheme with treatment allocation, maximum number of subjects to be included in the five groups (3 lots of the treatment group and 2 control groups), vaccination and blood draw schedule, and follow up times (both the last visit and the extended safety follow up (ESFU)).

6.3 Study Population

Subjects for whom the investigator believed that their parent(s)/Legally AccepTable Representative(s) (LAR[s]) could and would comply with the requirements of the protocol (e.g. completion of the diary card, return for follow-up visits) and written informed consent was obtained. A healthy male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination and born after a gestation period of minimum 36 weeks. Subjects with previous *Haemophilus influenza type b* infections or previous vaccination with *Haemophilus influenza* type b, diphtheria, tetanus, pertussis, pneumococcus, rotavirus and/or poliovirus and/or more than one previous dose of hepatitis B vaccine were excluded from the study.

6.3.1 Selection of Trial Population

Refer to the clinical review for the list of inclusion/exclusion criteria.

6.4 Study Treatments Dose and Mode of Administration

Table 2 presents a summary of the study vaccines that were administered for each group in the primary vaccination epochs.

Table 2: Dosage and administration of study vaccines

Group	Visit	Vaccine[1]	Route[2]	Site[3]	Side[4]
Hiberix A, Hiberix B and Hiberix C	1,2,3	Hiberix	IM	T	R
Hiberix A, Hiberix B and Hiberix	1,2,3	Pediarix	IM	T	L
Hiberix A, Hiberix B and Hiberix	1,2,3	Prevnar13	IM	T or D	L
Hiberix A, Hiberix B and Hiberix	1,2	Rotarix	O		
ActHIB	1,2,3	ActHIB	IM	T	R
ActHIB	1,2,3	Pediarix	IM	T	L
ActHIB	1,2,3	Prevnar13	IM	T or D	L
ActHIB	1,2	Rotarix	O		
Pentacel	1,2,3	Pentacel	IM	T	R
Pentacel	1,2,3	Engerix B	IM	T	L
Pentacel	1,2,3	Prevnar13	IM	T or D	L
Pentacel	1,2	Rotarix	O		

[1]Vaccine/ Control/Co-administered vaccine; [2]Oral (O)/ Intramuscular (IM); [3]Deltoid (D)/Thigh (T); [4]Left (L)/ Right (R)
Source: Adapted from - BLA 125347/231; Clinical Study Report 112957 (HIB-097), p.78

Randomization/Treatment Allocation Procedures

Randomization was performed at GSK Biologicals, Rixensart, using (b) (4) a program developed for use in SAS® by GSK Biologicals. The treatment allocation at the investigator site was performed using a central randomization system on the internet (SBIR). The randomization algorithm used a minimization procedure accounting for center. The first enrolled subjects were enrolled in the immunogenicity sub-cohorts.

After having checked the eligibility of the subject, the study staff in charge of vaccination accessed the randomization system on the Internet. Upon receipt of the subject identification number and age, the randomization system used the minimization algorithm to determine the treatment number to be used for the subject. The actual treatment number used for each vaccination of each subject was recorded in the electronic case report form (eCRF).

Blinding

The study was a partially-blinded study, as different blinding levels between different groups were defined:

- The study was double-blinded with respect to subjects' assignment in Groups Hiberix A, Hiberix B, or Hiberix C (receipt of different vaccine lots of Hiberix): the investigator and sponsor staff who were involved in the treatment or clinical evaluation of the subjects and review/analysis of data and subjects' parent(s)/LAR(s) were unaware of which Hiberix vaccine lot was administered to which Hiberix group.
- The study was single-blinded with respect to subjects' assignment in Group ActHIB vs. Groups Hiberix A, Hiberix B, and Hiberix C: the investigator and/or his staff were aware of the vaccine administered (Hiberix or ActHIB) but the subject's parent(s)/LAR(s) were not.

- Subjects' assignment in Group Pentacel vs. Groups Hiberix A, Hiberix B, and Hiberix C was open label, i.e., the investigator and/or his staff and the subject's parent(s)/LAR(s) were aware of the vaccine administered (Hiberix or Pentacel). The open-label condition was explained by the fact that the number of injections may have differed for this group (depending on the Engerix-B schedule applicable to this subject) and that the study vaccines differed in their appearance.

The level of blinding was maintained throughout the conduct of the trial, except for the subjects included in the Sub-cohorts Hiberix-A PRP, B-PRP, and C-PRP who were not blood sampled during the booster epoch. These subjects were identified to the investigator prior to initiation of the booster epoch at Visit 5 so they could undergo the appropriate study procedures; i.e., depending on the sequential order of entry of a subject, a blood sample would either be taken or not, at the time of the booster epoch.

6.6 Study Centers and Duration of Study

This study was conducted by multiple investigators in 63 sites (centers) in the United States. The duration of the study for each subject was approximately 17 months (approximately 11 months for the primary vaccination epoch and 6 months for the booster vaccination epoch).

6.8 Endpoints and Assessment Methods

6.8.1 Primary endpoints

Immunogenicity with respect to components of the study vaccines and the studied co-administered vaccines:

- anti-PRP GMCs and anti-PRP concentration ≥1.0 μg/mL and ≥0.15 μg/mL
- Anti-D antibody concentration ≥0.1 IU/mL
- Anti-T antibody concentration ≥0.1 IU/mL
- Anti-PT GMCs
- Anti-FHA GMCs
- Anti-PRN GMCs
- Anti-Poliovirus 1 antibody titers ≥8
- Anti-Poliovirus 2 antibody titers ≥8
- Anti-Poliovirus 3 antibody titers ≥8
- S. pneumonia GMCs for the 13 serotypes in Prevnar13
- Anti-PT, anti-FHA, and anti-PRN seroresponse defined as the percentage of subjects showing an antibody concentration above a threshold that led to 95% seroresponse in the control group one month after last dose of primary vaccination.

6.8.2 Secondary endpoints

6.8.2.1 Immunogenicity secondary endpoints

One month after last dose of primary vaccination:

- anti-PRP GMCs, anti-PRP concentrations ≥0.15 µg/mL and ≥1.0 µg/mL
- Anti-D GMCs and concentrations ≥0.1 IU/mL (seroprotection)
- Anti-T GMCs and concentrations ≥0.1 IU/mL (seroprotection)
- Anti-PT GMCs and concentrations ≥5 (b) (4) (seropositivity)
- Anti-FHA GMCs and concentrations ≥5 (b) (4) (seropositivity)
- Anti-PRN GMCs and concentrations ≥5 (b) (4) (seropositivity)
- Anti-poliovirus types 1, 2, and 3 GMTs and titers ≥8 (seroprotection)
- Anti-HBs GMCs and concentrations ≥10.0 mIU/mL (seroprotection) and concentrations ≥3.3 mIU/mL (seropositivity)
- S. pneumoniae antibody concentrations ≥0.05 µg/mL (seropositivity), ≥0.2 µg/mL and ≥1.0 µg/mL for the 13 serotypes in Prevnar13
- Anti-PT, anti-FHA, and anti-PRN seroresponse defined as the percentage of subjects showing an antibody concentration above a threshold that led to 90% seroresponse in the control group.

6.8.2.2 Safety secondary endpoints

Solicited local and general symptoms

- Occurrence of specifically solicited local symptoms (pain, redness, and swelling at the injection site) during a 4-day follow-up period (i.e., day of vaccination and 3 subsequent days) following each dose of vaccine.
- Occurrence of specifically solicited general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite) during a 4-day follow-up period (i.e., day of vaccination and 3 subsequent days) following each dose of vaccine.

Unsolicited adverse events

- Occurrence of all unsolicited symptoms within 31 days following each vaccination.

Serious adverse events

- Occurrence of all serious adverse events (SAEs) from Day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever came first.

Specific adverse events

- Occurrence of specific adverse events, i.e., new onset chronic diseases (e.g., autoimmune disorders, asthma, type I diabetes, and allergies) and conditions prompting ER visits from Day 0 until 6 months following the last primary dose or until receipt of the booster vaccination, whichever came first.

6.8.2 Measurement methods

Refer to the statistical assay review and clinical review for the immunogenicity antibody concentration measurement methods for the primary and secondary endpoints.

6.9 Statistical Considerations & Statistical Analysis Plan

6.9.1 Sample size determination

For the power calculation of immunological evaluation, approximately 704 subjects in each of the sub-cohorts *Hiberix* A-PRP, *Hiberix* B-PRP, and *Hiberix* C-PRP, and 352 subjects in each of the sub-cohorts *ActHIB* and *Pentacel* were blood sampled in the primary vaccination epoch. Assuming 75% of subjects would be evaluable in the primary vaccination epoch, the number of evaluable subjects was 528 per *Hiberix* lot, 264 in group *ActHIB*, and 264 in group *Pentacel*.

Control of the type I error below 2.5% was performed using a hierarchical procedure for the first three primary objectives in the primary epoch, with a 2.5% type I error. To conclude independently between the primary objective in the booster epoch and the objectives 4-7 in the primary epoch, a Bonferroni correction was used thereafter, i.e., the type-I error was split (one-sided=1.25%) for the evaluation of the booster primary objective and the evaluation of the rest of the co-primary objective in the primary epoch.

Endpoints for Estimation of Sample Size

The primary endpoint used for sample size determination is anti-PRP antibody response 1 month after 3 doses of Hiberix vaccine in Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP. The power estimation based on the primary objective of lot-to-lot consistency using the anti-PRP GMC endpoint, evaluable sample size of 528 per lot, and a standard deviation of 0.68 is 97.52%. The overall power after multiplicity adjustment for the 3 pair-wise lot comparisons is 92.56%.

The following power estimation was based on the co-primary objectives and the type-I error discussed above.

Co-primaryobjectives

Tables 3 presents the sample size and power for non-inferiority of Hiberix to ActHIB, each co-administered with Pediarix, Prevnar13, and Rotarix following 3 primary doses in terms of immune response to PRP (Anti-PRP ≥1.0 µg/mL and Anti-PRP ≥0.15 µg/ml).

Table 3: Sample size and Power for NI of Hiberix to ActHIB

Endpoint	N evaluable Pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, Hiberix C-PRP	N evaluable Sub-cohort ActHIB	True rate in both groups*	Power
Anti-PRP ≥1.0 µg/mL	1584	264	85.8%	99.72%
Anti-PRP ≥0.15 µg/mL	1584	264	95.7%	99.0%

* Ref: Hib-MenCY-TT005 ActHIB group

Source: Reviewer's compiled Table from sponsor's multiple Tables reported in the CSR.

Table 4 presents the sample size and power for non-inferiority of Pediarix co-administered with Hiberix, Prevnar13, and Rotarix compared to Pediarix co-administered with ActHIB, Prevnar13, and Rotarix following 3 primary vaccine doses in terms of immune response to diphtheria, tetanus (seroprotection), PT, FHA, PRN (GMCs), and 3 types of poliovirus (seroprotection).

Table 4: Sample size and Power for NI comparison in terms of immune response to diphtheria, tetanus (seroprotection), PT, FHA, PRN (GMCs) and 3 types of poliovirus.

Endpoint	N Hibrix-coAd subset	N ActHIB sub-cohort	True rate in both groups*	Standard deviation*	Power
Anti-D ≥0.1 IU/mL	396	264	99.5%	N/A	>99.99%
Anti-T ≥0.1 IU/mL	396	264	99.9%	N/A	>99.99%
Anti-PT	792	264	N/A	0.275	>99.99%
Anti-FHA	792	264	N/A	0.307	>99.99%
Anti-PRN	792	264	N/A	0.392	99.99%
Anti-Polio-1 ≥8	396	264	99.9%	N/A	>99.99%
Anti-Polio-2 ≥8	396	264	98.8%	N/A	99.51%
Anti-Polio-3 ≥8	396	264	99.9%	N/A	>99.99%

* Ref: Hib-MenCY-TT005 ActHIB group
N/A= Not applicable
Source: Reviewer's compiled Table from sponsor's multiple Tables reported in the CSR.

396 evaluable subjects in the Hiberix co-Ad sub-cohort and 264 evaluable subjects in the ActHIB sub-cohort will also provide a 99.9% overall power for the non-inferiority comparison of Prevnar13 co-administered with Hiberix, Pediarix, and Rotarix to Prevnar13 co-administered with ActHIB, Pediarix, and Rotarix, following 3 primary vaccine doses in terms of GMC of 13 S.pneumoniea serotypes.

6.9.2 Populations Analyzed

A total of seven cohorts were defined for the purpose of the analysis.

Primary Total Vaccinated cohort

The Primary Total Vaccinated cohort (Prim-TVC) included all vaccinated subjects. For the Prim-TVC analysis of safety, this included all subjects with at least one vaccine administration documented. For the Prim-TVC analysis of immunogenicity, this included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The Prim-TVC analysis was performed per treatment actually administered at the first dose in the primary vaccination epoch.

Primary According-to-protocol (ATP) cohort for safety

The Primary ATP cohort for safety included all eligible subjects: who met all inclusion criteria and no exclusion criteria for the study; who received at least 1 dose of study/control vaccine according to their treatment assignment during the primary vaccination course; for whom the injection site of study/control vaccine was known; who did not receive a vaccine not specified or forbidden in the protocol during the primary vaccination course, i.e., up to the post-dose 3 blood sample.

Primary ATP cohort for immunogenicity

The Primary ATP cohort for immunogenicity included all evaluable subjects (i.e., those who met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria during the study) from the Primary ATP cohort for safety to whom 3 vaccine doses were administered and assay results were available for antibodies against at least one antigen for the blood sample taken one month after the third vaccine dose.

Persistence cohort for immunogenicity (prior to the administration of a booster dose)
The persistence cohort for immunogenicity was to include all subjects who were included in the booster vaccination epoch, who received 3 vaccine doses in the primary study, for whom assay results from the blood sample taken before the booster dose were available and who were not eliminated for concomitant administration of forbidden medication or inter-current medical conditions.

6.9.3 Handling of Missing Data

Immunogenicity
For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

Reactogenicity and Safety
For a given subject and the analysis of solicited symptom within 4 days post-vaccination, missing or non-evaluable measurements were not to be replaced. Therefore, the analysis of the solicited symptoms based on the Total Vaccinated cohort included only vaccinated subjects for doses with documented safety data (i.e., symptom screen completed).

For analysis of unsolicited adverse events, such as serious adverse events or adverse events by primary MedDRA term, and for the analysis of concomitant medications, all vaccinated subjects were to be considered. Subjects who did not report the event or the concomitant medication were considered as subjects without the event or the concomitant medication, respectively.

6.9.4 Methodology of Computing CI and Sequence of Analysis

Confidence Interval calculations
All CIs were 2 sided 95% CI.

- The exact 95% CI for a proportion within a group was calculated from Proc StatXact.
- Proc StatXact was used to derive the standardized asymptotic 95% CI for the group difference in proportions.
- The 95% CIs for GMTs/GMCs were obtained within each group separately. The 95% CI for the mean log-transformed titer/concentration was first obtained assuming that log-transformed values were normally distributed with unknown variance. The 95% CIs for the GMTs/GMCs were then obtained by exponential-transformation of the 95% CI for the mean log-transformed titer/concentration.
- The group GMT/GMC ratio was obtained using an ANOVA model on the logarithm transformed concentrations/titers. The ANOVA model included only

the vaccine group as fixed effect. For the analysis of anti-HBs the ANOVA model also included Hepatitis B vaccination history (yes/no) as an additional fixed effect. The GMC/GMT ratio and its 95% CI were derived as exponential-transformation of the corresponding group contrast in the model.

Sequence of Analysis

Statistical tests for the primary objectives were performed in a hierarchical way so that the lot-to-lot consistency evaluation was followed by non-inferiority of Hiberix to ActHIB in terms of anti-PRP (≥1.0μg/mL and ≥0.15 μg/mL) at significance level of 0.025 (95% 2-sided CI). The type I error was then split for the remaining primary objectives in the primary epoch and the primary booster objective evaluation so that the overall type-I error was controlled (one-sided=2.5%).

6.10 Study Population and Disposition

6. 10.1 Disposition of Subjects

A summary of subjects who were randomized, completed, and withdrawn with a reason of withdrawal is presented in Table 5.

Table 5: Summary of Study Completion as Randomized, Completed and Withdrawn at last visit with reason of withdrawal

Number of subjects	**Hiberix**	**ActHIB**	**Pentacel**
Planned; N	3000	500	500
Vaccinated	2963	520	520
Completed to visit 4; n (%)	2625 (88.6)	470 (90.4)	457 (87.9)
Withdrawn (did not come to last visit)	338	50	63
Reason for withdrawal			
Subject died	0	0	0
Serious Adverse Event	5	1	0
Non-Serious Adverse Event	9	1	2
Eligibility criteria not fulfilled (inclusion and exclusion criteria)	0	0	0
Protocol violation	7	2	2
Consent withdrawal (not due to an adverse event)	109	17	21
Migrated/moved from study area	29	0	3
Lost to follow-up (subjects with incomplete vaccination course)	33	6	9
Lost to follow-up (subjects with complete vaccination course)	37	8	6
Sponsor study termination	0	0	0
Others	109	15	20

Source: Reviewer's Table based on submitted data.

6.10.2 Protocol Deviations and Amendments

Protocol amendments

The protocol dated 10 August 2009 was amended on 08 April 2010 to

- Replace Prevnar with Prevnar13 for routine S. pneumonia immunization at 2, 4, 6 months and 12 to 15 months of age as per the updated ACIP recommendations.
- Following the temporary suspension of the use of Rotarix in the United States, infants were to be vaccinated against rotavirus disease with Rotateq vaccine.

Amendment 1 was amended again (amendment 2) on 18 May 2010 to replace the use of Rotateq with Rotarix as vaccination against rotavirus disease in the study after the temporary suspension was withdrawn.

***Reviewer's comment**: No subject in the study received Rotateq vaccine.*

Amendment 3 was submitted April 2011 in order to:

- Ensure scheduling of study visit 3 so that subjects could receive final hepatitis B vaccination according to ACIP recommendations (minimum age of 24 weeks for the final hepatitis B dose, with an interval of at least 8 weeks between the 2nd and final hepatitis B dose),
- Update the footnote of Table 6 to clarify that it was preferred that subjects come in for Visit 6, at least 30 days after Visit 5.
- Update the sections on exclusion criteria for enrollment, contraindications to vaccination, and warnings and precautions with information from the updated US *Rotarix* label.

Other changes

The study was conducted according to the protocol and statistical analysis plan (SAP), except for a few changes listed below:

Changes made from the protocol in the SAP:

- The protocol section 10.7.2.2 proposed to use exploratory 95% CI on group difference to identify significant difference. Considering that the risk of erroneous difference was considerable in light of the number of comparisons, the 95% CI was provided descriptively without attempt for interpretation.
- Additional exploratory group comparisons were added in order to have a full assessment of *Hiberix* vs *ActHIB* and vs *Pentacel* with respect to GMC and % of subjects above cut-off.
- For HepB GMC group ratio, HepB vaccination history was to be included in the ANOVA model
- The protocol states that access to individual treatment codes and immunogenicity data would be restricted to the statistician in charge of the analyses and the authorized staff until all the follow-up activities for booster epoch were completed and the data unblinded. Considering that (1) the study was open-label for the Pentacel group and single blind for the ActHIB and Hiberix groups and (2) lot-to-lot consistency was part of the first analysis, the individual treatment codes were released upon completion of the first analysis. Note that laboratory assay testing continued to be independent from the treatment groups.
- The protocol states that subjects who were screened but ineligible as well as those who were excluded from the various analysis sets, would be listed in the by-subject data listings. Since the data on screening was not recorded, there was no individual listing for screened subjects.
- The protocol states that the incidence of solicited local and general symptoms would be tabulated for all age strata, and then per age stratum. However, this was not performed as there was no age stratum defined.

- Details on inclusion/exclusion criteria of the primary ATP cohort for immunogenicity were added.
- An additional analysis on the Booster According to Protocol cohort to evaluate the primary objectives 1 to 4 of the primary epoch was added.
- An analysis that summarized anti-PRP results one month post primary vaccination according to inclusion of Booster immunogenicity sub-cohort was added.
- Since the persistence cohort for immunogenicity (prior to the administration of a booster dose) was almost the same as the Booster ATP cohort for immunogenicity, the persistence analysis was done on the Booster ATP cohort for immunogenicity.

6.10.3 Demographic and Baseline Characteristics

The demographic characteristics are presented in Tables 6 and 7. Approximately 48% of the subjects in the Hiberix group were females and 52% of the subjects were males. The distributions of subjects for all demographic characteristics were similar in all groups.

Table 6: Summary of demographic characteristics (ATP-immunogenicity)

Characteristics	Parameters	Hiberix N=1592	ActHIB N = 275	Pentacel N = 253	Total N = 2120
Age[W]	Mean	8.6	8.6	8.7	8.6
	SD	1.04	1.09	1.07	1.05
	Median	9.0	9.0	8.0	9.0
	Minimum	6	6	6	6
	Maximum	12	12	12	12
Height[cm]	Mean	58.5	58.3	58.9	58.5
	SD	3.50	2.85	3.28	3.40
	Median	58.0	58.0	58.0	58.0
	Minimum	28	41	51	28
	Maximum	89	66	86	89
Weight[Kg]	Mean	5.4	5.4	5.4	5.4
	SD	0.71	0.67	0.65	0.70
	Median	5.3	5.3	5.4	5.3
	Minimum	3	4	3	3
	Maximum	8	7	7	8

Age[W] = age expressed in Weeks; SD=Standard deviation
Source: Adapted from BLA 125347/231 Clinical Study Report

Table 7: Summary of demographic characteristics (ATP-immunogenicity)

Characteristics	Parameters or categories	Hiberix N= 1592	ActHIB N=275	Pentacel N=253	Total N=2120
		n (%)	n (%)	n (%)	n (%)
Gender	Female	759 (47.7)	149 (54.2)	117 (46.2)	1025 (48.3)
	Male	833 (52.3)	126 (45.8)	136 (53.8)	1095 (51.7)
Race	African heritage / African American	122 (7.7)	20 (7.3)	15 (5.9)	157 (7.4)
	American Indian or Alaskan Native	134 (8.4)	28 (10.2)	25 (9.9)	187 (8.8)
	Asian - Central / South Asian heritage	33 (2.1)	5 (1.8)	3 (1.2)	41 (1.9)
	Asian - East Asian heritage	28 (1.8)	5 (1.8)	3 (1.2)	36 (1.7)
	Asian - Japanese heritage	9 (0.6)	0 (-)	1 (0.4)	10 (0.5)
	Asian - South East Asian heritage	75 (4.7)	17 (6.2)	13 (5.1)	105 (5)
	Native Hawaiian or other Pacific Islander	12 (0.8)	3 (1.1)	3 (1.2)	18 (0.8)
	White - Arabic / North African heritage	14 (0.9)	1 (0.4)	1 (0.4)	16 (0.8)
	White - Caucasian / European heritage	954 (59.9)	165 (60)	146 (57.7)	1265 (59.7)
	Other	211 (13.3)	31 (11.3)	43 (17)	285 (13.4)
Hepatitis B Vaccine at Birth	No	136 (8.5)	31 (11.3)	21 (8.3)	188 (8.9)
	Yes	1456 (91.5)	244 (88.7)	232 (91.7)	1932 (91.1)

N = number of subjects; n = number of subjects in a given category; % = n / N x 100
Source: Adapted from BLA 125347/231 Clinical Study Report

6.11 Immunogenicity and Efficacy Results

6.11.1 Lot-to-lot consistency in terms of anti-PRP GMCs

The GMC ratio between Hiberix lot A, B, and C of anti-PRP one month after primary vaccination is presented in Table 8.

Table 8: GMC ratio of anti-PRP one month after primary vaccination (Primary ATP cohort for immunogenicity)

					95%CI
Group	N	GMC	Ratio	Value	(LL, UL)
Hiberix Lot A	527	4.994	Hiberix Lot A /Hiberix Lot B	0.790	(0.641, 0.974)
Hiberix Lot B	537	6.323	Hiberix Lot A /Hiberix Lot C	1.131	**(0.916, 1.396)**
Hiberix Lot C	526	4.416	Hiberix Lot B /Hiberix Lot C	1.432	(1.161, 1.765)

N = Number of subjects with post-vaccination results available
Bold: Result satisfied the pre-specified success criteria
Source: Reviewer's analysis result based on submitted data

One month after primary vaccination: The two-sided 95% confidence limits on the anti-PRP GMC ratio between Hiberix Lot A and Hiberix Lot C was within the [0.67, 1.5] interval. However, the two-sided 95% confidence limits on the anti-PRP GMC ratio between Hiberix Lot A and Hiberix Lot B [0.641, 0.974] and between Hiberix Lot B and Hiberix Lot C [1.161, 1.765] were not within the predefined [0.67; 1.5] interval. Thus, the primary objective of lot-to-lot consistency of 3 manufacturing lots of Hiberix was not met according to the pre-specified statistical criteria.

Due to the hierarchical nature of the statistical testing, no further tests were to be performed or conclusions drawn for the subsequent objectives.

6.11.2 Non-inferiority in terms of seroprotection rates of anti-PRP

Table 9 presents the difference between Hiberix and ActHIB groups in percentage of subjects with antibody concentration ≥ 0.15 μg/mL and ≥ 1.0 μg/mL to PRP one month after primary vaccination.

Table 9: Difference between groups in percentage of subjects with antibody concentration ≥ 0.15 ug/mL, ≥ 1.0 ug/mL to PRP by (b) (4)

						Difference	Difference
		Hiberix	Hiberix	ActHIB	ActHIB		95% CI
Antibody	**Cut-off**	**N**	**n (%)**	**N**	**n (%)**	**%**	**(LL, UL)**
Anti-PRP	0.15 μg/mL	1590	1536 (96.6)	274	265 (96.7)	-0.11	(-1.98,2.82)
Anti-PRP	1 μg/mL	1590	1291 (81.2)	274	246 (89.8)	-8.59	(-12.28,-4.07)

N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
Difference= Difference in percentage (Hiberix minus ActHIB)
Source: Reviewer's analysis result based on submitted data.

One month after primary vaccination:

- The lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥1.0 μg/mL was -12.28%, which was slightly lower than -10% (pre-specified limit for non-inferiority).
- The lower limit of the standardized asymptotic 95% CI for the difference (pooled Sub-cohorts Hiberix A-PRP, Hiberix B-PRP, and Hiberix C-PRP minus Sub-cohort ActHIB) in the percentage of subjects with anti-PRP concentrations ≥0.15 μg/mL was -1.98% which was greater than -5% (pre-specified limit for non-inferiority).

Hence, the statistical criterion for the primary objective of non-inferiority of this study in terms of anti-PRP was slightly missed for anti-PRP concentrations ≥ 1.0 μg/mL, but was met for anti-PRP concentrations ≥0.15 μg/mL.

6.11.3 Non-inferiority to D, T, PT, FHA, PRN, and poliovirus 1, 2, and 3

The non-inferiority analysis results in terms of immune response to D, T, PT, FHA, PRN, and poliovirus 1,2, and 3 are presented in Tables 10 and 11.

Table 10: Difference between groups (Hiberix and ActHIB) in percentage of subjects by the given parameter one month after primary vaccination

						Difference	Difference
		Hiberix	Hiberix	ActHIB	ActHIB		95% CI
Antibody	**Cut-off**	**N**	**n (%)**	**N**	**n (%)**	**%**	**(LL, UL)**
Anti-D	0.1 IU/ml	393	393 (100)	273	273 (100)	0.00	(-1.26,1.81)
Anti-T	0.1 IU/ml	393	393 (100)	274	274 (100)	0.00	(-1.26,1.8)
Anti-Polio 1	8 ED50	248	246 (99.2)	181	181 (100)	-0.81	(-3.38,1.91)
Anti-Polio 2	8 ED50	280	275 (98.2)	192	188 (97.9)	0.30	(-2.84,4.28)
Anti-Polio 3	8 ED50	257	254 (98.8)	181	181 (100)	-1.17	(-3.87,1.55)

N = number of subjects with available results
% = percentage of subjects anti-T/anti-D concentration ≥ 0.1 IU/mL and anti-polio titers ≥8
Difference= Difference in percentage (Hiberix minus ActHIB)
Source: Reviewer's analysis result based on submitted data.

Table 11: GMC ratio of anti-PT, FHA, and PRN one month after primary vaccination

					GMC ratio	GMC ratio
	Hiberix	Hiberix	ActHIB	ActHIB		97.5% CI
Antibody	N	GMC	N	GMC	Value	(LL, UL)
Anti-PT (b) (4)	792	73.2	275	71.9	1.017	(0.918,1.127)
Anti-FHA ((b) (4)	791	321.8	275	295.8	1.088	(0.983,1.204)
Anti-PRN ((b) (4))	789	111.6	275	93.5	1.193	(1.03,1.382)

N = Number of subjects with post-vaccination results available

Ratio= Hiberix/ActHIB

Source: Reviewer's analysis result based on submitted data.

One month after primary vaccination:

- The lower limit of the standardized asymptotic 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) in the percentages of subjects with seroprotective concentrations (≥0.1 IU/mL) of anti-diphtheria and anti-tetanus antibodies was -1.26% which was greater than -10% (pre-specified limit for non- inferiority).
- The lower limit of the 97.5% CIs on the GMC ratios (Subset Pertussis Co-Ad divided by Sub-cohort ActHIB) for antibodies to each of the pertussis antigens (PT, FHA, and PRN) was 0.918, 0.983, and 1.030, respectively, which was greater than 0.67 (pre-specified limit for non-inferiority).
- The lower limit of the 97.5% CIs on the differences (Subset Hiberix Co-Ad minus Sub-cohort ActHIB) for antibodies to each of the poliovirus antigens (type 1, type 2, and type 3) was-3.38%, -2.84%, and -3.87%, which was greater than -5% (pre-specified limit for non-inferiority).

The statistical criteria for the primary test of non-inferiority of Hiberix compared to ActHIB in terms of D, T, PT, FHA, PRN, and poliovirus 1, 2, and 3 were demonstrated as the predefined criteria were met.
(See objective #3 and #4 and pre-defined criteria in section 6.1.1 above)

However, due to the hierarchical nature of the statistical testing, no conclusions were to be drawn for these subsequent tests.

6.11.4 Immune response to poliovirus 1, 2, and 3

The immune response to poliovirus types 1, 2, and 3 is presented in Table 12.

Table 12: Percentage of subjects with anti-Polio-1,2,3 antibody titers greater than or equal to 8 for Hiberix group one month after primary vaccination

				≥ 8 ED50	≥ 8 ED50	GMT	GMT
					97.5% CI		97.5% CI
Antibody	Group	Timing	N	n (%)	(LL, UL)	value	(LL, UL)
Anti-Polio 1	Hiberix	POS 3 M 5	248	246 (99.2)	(96.8,99.9)	604.7	(502,728.3)
Anti-Polio 2	Hiberix	POS 3 M 5	280	275 (98.2)	(95.5,99.5)	499.5	(407.7,612)
Anti-Polio 3	Hiberix	POS 3 M 5	257	254 (98.8)	(96.3,99.8)	1110.5	(906.9,1359.7)

POS 3 M 5 = one month post dose 3 at Month 5

N = number of subjects with available results

n/% = number/percentage of subjects with antibody titers above the specified cut-off

Source: Reviewer's analysis result based on submitted data.

One month after primary vaccination, the lower limit of the 97.5% CIs on the percentage of subjects (Subset Hiberix Co-Ad) with seroprotective titers (≥8) was greater than 90% for each poliovirus antigen.

The statistical criteria for the primary objective of the acceptability of the immune response of Pediarix when co-administered with Hiberix following 3 primary vaccine doses, in terms of immune response to poliovirus 1, 2, and 3, were satisfied.
(See objective #5 and pre-defined criteria in section 6.1.1 above)

However, due to the hierarchical nature of the statistical testing, no conclusions were to be drawn for these subsequent tests.

6.11.5 Non-inferiority in terms of S. pneumonia post-vaccination antibody GMCs

One month after primary vaccination, the lower limit of the 97.5% CIs on the GMC ratios (Subset Hiberix Co-Ad over Sub-cohort ActHIB) for each S. pneumonia serotype (anti-1, anti-3, anti-4, anti-5, anti-6A, anti-6B, anti-7F, anti-9V, anti-14, anti-18C, anti-19A, anti-19F, and anti- 23F) was at least 0.8, which was greater than 0.5 (pre-specified limit for non-inferiority).

The statistical criteria for the primary objective of non-inferiority of Prevnar13 co-administered with Hiberix (pooled lots) compared to Prevnar13 co-administered with ActHIB in terms of S. pneumonia GMCs were satisfied.
(See objective #6 and pre-defined criteria in section 6.1.1 above)

However, due to the hierarchical nature of the statistical testing, no conclusions were to be drawn for these subsequent tests.

6.11.6 Non-inferiority of Hiberix versus ActHIB with respect to seroresponse rates for PT, FHA, and PRN

The results are presented in Table 13:

Table 13: P-value for test on the difference in percentage of subjects with primary seroresponse to Pertussis antigens between groups (Hiberix and ActHIB)

	Cut-off	Treatment Group	Treatment Group	Control Group	Control Group	P-value
Antibody	**Value**	**N**	**n (%)**	**N**	**n (%)**	**H_0:P(t)≤ 85%**
Anti-FHA	117	791	744 (94.1)	275	263 (95.6)	<.0001
Anti-PRN	19	789	762 (96.6)	275	262 (95.3)	<.0001
Anti-PT	24	792	764 (96.5)	275	264 (96)	<.0001

N = number of subjects with available results; n/% = number/percentage of results above the cut-off
Cut-off is the antibody level that leads to 95% response in the control group
P-value is computed by integrating on the p-values of one-sided test with alpha=0.025 and the posterior probability of the cut-off in the control group.
Source: Adapted from BLA 125347/231 Clinical Study Report

One month after primary vaccination; the p-value for the difference in seroresponse between the pooled Hiberix and ActHIB groups was <0.01% for each of PT, FHA, and PRN antigens, which was less than 1.25%. Therefore, a 10% decrease in seroresponse to

PT, FHA, and PRN in subjects receiving Pediarix co-administered with Hiberix in comparison with subjects receiving Pediarix co-administered with ActHIB was ruled out. (See objective #7 and pre-defined criteria in section 6.1.1 above.)

However, due to the hierarchical nature of the testingg, no conclusions were to be drawn for these subsequent statistical tests.

6.11.7 Immune response to the vaccine antigens

6.11.7. 1 Anti-PRP response

The percentage of subjects with anti-PRP antibody concentrations ≥0.15 μg/mL, ≥1.0 μg/mL and GMCs by group, one month after primary vaccination, is analyzed using descriptive analysis.

One month after primary vaccination:

- At least 92.5% of subjects had anti-PRP antibody concentrations ≥0.15 μg/mL in the Hiberix, ActHIB, and Pentacel groups.
- In the three Hiberix Lot groups (A, B, and C), at least 95.6% of subjects had anti-PRP antibody concentrations ≥0.15 μg/mL.
- Percentages of subjects with anti-PRP antibody concentrations ≥1.0 μg/mL were 81.2%, 89.8%, and 78.3% in the Hiberix, ActHIB, and Pentacel groups, respectively. Anti-PRP antibody concentrations ≥1.0 μg/mL were seen in 81.6%, 84.9%, and 77.0% of subjects in the Hiberix Lot A, Hiberix Lot B, and Hiberix Lot C groups, respectively.

6.11.7. 2 Anti-diphtheria and anti-tetanus response

One month after primary vaccination:

- All subjects in the Hiberix and ActHIB groups and at least 99.6% of subjects in the Pentacel group had anti-diphtheria and anti-tetanus seroprotective concentrations (≥0.1 IU/mL).
- At least 85.2% of subjects in the Hiberix and ActHIB groups had anti-diphtheria and anti-tetanus antibody concentrations ≥1.0 IU/mL. In the Pentacel group, at least 76.4% of subjects had anti-diphtheria and anti-tetanus antibody concentrations ≥1.0 IU/mL.
- The percentage of subjects with anti-diphtheria and anti-tetanus antibody concentrations ≥1.0 IU/mL ranged from 84.1% to 95.2% in the Hiberix Lot groups.

6.11.7. 3 Anti-PT, anti-FHA, and anti-PRN response

One month after primary vaccination:

- Anti-PT, anti-FHA, and anti-PRN seropositive concentrations were seen in at least 97.6% of subjects in the three groups (Hiberix, ActHIB, and Pentacel).
- Anti-PT, anti-FHA, and anti-PRN seropositive concentrations were seen in at least 99.2% of subjects in the Hiberix Lot groups.

6.11.7. 4 Anti-poliovirus types 1, 2, and 3 response

One month after primary vaccination:

- Anti-poliovirus type 1, type 2, and type 3 seroprotective titers (≥8) were seen in at least 98.2% of subjects in the Hiberix group, at least 97.9% of subjects in the ActHIB group, and at least 93.7% of subjects in the Pentacel group.
- Anti-poliovirus type 1, type 2, and type 3 seroprotective titers (≥8) were seen in at least 97.0% of subjects in all three Hiberix Lot groups.

6.11.7. 5 Anti-HBs response

One month after primary vaccination:

- At least 99.6% of subjects had seroprotective concentrations (≥10 mIU/mL) in all three groups (Hiberix, ActHIB, and Pentacel).
- All subjects (100%) in the Hiberix Lot A and Hiberix Lot B groups and 99.1% of subjects in Hiberix Lot C group had anti-HBs antibody concentrations ≥10 mIU/mL.

6.11.7. 6 Anti S. pneumonia antibody (13 serotypes) concentrations

One month after primary vaccination:

- At least 97.4% of subjects in each group (Hiberix, ActHIB, and Pentacel) had anti-S.pneumoniae antibody concentrations ≥0.05 µg/mL, against all serotypes.
- At least 90.6% of subjects had anti-S.pneumoniae antibody concentrations ≥0.2 µg/mL, against all serotypes in all three groups (Hiberix, ActHIB, and Pentacel).
- For each of the vaccine pneumococcal serotypes, at least 97.7% of subjects in the Hiberix Lot groups had antibody concentrations ≥0.05 µg/mL.
- For each of the vaccine pneumococcal serotypes, at least 89.7% of subjects in the Hiberix Lot groups had antibody concentrations ≥0.2 µg/mL.

6.11.8 Immunogenicity Subgroup Analysis

The percentage of subjects with anti-PRP antibody concentrations ≥0.15 µg/mL, ≥1.0µg/mL GMC by sex and race, one month after primary vaccination for the Primary ATP cohort for immunogenicity, is presented in Tables 14 and 15, respectively.

Table 14: Immunogenicity subgroup analysis by sex

				≥ 0.15 µg/mL	**≥ 0.15 µg/mL**	**≥ 1 µg/mL**	**≥ 1 µg/mL**	GMC	**GMC**
					95% CI		**95% CI**		**95% CI**
Antibody	**Sub-group**	**Group**	**N**	**n (%)**	(LL,UL)	**n (%)**	(LL,UL)	**value**	(LL,UL)
Anti-PRP	Male	Hiberix	833	801 (96.2)	(94.6,97.4)	661 (79.4)	(76.4,82.1)	4.56	(4.04,5.15)
		ActHIB	125	120 (96)	(90.9,98.7)	112 (89.6)	(82.9,94.3)	6.99	(5.27,9.27)
		Pentacel	136	123 (90.4)	(84.2,94.8)	102 (75.0)	(66.9,82.0)	3.54	(2.52,4.98)
	Female	Hiberix	757	735 (97.1)	(95.6,98.2)	630 (83.2)	(80.4,85.8)	5.99	(5.30,6.76)
		ActHIB	149	145 (97.3)	(93.3,99.3)	134 (89.9)	(83.9,94.3)	6.54	(5.08,8.42)
		Pentacel	117	111 (94.9)	(89.2,98.1)	96 (82.1)	(73.9,88.5)	3.75	(2.76,5.11)

N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value
Source: Adapted from BLA 125347/231 Clinical Study Report

Similar results were observed between males and females in all three groups.

Table 15: Immunogenicity subgroup analysis by race

				≥ 0.15 µg/mL	≥ 0.15 µg/mL	≥ 1 µg/mL	≥ 1 µg/mL	GMC	GMC
					95% CI		95% CI		95% CI
Antibody	**Sub-group**	**Group**	**N**	**n (%)**	**(LL,UL)**	**n (%)**	**(LL,UL)**	**value**	**(LL,UL)**
Anti-PRP	White	Hiberix	953	913 (95.8)	(94.3,97.0)	741 (77.8)	(75,80.4)	3.99	(3.58,4.45)
		ActHIB	164	155 (94.5)	(89.8,97.5)	143 (87.2)	(81.1,91.9)	5.23	(4.02,6.79)
		Pentacel	146	136 (93.2)	(87.8,96.7)	109 (74.7)	(66.8,81.5)	2.86	(2.13,3.84)
	Other	Hiberix	637	623 (97.8)	(96.3,98.8)	550 (86.3)	(83.4,88.9)	7.70	(6.75,8.79)
		ActHIB	110	110 (100)	(96.7,100)	103 (93.6)	(87.3,97.4)	9.86	(7.75,12.54)
		Pentacel	107	98 (91.6)	(84.6,96.1)	89 (83.2)	(74.7,89.7)	5.05	(3.52,7.27)

White = The most frequent race; Other = All other races
N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value
Source: Adapted from BLA 125347/231 Clinical Study Report

Similar results were observed between the two races in all three groups. Highest difference (8.6%) was observed between the two races in the Hiberix group for the anti-PRP antibody concentration ≥1.0 µg/mL.

The percentage of subjects with anti-D, Anti-T antibody concentrations ≥0.1 IU/mL, ≥1.0 µg/mL, and GMCs by sex and race one month after primary vaccination for Primary ATP cohort for immunogenicity is presented in Tables 16 and 17, respectively.

Table 16: Subgroup analysis by sex for anti-D, Anti-T antibody concentrations

				≥ 0.1 IU/ml	≥ 0.1 IU/ml	≥ 1 IU/ml	≥ 1 IU/ml	GMC	GMC
					95% CI		95% CI		95% CI
Antibody	**Sub-group**	**Group**	**N**	**n (%)**	**(LL,UL)**	**n (%)**	**(LL,UL)**	**value**	**(LL,UL)**
Anti-D	Male	Hiberix	203	203 (100)	(98.2,100)	186 (91.6)	(86.9,95.0)	2.76	(2.49,3.05)
		ActHIB	124	124 (100)	(97.1,100)	108 (87.1)	(79.9,92.4)	2.48	(2.15,2.87)
		Pentacel	134	133 (99.3)	(95.9,100)	105 (78.4)	(70.4,85.0)	1.90	(1.65,2.2)
	Female	Hiberix	190	190 (100)	(98.1,100)	167 (87.9)	(82.4,92.2)	2.69	(2.42,2.98)
		ActHIB	149	149 (100)	(97.6,100)	129 (86.6)	(80.0,91.6)	2.42	(2.15,2.71)
		Pentacel	116	116 (100)	(96.9,100)	86 (74.1)	(65.2,81.8)	1.85	(1.59,2.16)
Anti-T	Male	Hiberix	203	203 (100)	(98.2,100)	168 (82.8)	(76.8,87.7)	2.28	(2.03,2.57)
		ActHIB	125	125 (100)	(97.1,100)	110 (88)	(81.0,93.1)	2.84	(2.43,3.32)
		Pentacel	134	133 (99.3)	(95.9,100)	99 (73.9)	(65.6,81.1)	1.73	(1.49,2.01)
	Female	Hiberix	190	190 (100)	(98.1,100)	167 (87.9)	(82.4,92.2)	2.18	(1.97,2.41)
		ActHIB	149	149 (100)	(97.6,100)	125 (83.9)	(77.0,89.4)	2.15	(1.88,2.47)
		Pentacel	116	116 (100)	(96.9,100)	95 (81.9)	(73.7,88.4)	1.70	(1.47,1.97)

n/% = number/percentage of subjects with concentration equal to or above specified value
Source: Adapted from BLA 125347/231 Clinical Study Report

Similar results were observed between males and females in all three groups.

Table 17: Subgroup analysis by race for anti-D, Anti-T antibody concentrations

				≥ 0.1 IU/ml	≥ 0.1 IU/ml	≥ 1 IU/ml	≥ 1 IU/ml	GMC	GMC
					95% CI		95% CI		95% CI
Antibody	**Sub-group**	**Group**	**N**	**n (%)**	**(LL,UL)**	**n (%)**	**(LL,UL)**	**value**	**(LL,UL)**
Anti-D	White	Hiberix	230	230 (100)	(98.4 ,100)	204 (88.7)	(83.9 ,92.5)	2.61	(2.38 ,2.86)
		ActHIB	164	164 (100)	(97.8 ,100)	140 (85.4)	(79 ,90.4)	2.21	(1.97 ,2.47)
		Pentacel	144	143 (99.3)	(96.2 ,100)	109 (75.7)	(67.9 ,82.4)	1.76	(1.54 ,2.01)
	Other	Hiberix	163	163 (100)	(97.8 ,100)	149 (91.4)	(86 ,95.2)	2.89	(2.58 ,3.24)
		ActHIB	109	109 (100)	(96.7 ,100)	97 (89.0)	(81.6 ,94.2)	2.86	(2.48 ,3.31)
		Pentacel	106	106 (100)	(96.6 ,100)	82 (77.4)	(68.2 ,84.9)	2.06	(1.74 ,2.43)
Anti-T	White	Hiberix	230	230 (100)	(98.4 ,100)	189 (82.2)	(76.6 ,86.9)	1.94	(1.75 ,2.14)
		ActHIB	165	165 (100)	(97.8 ,100)	135 (81.8)	(75.1 ,87.4)	1.99	(1.75 ,2.27)
		Pentacel	144	143 (99.3)	(96.2 ,100)	103 (71.5)	(63.4 ,78.7)	1.50	(1.3 ,1.73)
	Other	Hiberix	163	163 (100)	(97.8 ,100)	146 (89.6)	(83.8 ,93.8)	2.73	(2.42 ,3.07)
		ActHIB	109	109 (100)	(96.7 ,100)	100 (91.7)	(84.9 ,96.2)	3.32	(2.83 ,3.9)
		Pentacel	106	106 (100)	(96.6 ,100)	91 (85.8)	(77.7 ,91.9)	2.06	(1.78 ,2.38)

White = the most frequent race; Other = All other races; POS 3 M 5 = one month post dose 3 at Month 5;
N = number of subjects with available results; n/% = number/percentage of subjects with concentration equal to or above specified value
Source: Adapted from BLA 125347/231 Clinical Study Report

Similar results were observed between the two races in all three groups.

6.11.9 Immunogenicity Conclusion

Lot-to-lot consistency
The primary objective of lot-to-lot consistency of 3 manufacturing lots of Hiberix in terms of anti-PRP GMC ratio was not demonstrated, since the two-sided 95% confidence limits of the GMC ratio between Hiberix Lot A and Hiberix Lot B [(0.641, 0.974)], and the GMC ratio between Hiberix Lot B and Hiberix Lot C [(1.161, 1.765)] were not within the predefined [0.67; 1.5] interval (see Table 9 section 6.11.1).

Due to the hierarchical nature of the statistical testing, no conclusions were to be drawn for the subsequent tests.

Non-inferiority in terms of anti-PRP:

- The statistical criterion for the primary objective of non-inferiority of Hiberix compared to ActHIB in terms of anti-PRP antibody concentrations ≥1.0 µg/mL was not met, as the lower limit of the 95% CI for the difference was -12.28% which is less than -10%, the pre-specified success criterion.
- The statistical criterion for the primary objective of non-inferiority of Hiberix compared to ActHIB in terms of anti-PRP antibody concentrations ≥0.15 µg/mL was met, as the lower limit of the 95% CI for the difference was -1.98% which was greater than -5%, the pre-specified success criterion.

Non-inferiority in terms of the other antigens (D, T, PT, FHA, PRN, and 13 S. pneumonia serotypes and poliovirus 1, 2, and 3):

- The statistical criterion for the primary objective of non-inferiority of Hiberix compared to ActHIB in terms of all other antigens (D, T, PT, FHA, PRN, 13 S.

pneumonia serotypes and poliovirus 1, 2, and 3) were demonstrated as the predefined criteria were met.

- The statistical criteria for the primary objective of the acceptability of the immune response of Pediarix when co-administered with Hiberix following 3 primary vaccine doses in terms of immune response to poliovirus 1, 2, and 3 was satisfied, as the lower limit of the 97.5% CIs on the percentage of subjects with seroprotective titers (>8) of antibodies to each of the poliovirus antigens were greater than 90%.
- A 10% decrease in seroresponse to PT, FHA, and PRN in subjects receiving Pediarix co-administered with Hiberix in comparison with subjects receiving Pediarix co-administered with ActHIB was ruled out, as the p-value on the difference in seroresponse between the pooled Hiberix and ActHIB groups was less than 0.01% for each antigen which was less than 1.25% (pre-specified success criterion).

6.12 Safety Results and Evaluation

6.12.1 Overall incidence of adverse events

The incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall for the primary total vaccinated cohort is presented in Table 18.

Table 18: Incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day post-vaccination period per dose and overall.

		Any	Any	Any	General	General	General	Local	Local	Local
				95% CI			95% CI			95% CI
	Group	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)
Dose 1	Hiberix	2830	2454 (86.7)	(85.4 ,87.9)	2830	2312 (81.7)	(80.2 ,83.1)	2828	1562 (55.2)	(53.4 ,57.1)
	ActHIB	499	451 (90.4)	(87.4 ,92.8)	499	429 (86.0)	(82.6 ,88.9)	498	319 (64.1)	(59.7 ,68.3)
	Pentacel	492	437 (88.8)	(85.7 ,91.5)	492	419 (85.2)	(81.7 ,88.2)	492	313 (63.6)	(59.2 ,67.9)
Dose 2	Hiberix	2669	2305 (86.4)	(85 ,87.6)	2669	2177 (81.6)	(80 ,83)	2668	1432 (53.7)	(51.8 ,55.6)
	ActHIB	481	416 (86.5)	(83.1 ,89.4)	480	393 (81.9)	(78.1 ,85.2)	481	295 (61.3)	(56.8 ,65.7)
	Pentacel	469	399 (85.1)	(81.5 ,88.2)	469	367 (78.3)	(74.2 ,81.9)	469	286 (61.0)	(56.4 ,65.4)
Dose 3	Hiberix	2554	2137 (83.7)	(82.2 ,85.1)	2553	2012 (78.8)	(77.2 ,80.4)	2553	1364 (53.4)	(51.5 ,55.4)
	ActHIB	463	384 (82.9)	(79.2 ,86.3)	463	365 (78.8)	(74.8 ,82.5)	463	261 (56.4)	(51.7 ,60.9)
	Pentacel	443	383 (86.5)	(82.9 ,89.5)	443	348 (78.6)	(74.4 ,82.3)	443	277 (62.5)	(57.8 ,67.1)
Overall/ dose	Hiberix	8053	6896 (85.6)	(84.8 ,86.4)	8052	6501 (80.7)	(79.9 ,81.6)	8049	4358 (54.1)	(53.0 ,55.2)
	ActHIB	1443	1251 (86.7)	(84.8 ,88.4)	1442	1187 (82.3)	(80.2 ,84.3)	1442	875 (60.7)	(58.1 ,63.2)
	Pentacel	1404	1219 (86.8)	(84.9 ,88.5)	1404	1134 (80.8)	(78.6 ,82.8)	1404	876 (62.4)	(59.8 ,64.9)
Overall/ subject	Hiberix	2848	2738 (96.1)	(95.4 ,96.8)	2848	2679 (94.1)	(93.1 ,94.9)	2846	2117 (74.4)	(72.7 ,76.0)
	ActHIB	503	484 (96.2)	(94.2 ,97.7)	503	470 (93.4)	(90.9 ,95.4)	503	404 (80.3)	(76.6 ,83.7)
	Pentacel	496	477 (96.2)	(94.1 ,97.7)	496	459 (92.5)	(89.9 ,94.7)	496	412 (83.1)	(79.5 ,86.3)

For each dose and overall/subject:
N= number of subjects with at least one documented dose; n/%= number/percentage of subjects presenting at least one type of symptom
For overall/dose:
N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom
Source: Adapted from BLA 125347/231 Clinical Study Report

In all three groups (Hiberix, ActHIB, and Pentacel), adverse events (solicited and/or unsolicited, local, and/or general) were reported for 96.1%-96.2% of subjects, and Grade 3 adverse events were reported for 21.1%-30.4% of subjects.
Adverse events with a causal relationship to vaccination were reported for 94.4%, 95.2%, and 94.8% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively.

6.12.2 Solicited local adverse events

Pain was the most frequently reported solicited local adverse event reported in 67.9% of subjects in the Hiberix group, in 72.8% of subjects in the ActHIB group, and in 74.6% of subjects in the Pentacel group.

Pain was also the most frequently reported Grade 3 solicited local adverse event reported in 7.1% of subjects in the Hiberix group, 13.5% of subjects in the ActHIB group, and 12.9% of subjects in the Pentacel group.
Medical advice was sought for less than 0.6% of subjects following any of the symptoms.

6.12.3 Solicited general adverse events

Irritability was the most frequently reported solicited general symptom in all the groups, reported in 87.0% of subjects in the Hiberix group, in 89.3% of subjects in the ActHIB group, and in 87.5% of subjects in the Pentacel group.
Irritability was also the most commonly reported solicited general symptom Graded 3 in intensity: reported for 12.3% of subjects in the Hiberix group, 15.9% of subjects in the ActHIB group, and 10.7% of subjects in the Pentacel group.

Grade 3 fever (>39.5 ^{o}C rectal temperature) was reported for 1.4% of subjects in the Hiberix and ActHIB groups and for 0.4% of subjects in the Pentacel group.

Medical advice was sought in less than 1.9% of subjects following any one symptom.
The majority of solicited general symptoms following vaccination were considered by the investigator to be causally related to vaccination in the three groups.

6.12.4 Unsolicited adverse events

At least one unsolicited adverse event within the 31-day post-vaccination period after each vaccination, classified by MedDRA primary system organ class and preferred term, was reported for 63.4%, 67.3%, and 62.3% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively.

The most commonly reported unsolicited adverse event in the Hiberix group was upper respiratory tract infection (URTI) (19.2%), followed by cough (10.4%) and otitis media (9.7%). In the ActHIB group, the most commonly reported symptom was URTI (19.2%), followed by cough (9.4%) and otitis media (8.7%). The most commonly reported symptoms in the Pentacel group were URTI (18.1%) followed by otitis media (10.6%) and cough (9.6%).

A Grade 3 unsolicited adverse event was reported for 10.7%, 12.5%, and 9.6% of subjects in Hiberix, ActHIB, and Pentacel groups, respectively. The most commonly

reported Grade 3 unsolicited adverse event was otitis media (at least 2.2%), followed by URTI (at least 1.8%) in the Hiberix and ActHIB groups. In the Pentacel group, the most commonly reported Grade 3 unsolicited adverse event was otitis media (2.1%), followed by pyrexia (1.5%).

The investigator assessed causal relationship to vaccination for 6.5%, 7.9%, and 5.8% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively.

6.12.5 Serious adverse events (SEA)

6.12.5.1 Fatal events

No fatal SAEs were reported during the course of the study.

6.12.5.2 Non-fatal events

Non-fatal SAEs were reported for 107 (3.6%) subjects in the Hiberix group, 24 (4.6%) subjects in the ActHIB group, and 21(4.0%) subjects in the Pentacel group during the primary epoch of the study. All except 9 events (five in the Hiberix group, three in the ActHIB group, and one in the Pentacel group) had recovered/resolved by the end of the primary epoch, and an additional three events (two in the Hiberix group and one in the ActHIB group) were recovered/resolved with sequelae.

Five of these SAEs reported for four subjects in the Hiberix group were considered by the investigator as related to the study vaccination. Normal sleep myoclonus was reported for one subject at 5 and 6 months of age, whorecovered with sequelae at the end of the primary epoch. Kawasaki's disease was reported for one subject at 6 months of age, who recovered by the end of the primary epoch. Seizure for one subject at 2 months of age resolved at the end of the primary epoch. Involuntary muscle contraction of leg for one subject at 4 months of age resolved by the end of the primary epoch, and one SAE reported for a subject in the ActHIB group (possible seizure at 1 month of age) resolved by the end of the primary epoch.

6.12.6 Adverse events leading to premature discontinuation of study vaccine and/or study

A total of 18 subjects were withdrawn from the study due to an adverse event (6 due to SAEs and 12 due to non-serious AEs).

Five of the SAEs reported were considered by the investigator as related to the study vaccination. One SAE (seizure disorder) was considered as not related to vaccination.

6.12.7 Other Significant Adverse Events

AEs of specific interest (new onset of chronic diseases (NOCD)) were reported for 3.6% of subjects in the Hiberix group, 4.2% of subjects in the ActHIB group, and 2.9% of subjects in the Pentacel group.

The most commonly reported symptom in the Hiberix group was atopic dermatitis (0.9%) followed by asthma (0.8%). In the ActHIB group, the most commonly reported symptom was asthma (1.2%) followed by eczema (1.0%). The most commonly reported symptoms in the Pentacel group were food allergy and asthma (0.8%) followed by eczema (0.6%).

6.12.8 Concomitant medications /vaccinations

The intake of any concomitant medication was reported for at least 58.7% of subjects in all three groups (Hiberix, ActHIB, and Pentacel) during the 4-day (Day 0-3) post-vaccination period.

At least 48.7% of subjects received any antipyretic and at least 15.6% of subjects received a prophylactic antipyretic in all three groups (Hiberix, ActHIB, and Pentacel).

The intake of any antibiotic was reported for at least 8.4% of subjects in all three groups. None of them were prophylactic in nature.

6.12.9 Safety Subgroup Analysis

6.12.9.1 Overall incidence of adverse events by Sex and Race

The incidence and nature of symptoms (solicited and unsolicited) reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall for the primary TVC by sex and race are presented in Tables 19 and 20.

Table 19: Overall incidence of adverse events (Any, General, and Local symptoms) reported during the 4-day (Days 0-3) post-vaccination by sex

			Any	Any	Any	Genera	General	General	Local	Local	Local
					95% CI			95% CI			95% CI
	Sub-group	Group	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)
Overall/ dose	Male	*Hiberix*	4192	3614 (86.2)	(85.1 ,87.2)	4192	3404 (81.2)	(80.0 ,82.4)	4189	2279 (54.4)	(52.9 ,55.9)
		ActHIB	685	585 (85.4)	(82.5 ,88.0)	684	558 (81.6)	(78.5 ,84.4)	685	407 (59.4)	(55.6 ,63.1)
		Pentace	696	613 (88.1)	(85.4 ,90.4)	696	568 (81.6)	(78.5 ,84.4)	696	451 (64.8)	(61.1 ,68.3)
	Female	*Hiberix*	3861	3282 (85.0)	(83.8 ,86.1)	3860	3097 (80.2)	(78.9 ,81.5)	3860	2079 (53.9)	(52.3 ,55.4)
		ActHIB	758	666 (87.9)	(85.3 ,90.1)	758	629 (83.0)	(80.1 ,85.6)	757	468 (61.8)	(58.3 ,65.3)
		Pentace	708	606 (85.6)	(82.8 ,88.1)	708	566 (79.9)	(76.8 ,82.8)	708	425 (60.0)	(56.3 ,63.7)
Overall/ subject	Male	*Hiberix*	1477	1424 (96.4)	(95.3 ,97.3)	1477	1399 (94.7)	(93.5 ,95.8)	1476	1099 (74.5)	(72.2 ,76.7)
		ActHIB	238	228 (95.8)	(92.4 ,98.0)	238	219 (92.0)	(87.8 ,95.1)	238	192 (80.7)	(75.1 ,85.5)
		Pentace	246	239 (97.2)	(94.2 ,98.8)	246	229 (93.1)	(89.2 ,95.9)	246	200 (81.3)	(75.9 ,86.0)
	Female	*Hiberix*	1371	1314 (95.8)	(94.6 ,96.8)	1371	1280 (93.4)	(91.9 ,94.6)	1370	1018 (74.3)	(71.9 ,76.6)
		ActHIB	265	256 (96.6)	(93.7 ,98.4)	265	251 (94.7)	(91.3 ,97.1)	265	212 (80.0)	(74.7 ,84.6)
		Pentace	250	238 (95.2)	(91.8 ,97.5)	250	230 (92.0)	(87.9 ,95.0)	250	212 (84.8)	(79.7 ,89.0)

For overall/dose:
N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom
For overall/subject:
N= number of subjects with at least one documented dose; n/%= number/percentage of subjects presenting at least one type of symptom
Source: Adapted from BLA 125347/231 Clinical Study Report

Table 20: Overall incidence of adverse events reported during the 4-day (Days 0-3) post-vaccination by race

			Any	Any	Any	Genera	General	General	Local	Local	Local
					95% CI			95% CI			95% CI
	Sub-group	Group	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)
Overall/ dose	White	*Hiberix*	4923	4272 (86.8)	(85.8 ,87.7)	4922	4044 (82.2)	(81.1 ,83.2)	4919	2703 (55.0)	(53.5 ,56.3)
		ActHIB	913	817 (89.5)	(87.3 ,91.4)	912	781 (85.6)	(83.2 ,87.8)	913	573 (62.8)	(59.5 ,65.9)
		Pentace	863	774 (89.7)	(87.5 ,91.6)	863	724 (83.9)	(81.3 ,86.3)	863	557 (64.5)	(61.2 ,67.7)
	Other	*Hiberix*	3130	2624 (83.8)	(82.5 ,85.1)	3130	2457 (78.5)	(77 ,79.9)	3130	1655 (52.9)	(51.1 ,54.6)
		ActHIB	530	434 (81.9)	(78.3 ,85.1)	530	406 (76.6)	(72.8 ,80.1)	529	302 (57.1)	(52.7 ,61.4)
		Pentace	541	445 (82.3)	(78.8 ,85.4)	541	410 (75.8)	(71.9 ,79.3)	541	319 (59.0)	(54.7 ,63.1)
Overall/ subject	White	*Hiberix*	1713	1652 (96.4)	(95.4 ,97.3)	1713	1622 (94.7)	(93.5 ,95.7)	1711	1293 (75.6)	(73.5 ,77.6)
		ActHIB	316	309 (97.8)	(95.5 ,99.1)	316	301 (95.3)	(92.3 ,97.3)	316	264 (83.5)	(79.0 ,87.5)
		Pentace	300	291 (97)	(94.4 ,98.6)	300	286 (95.3)	(92.3 ,97.4)	300	258 (86.0)	(81.6 ,89.7)
	Other	*Hiberix*	1135	1086 (95.7)	(94.3 ,96.8)	1135	1057 (93.1)	(91.5 ,94.5)	1135	824 (72.6)	(69.9 ,75.2)
		ActHIB	187	175 (93.6)	(89.1 ,96.6)	187	169 (90.4)	(85.2 ,94.2)	187	140 (74.9)	(68.0 ,80.9)
		Pentace	196	186 (94.9)	(90.8 ,97.5)	196	173 (88.3)	(82.9 ,92.4)	196	154 (78.6)	(72.2 ,84.1)

For overall/dose:
N= number of documented doses; n/%= number/percentage of doses followed by at least one type of symptom
For overall/subject:
N= number of subjects with at least one documented dose; n/%= number/percentage of subjects presenting at least one type of symptom
Source: Adapted from BLA 125347/231 Clinical Study Report

The incidence and nature of symptoms (solicited and unsolicited), Grade 3 symptoms, and symptoms with a causal relationship to vaccination reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall were similar between male and female subjects, as well as between the two races.

6.12.9.2 Solicited Local Adverse Events by Sex and Race

The incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period for the TVC by gender and race is presented in Tables 21 and 22, respectively.

Similar results were observed between all the subgroups considered.

Table 21: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period by gender

		Mal	Male	Male	Male	Male	Male	Male	Male	Male	Female	Female	Female	Female	Female	Female	Female	Female	Female
		Hib	Hib	Hib	Act	Act	Act	Pent	Pent	Pent	Hib	Hib	Hib	Act	Act	Act	Pent	Pent	Pent
				95% CI			95 % CI			95 % CI			95 % CI			95 % CI			95 % CI
Symptom	Type	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)
Pain	All	1476	1008 (68.3)	(65.9 ,70.7)	238	176 (73.9)	(67.9 ,79.4)	246	180 (73.2)	(67.2 ,78.6)	1370	924 (67.4)	(64.9 ,69.9)	265	190 (71.7)	(65.9 ,77)	250	190 (76)	(70.2 ,81.2)
	Grade 2 or 3	1476	413 (28.0)	(25.7 ,30.3)	238	101 (42.4)	(36.1 ,49)	246	87 (35.4)	(29.4 ,41.7)	1370	412 (30.1)	(27.7 ,32.6)	265	103 (38.9)	(33 ,45)	250	88 (35.2)	(29.3 ,41.5)
	Grade 3	1476	103 (7.0)	(5.7 ,8.4)	238	32 (13.4)	(9.4 ,18.4)	246	35 (14.2)	(10.1 ,19.2)	1370	100 (7.3)	(6.0 ,8.8)	265	36 (13.6)	(9.7 ,18.3)	250	29 (11.6)	(7.9 ,16.2)
	Med	1476	6 (0.4)	(0.1 ,0.9)	238	1 (0.4)	(0 ,2.3)	246	1 (0.4)	(0 ,2.2)	1370	2 (0.1)	(0.0 ,0.5)	265	0 (0)	(0 ,1.4)	250	1 (0.4)	(0.0 ,2.2)
Redness (mm)	All	1476	596 (40.4)	(37.9 ,42.9)	238	99 (41.6)	(35.3 ,48.1)	246	134 (54.5)	(48 ,60.8)	1370	569 (41.5)	(38.9 ,44.2)	265	134 (50.6)	(44.4 ,56.7)	250	123	(42.8 ,55.6)
	[5.1 - .	1476	129 (8.7)	(7.3 ,10.3)	238	29 (12.2)	(8.3 ,17)	246	48 (19.5)	(14.8 ,25)	1370	141 (10.3)	(8.7 ,12)	265	41 (15.5)	(11.3 ,20.4)	250	56 (22.4)	(17.4 ,28.1)
	>20.0	1476	25 (1.7)	(1.1 ,2.5)	238	6 (2.5)	(0.9 ,5.4)	246	16 (6.5)	(3.8 ,10.3)	1370	31 (2.3)	(1.5 ,3.2)	265	11 (4.2)	(2.1 ,7.3)	250	10 (4)	(1.9 ,7.2)
	Med	1476	1 (0.1)	(0 ,0.4)	238	0 (0)	(0 ,1.5)	246	0 (0)	(0 ,1.5)	1370	0 (0)	(0.0 ,0.3)	265	0 (0)	(0 ,1.4)	250	1 (0.4)	(0.0 ,2.2)
Swelling (mm)	All	1476	438 (29.7)	(27.4 ,32.1)	238	81 (34)	(28 ,40.4)	246	97 (39.4)	(33.3 ,45.8)	1370	396 (28.9)	(26.5 ,31.4)	265	93 (35.1)	(29.4 ,41.2)	250	98 (39.2)	(33.1 ,45.6)
	[5.1 - .	1476	108 (7.3)	(6 ,8.8)	238	30 (12.6)	(8.7 ,17.5)	246	33 (13.4)	(9.4 ,18.3)	1370	114 (8.3)	(6.9 ,9.9)	265	39 (14.7)	(10.7 ,19.6)	250	41 (16.4)	(12 ,21.6)
	>20.0	1476	31 (2.1)	(1.4 ,3)	238	13 (5.5)	(2.9 ,9.2)	246	16 (6.5)	(3.8 ,10.3)	1370	39 (2.8)	(2.0 ,3.9)	265	18 (6.8)	(4.1 ,10.5)	250	14 (5.6)	(3.1 ,9.2)
	Med	1476	1 (0.1)	(0 ,0.4)	238	1 (0.4)	(0 ,2.3)	246	0 (0)	(0 ,1.5)	1370	1 (0.1)	(0.0 ,0.4)	265	2 (0.8)	(0.1 ,2.7)	250	1 (0.4)	(0.0 ,2.2)

N= number of subjects with at least one documented dose
n/%= number/percentage of subjects reporting the symptom at least once
Hib=Hiberix group
Act=ActHIB group
Pent= Pentacel group
Source: Adapted from BLA 125347/231 Clinical Study Report

Table 22: Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period by race

		White	White	White	White	White	White	White	White	White	Other	Other	Other	Other	Other	Other	Other	Other	Other
		Hib	Hib	Hib	Act	Act	Act	Pent	Pent	Pent	Hib	Hib	Hib	Act	Act	Act	Pent	Pent	Pent
				95% CI			95 % CI			95 % CI			95 % CI			95 % CI			95 % CI
Symptom	Type	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)	N	n (%)	(LL ,UL)
Pain	All	1711	1176	(66.5 ,70.9)	316	238 (75.3)	(70.2 ,80)	300	229 (76.3)	(71.1 ,81)	1135	756 (66.6)	(63.8 ,69.3)	187	128	(61.3 ,75)	196	141 (71.9)	(65.1 ,78.1)
	Grade 2 or 3	1711	499 (29.2)	(27 ,31.4)	316	129 (40.8)	(35.4 ,46.5)	300	105 (35)	(29.6 ,40.7)	1135	326 (28.7)	(26.1 ,31.5)	187	75 (40.1)	(33 ,47.5)	196	70 (35.7)	(29 ,42.9)
	Grade 3	1711	116 (6.8)	(5.6 ,8.1)	316	34 (10.8)	(7.6 ,14.7)	300	42 (14)	(10.3 ,18.4)	1135	87 (7.7)	(6.2 ,9.4)	187	34 (18.2)	(12.9 ,24.5)	196	22 (11.2)	(7.2 ,16.5)
	Med	1711	3 (0.2)	(0 ,0.5)	316	0 (0)	(0 ,1.2)	300	1 (0.3)	(0 ,1.8)	1135	5 (0.4)	(0.1 ,1)	187	1 (0.5)	(0 ,2.9)	196	1 (0.5)	(0 ,2.8)
Redness (mm)	All	1711	757 (44.2)	(41.9 ,46.6)	316	156 (49.4)	(43.7 ,55)	300	174 (58)	(52.2 ,63.6)	1135	408 (35.9)	(33.2 ,38.8)	187	77 (41.2)	(34 ,48.6)	196	83 (42.3)	(35.3 ,49.6)
	[5.1 - .	1711	179 (10.5)	(9.1 ,12)	316	44 (13.9)	(10.3 ,18.2)	300	76 (25.3)	(20.5 ,30.7)	1135	91 (8)	(6.5 ,9.8)	187	26 (13.9)	(9.3 ,19.7)	196	28 (14.3)	(9.7 ,20)
	>20.0	1711	32 (1.9)	(1.3 ,2.6)	316	10 (3.2)	(1.5 ,5.7)	300	18 (6)	(3.6 ,9.3)	1135	24 (2.1)	(1.4 ,3.1)	187	7 (3.7)	(1.5 ,7.6)	196	8 (4.1)	(1.8 ,7.9)
	Med	1711	1 (0.1)	(0 ,0.3)	316	0 (0)	(0 ,1.2)	300	1 (0.3)	(0 ,1.8)	1135	0 (0)	(0 ,0.3)	187	0 (0)	(0 ,2)	196	0 (0)	(0 ,1.9)
Swelling (mm)	All	1711	503 (29.4)	(27.2 ,31.6)	316	112 (35.4)	(30.2 ,41)	300	117 (39)	(33.4 ,44.8)	1135	331 (29.2)	(26.5 ,31.9)	187	62 (33.2)	(26.5 ,40.4)	196	78 (39.8)	(32.9 ,47)
	[5.1 - .	1711	145 (8.5)	(7.2 ,9.9)	316	42 (13.3)	(9.7 ,17.5)	300	49 (16.3)	(12.3 ,21)	1135	77 (6.8)	(5.4 ,8.4)	187	27 (14.4)	(9.7 ,20.3)	196	25 (12.8)	(8.4 ,18.3)
	>20.0	1711	43 (2.5)	(1.8 ,3.4)	316	18 (5.7)	(3.4 ,8.9)	300	20 (6.7)	(4.1 ,10.1)	1135	27 (2.4)	(1.6 ,3.4)	187	13 (7)	(3.8 ,11.6)	196	10 (5.1)	(2.5 ,9.2)
	Med	1711	0 (0)	(0 ,0.2)	316	3 (0.9)	(0.2 ,2.7)	300	1 (0.3)	(0 ,1.8)	1135	2 (0.2)	(0 ,0.6)	187	0 (0)	(0 ,2)	196	0 (0)	(0 ,1.9)

White = The most frequent race;
Other = All other races
N= number of subjects with at least one documented dose;
n/%= number/percentage of subjects reporting the symptom at least once
Hib=Hiberix group
Act=ActHIB group
Pent= Pentacel group
Source: Adapted from BLA 125347/231 Clinical Study Report

6.12.9.3 Solicited General Adverse Events by Sex and Race

The incidence of solicited general symptoms reported during the 4-day (Days 0-3) post-vaccination period following each dose and overall for the TVC were similar between males and females, as well as between whites (the most frequent race) and all other races.

6.12.9.4 Unsolicited Adverse Events by Sex and Race

The percentage of subjects for whom the occurrence of unsolicited symptoms, Grade 3 unsolicited symptoms, and unsolicited symptoms with causal relationship to vaccination wasreported within the 31-day (Days 0-30) post-vaccination period for TVC were similar between males and females, as well as between whites (the most frequent race) and all other races.

6.12.10 Safety Conclusion

Pain was the most frequently reported solicited local adverse event (67.9%-74.6% of subjects) and Grade 3 solicited local adverse event (7.1%-13.5% of subjects) in all three groups.

Irritability was the most frequently reported solicited general adverse event (87.0%-89.3% of subjects) and Grade 3 solicited general adverse event (10.7%-15.9% of subjects) in all three groups. Grade 3 fever (>39.5 °C rectal temperature) was reported for 0.4%-1.4% of subjects.

At least one unsolicited adverse event within the 31-day post-vaccination period after each vaccination, classified by MedDRA primary system organ class and preferred term, was reported for 63.4%, 67.3%, and 62.3% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively. The investigator assessed causal relationship to vaccination for 6.5%, 7.9%, and 5.8% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively.

The most commonly reported unsolicited adverse event in the Hiberix group was upper respiratory tract infection (URTI) (19.2%) followed by cough (10.4%) and otitis media (9.7%). In the ActHIB group, the most commonly reported symptom was URTI (19.2%) followed by cough (9.4%) and otitis media (8.7%). The most commonly reported symptoms in the Pentacel group were URTI (18.1%) followed by otitis media (10.6%) and cough (9.6%).

A Grade 3 unsolicited adverse event was reported for 10.7%, 12.5%, and 9.6% of subjects in Hiberix, ActHIB, and Pentacel groups, respectively. The most commonly reported Grade 3 unsolicited adverse event was otitis media (at least 2.2%) followed by URTI (at least 1.8%) in the Hiberix and ActHIB groups. In the Pentacel group, the most commonly reported Grade 3 unsolicited adverse event was otitis media (2.1%) followed by pyrexia (1.5%).

AEs of specific interest (new onset of chronic diseases (NOCD)) were reported for 3.6% of subjects in the Hiberix group, 4.2% of subjects in the ActHIB group, and 2.9% of

subjects in the Pentacel group. The most commonly reported symptom in the Hiberix group was atopic dermatitis (0.9%) followed by asthma (0.8%). In the ActHIB group, the most commonly reported symptom was asthma (1.2%) followed by eczema (1.0%). The most commonly reported symptoms in the Pentacel group were food allergy and asthma (0.8%) followed by eczema (0.6%).

SAEs were reported for 107 (3.6%) subjects in the Hiberix group, 24 (4.6%) subjects in the ActHIB group, and 21(4.0%) subjects in the Pentacel group. All SAEs, except 12 (seven in the Hiberix group, three in the ActHIB group, and two in the Pentacel group), had resolved by the end of the study (primary epoch), and five additional events (four in the Hiberix group and one in the ActHIB group) were resolved with sequelae.

Five of these SAEs reported for four subjects in the Hiberix group were considered by the investigator to be related to the study vaccination. Normal sleep myoclonus reported for one subject at 5 and 6 months of age resolved with sequelae at the end of the primary epoch. Kawasaki was reported for one subject at 6 months of age and resolved by the end of the primary epoch. Seizure for one subject at 2 months of age resolved by the end of the primary epoch; involuntary muscle contraction of leg for one subject at 4 months of age resolved by the end of the primary epoch; and one SAE reported for a subject in the ActHIB group (possible seizure at 1 month of age) resolved by the end of the primary epoch.

No fatal SAEs were reported during the study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The first primary objective regarding the lot-to-lot consistency of anti-PRP GMCs was not met according to the pre-specified statistical criteria, since the two-sided 95% CI of the GMC ratio between Hiberix Lot A and Hiberix Lot B was (0.641,0.974), and between Hiberix Lot B and Hiberix Lot C was (1.61,1.765) and both were not within the pre-defined [0.67, 1.5] interval. Thus, for subsequent statistical tests in the hierarchy, no conclusions were to be drawn.

The pre-specified statistical criterion for the primary objective of non-inferiority of Hiberix (pooled lots) compared to ActHIB in terms of anti-PRP antibody concentrations ≥1.0 μg/mL was not satisfied, as the lower limit of the 95% CI for the difference was -12.28%, which was less than the criterion of -10%.

The statistical criterion for the primary objective of non-inferiority of Hiberix (pooled lots) compared to ActHIB in terms of anti-PRP antibody concentrations ≥0.15 μg/mL was satisfied, as the lower limit of the 95% CI for the difference was - 1.98%, which was greater than -5%.

The statistical criterion for the primary objective of non-inferiority of Pediarix co-administered with Hiberix (pooled lots) compared to Pediarix co-administered with

ActHIB, in terms of anti-diphtheria and anti-tetanus antibody concentrations ≥0.1 IU/mL, was satisfied as the lower limit of the 97.5% CI for the difference was -1.26%, which was greater than the non-inferiority margin of -10%.

The statistical criteria for the primary objective of non-inferiority of Pediarix co-administered with Hiberix (pooled lots) compared to Pediarix co-administered with ActHIB in terms of anti-pertussis GMC ratios were satisfied, as the lower limits of the 97.5% CIs for the GMC ratios for antibodies to PT, FHA, and PRN were 0.918, 0.983, and 1.030, respectively, which were greater than the margin 0.67.

The statistical criteria for the primary objective of non-inferiority of Pediarix co-administered with Hiberix (pooled lots) compared to Pediarix co-administered with ActHIB, in terms of anti-poliovirus types 1, 2, and 3 antibody titers ≥8, were satisfied. That is, the lower limit of the 97.5% CI for the difference were -3.38%, -2.84%, and -3.87% for anti-poliovirus 1, 2, and 3, respectively, which were greater than the margin -5%.

The statistical criteria for the primary objective of the acceptability of the immune response of Pediarix when co-administered with Hiberix following 3 primary vaccine doses, in terms of immune response to poliovirus 1, 2, and 3, were satisfied. The lower limit of the 97.5% CIs on the percentage of subjects with seroprotective titers (8) of antibodies to each of the poliovirus antigens were 96.8%, 95.5%, and 96.3%, respectively. These lower limits were all greater than the pre-specified criterion of 90%.

The statistical criteria for the primary objective of non-inferiority of Prevnar13 co-administered with Hiberix (pooled lots) compared to Prevnar13 co-administered with ActHIB in terms of S. pneumonia GMCs was satisfied. The lower limit of the 97.5% CIs on the GMC ratio for each serotype was at least 0.8 or more, which was greater than the 0.5 pre-specified non-inferiority margin.

A 10% decrease in seroresponse to PT, FHA, and PRN in subjects receiving Pediarix co-administered with Hiberix, in comparison with subjects receiving Pediarix co-administered with ActHIB, was ruled out. That is,the p-value on the difference in seroresponse between the pooled Hiberix and ActHIB groups was less than 0.0125 for each antigen.

At least one unsolicited AE was observed in 63.4%, 67.3%, and 62.3% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively, during the 31 day (Day 0-30) post-vaccination period. Of these, 10.7%, 12.5%, and 9.6% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively, reported Grade 3 unsolicited symptoms. Unsolicited AEs that were assessed by the investigator to be causally related to vaccination were reported in 6.5%, 7.9%, and 5.8% of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively.

AEs of specific interest were observed in 108 (3.6%), 22 (4.2%), and 15 (2.9%) of subjects in the Hiberix, ActHIB, and Pentacel groups, respectively, from Day 0 of primary vaccination to the end of ESFU.

SAEs were reported for 107 (3.6%) subjects in the Hiberix group, 24 (4.6%) subjects in the ActHIB group, and 21 (4.0%) subjects in the Pentacel group. Of these, five subjects (four in the Hiberix group and one in the ActHIB group) had SAEs that were considered by the investigator as related to the study vaccination (normal sleep myoclonus, Kawasaki, seizure, involuntary muscle contraction in the Hiberix group and possible seizure in the ActHIB group). These SAEs resolved at the end of the primary vaccination epoch. No fatal SAEs were reported.

10.2 Conclusions and Recommendations

While the clinical study results did not meet the predefined statistical criteria for lot consistency and non-inferiority of Hiberix to ActHIB, the overall data generated in this study indicate that the consistency of the immune response in terms of GMCs were within observed variability of two US-licensed Hib vaccines, and non-inferiority criteria were met versus *Pentacel*, a US-licensed Hib vaccine. Furthermore, non-inferiority to *ActHIB* was observed at the 0.15 mcg/mL threshold. No immune interferences with co-administered antigens were observed, and the safety profile appears accepTable and similar to two US-licensed Hib vaccines.

Since some but not all pre-specified statistical criteria were met, I defer to the medical reviewers regarding whether the totality of the data suggest that *Hiberix* is an effective Hib conjugate vaccine for US infants and toddlers when administered as a three primary-dose schedule at 2, 4, and 6 months.