DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DVRPA

Date: July 8, 2009

From: Karen M. Farizo, M.D.
Medical Officer, Clinical Review Branch 1

Through: Douglas Pratt, M.D.
Chief, Clinical Review Branch 1

Subject: Clinical Review of Biologics License Application for GlaxoSmithKline Biologicals' Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (proposed proprietary name: Hiberix)

To: BLA STN# 125347

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA #: 125347

1.1.2 Related Master File and INDs:

- Master File --b(4)--: Hiberix
- IND ----------b(4)----------
- IND ----------b(4)----------

1.1.3 Reviewer Name, Division, and Mail Code

Karen Farizo, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA: March 17, 2009

1.2 Product

1.2.1 Proper Name: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

1.2.2 Proposed Proprietary Name: Hiberix

1.2.3 Product Formulation:

Hiberix is a lyophilized vaccine of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b, covalently bound to tetanus toxoid. Hiberix is reconstituted at the time of use with the supplied saline diluent. Each 0.5 ml single dose of Hiberix is formulated to contain 10 mcg of purified PRP covalently bound to --b(4)--mcg of tetanus toxoid. Each dose of Hiberix also contains 12.6 mg of lactose (excipient), which is used as a stabilizer during manufacturing. The diluent used to reconstitute the lyophilized vaccine is 0.9% sodium chloride (--b(4)--mg sodium chloride per dose).

1.3 Applicant: GlaxoSmithKline Biologicals

1.4 Pharmacologic Class: Vaccine

1.5 Proposed Indication:

Active immunization as a booster dose for the prevention of invasive disease caused by *H. influenzae* type b. The proposed age range for use is 15 months through 4 years of age (prior to fifth birthday).

1.6 Dosage Forms and Route of Administration:

Hiberix is a solution for intramuscular injection (0.5 ml dose) supplied as vials of lyophilized vaccine to be reconstituted with the accompanying saline diluent in prefilled syringes.

2 Table of Contents

3 Executive Summary

Background

With this BLA, GSK is seeking approval of their Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (proposed proprietary name, Hiberix) for active immunization as a booster dose for the prevention of invasive disease caused by *Haemophilus influenzae* type b. The proposed age range for use of Hiberix is 15 months through 4 years of age (prior to the fifth birthday).

Hiberix is a non-infectious vaccine that contains as active ingredient capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP) prepared from a strain of *H. influenzae* type b, covalently bound to tetanus toxoid. After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. The vaccine is reconstituted prior to intramuscular injection, with a liquid saline diluent. Each 0.5 mL dose of Hiberix contains 10 mcg of purified PRP conjugated to approximately 25 mcg of tetanus toxoid, and 12.6 mg of lactose.

Hiberix was first licensed in Germany in 1996 and is now registered in 98 countries as a stand-alone vaccine and in more than 100 countries when combined with other vaccines. Generally, Hiberix has been used as a primary series of three doses administered in the first 6 months of life and a booster dose in the second year of life. From launch in 1996 through November 30, 2008, approximately --b(4)--million doses of Hiberix were distributed worldwide.

Currently, there are two other manufacturers of licensed Haemophilus b Conjugate Vaccines in the U.S. Merck & Co., Inc. produces PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine]. Sanofi Pasteur produces ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], TriHIBit [ActHIB reconstituted with Tripedia (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)], and Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine]. All of these vaccines are approved for primary and booster immunization against invasive disease due to *H. influenzae* type b, with the exception of TriHIBit, which is approved for booster immunization only.

In the U.S., a nationwide shortage of Haemophilus b Conjugate Vaccine began in December 2007 due to a voluntary recall of certain lots of PedvaxHIB and COMVAX and suspended production of these two vaccines.[1] The shortage resulted in a recommendation by the Centers for Disease Control and Prevention (CDC) to defer the Haemophilus b Conjugate Vaccine booster (routinely administered in the second year of life) for children who are not at high risk of infection with *H. influenzae* type b, temporarily, until restoration of the vaccine supply.[1] The recommendation for deferral of booster vaccination was in effect from December 18, 2007 through June 25, 2009.[1,2] On June 26, 2009, coinciding with an increase in the number of doses of ActHIB and Pentacel available in the U.S., the CDC recommended reinstatement of the booster dose for children 12-15 months of age who have completed a primary series with Haemophilus b Conjugate Vaccine.[2] In their June 26, 2009 recommendation, the CDC indicated that older children for whom the booster dose was deferred should receive their booster dose at the next routinely scheduled visit or medical encounter.[2] As of June 26, 2009, although supply is sufficient to reinstate the booster dose and begin catch-up vaccination, supply is not yet ample enough to support a mass notification process to contact all children with deferred booster doses.[2]

Application of Accelerated Approval Regulations

Although not studied under U.S. IND, Hiberix has been evaluated in clinical studies that supported its first licensure in Germany in 1996 and subsequent licensure in other countries. Prior to submission of this BLA, CBER reviewed clinical studies data on Hiberix provided by GSK. CBER determined that the available data on the effectiveness of Hiberix for primary and/or booster immunization were not sufficient to support traditional approval. Limitations of the studies included lack of racial/ethnic diversity of study populations, lack of concomitant administration data with certain other vaccines that are used on the same schedule in the U.S., limited data comparing Hiberix to a U.S. licensed vaccine, ----------b(4)----------, and limited data on booster vaccination in subjects previously primed with a U.S. licensed vaccine on a U.S. schedule. However, CBER viewed the safety and effectiveness data from available clinical studies, combined with the post-marketing experience with Hiberix, as reasonably predictive of clinical benefit of booster immunization with Hiberix. In view of the shortage of Haemophilus b Conjugate Vaccine, with concurrence from its Office of General Counsel, CBER agreed to consider a BLA for Hiberix for booster immunization under the accelerated approval regulations, 21 CFR Part 601, Subpart E.

Accelerated approval may be granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. CBER stipulated that accelerated approval of Hiberix for booster immunization could only be granted in the context of a shortage in the supply of the existing, licensed Haemophilus b Conjugate Vaccines. CBER also stipulated that accelerated approval of Hiberix for booster immunization would be subject to the requirement that GSK conduct an adequate and well-controlled safety and immunogenicity study to verify the clinical benefit of booster immunization with Hiberix.

General Description of Clinical Studies

This BLA for licensure of Hiberix for booster immunization under the accelerated approval regulations contains reports of seven clinical studies in which Hiberix was used for booster immunization and two supportive primary immunization studies. None of the Hiberix booster immunization studies included a comparator group that received a booster dose with a U.S. licensed Haemophilus b Conjugate Vaccine. These seven clinical studies provide safety data on a total of 1,008 children who received Hiberix as a booster dose and 1,396 infants who received Hiberix for primary immunization. The clinical studies were conducted in Europe, Latin America, and Canada. For studies in which information on race/ethnicity was provided, nearly all subjects were Caucasian. Approximately half of subjects were male. Across the seven booster immunization studies, the mean age at receipt of Hiberix ranged from 15.9 to 18.7 months. Of the 1,008 subjects who received Hiberix as a booster dose, 172 (17.1%) were 11 to 14 months of age, 642 (63.7%) were 15 to 18 months of age, and 194 (19.2%) were 19 to 25 months of age at the time of vaccination. In the booster immunization studies, Hiberix was administered concomitantly with one of the following vaccines manufactured by GSK: Infanrix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, DTaP]; DTaP combined with Hepatitis B Vaccine (DTaP-HBV, not licensed in the U.S.); Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, DTaP-HBV-IPV]; or Kinrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine, DTaP-IPV). The formulations of Infanrix, Pediarix, and Kinrix used in the booster studies of Hiberix were the same as the U.S. licensed vaccines except that in most instances, they also contained 2-phenoxyethanol as preservative. In the booster immunization studies, Pediarix and Kinrix were used in schedules not approved in the U.S. Among 1,008 subjects in the booster immunization studies who were evaluated for safety, 530 had been primed with Hiberix, 235 with ActHIB, 217 with HibTITER

(PRP-diphtheria CRM_{197} protein conjugate; no longer licensed in the U.S.) and 26 with PedvaxHIB.

Clinical Studies Effectiveness Data

The evaluation of effectiveness of Hiberix for booster immunization was based on immunogenicity data, using widely accepted serological correlates of protection against invasive disease due to *H. influenzae* type b. Based on an efficacy study with an unconjugated Haemophilus b polysaccharide vaccine[3] and data from passive antibody studies,[4] an anti-PRP level of 0.15 mcg/ml has been accepted as a minimum protective level. An anti-PRP level of 1.0 mcg/ml has been accepted as predicting long-term (at least one year) protection.[5,6]

Across six booster immunization studies that evaluated the immunogenicity of Hiberix, the According to Protocol (ATP) cohorts for immunogenicity included a total of 415 subjects (range per study: 42 to 108 subjects) who received Hiberix. Of these subjects, 30 subjects were 11 to 14 months of age, 316 subjects were 15 to 18 months of age, and 69 subjects were 19 to 25 months of age. Approximately 75% (N=306) of subjects had been primed with Hiberix; 89 subjects from three different studies had been primed with ActHIB; 11 subjects had been primed with HibTITER; and 9 subjects had been primed with PedvaxHIB. Anti-PRP antibodies were measured by either a ----------b(4)----------, depending on the study. The anti-PRP assays used in the clinical studies have been reviewed by CBER and are considered acceptable for the evaluation of the effectiveness of Hiberix for booster immunization. Across the six studies, the proportion of subjects with a pre-booster vaccination anti-PRP level $\geq$0.15 mcg/ml ranged from 71.4% to 97.6%. All subjects had an anti-PRP level $\geq$0.15 mcg/ml following a booster dose of Hiberix. The proportion of subjects with a pre-booster vaccination anti-PRP level $\geq$1.0 mcg/ml ranged from 12.7% to 65.9%. All but three subjects had an anti-PRP level $\geq$1.0 mcg/ml following a booster dose of Hiberix. Across the six studies, pre-booster vaccination anti-PRP GMCs ranged from 0.25 mcg/ml to 1.9 mcg/ml. Following a booster dose with Hiberix, anti-PRP GMCs ranged from 47.8 mcg/ml to 137 mcg/ml, corresponding to a pre- to post-booster increase in anti-PRP GMCs ranging from 45-fold to 188-fold.

In one of the supportive primary immunization studies, one month after three priming doses with Hiberix, all 202 subjects had an anti-PRP level $\geq$0.15 mcg/ml and 96% had an anti-PRP level $\geq$1.0 mcg/ml; the post-vaccination anti-PRP GMC was 7.2 mcg/ml.

Clinical Studies Safety Data

In the Hiberix studies included in the BLA, specific solicited adverse events were monitored during Days 0-4 post-vaccination. Serious and non-serious unsolicited adverse events were monitored during Days 0-30 post-vaccination. Across the seven booster immunization studies, there were no drop outs due to an adverse event among 1,008 subjects who received Hiberix.

In the seven booster immunization studies, no deaths were reported following receipt of Hiberix. Among 1,396 infants who received Hiberix and Pediarix in a supportive primary immunization study, there were two deaths. One infant died of Sudden Infant Death Syndrome (SIDS) 18 days post-vaccination. One infant died 36 days post-vaccination, presumably due to a convulsive disorder of undetermined etiology that had initially manifested four days post-vaccination. Among 4,625 infants who received another Haemophilus b Conjugate Vaccine in the primary immunization studies, there were two deaths, including one case of SIDS. Another infant with an unspecified immune deficiency identified at autopsy, died of respiratory arrest following seizures, hypoxic cerebral damage, and sepsis.

Across the seven booster immunization studies, two subjects reported a serious adverse event occurring within 31 days following receipt of Hiberix. One subject had impaired consciousness due to accidental drug ingestion. One subject developed pneumonia 12 days post-vaccination. In the largest of the two supportive primary immunization studies, subjects received three doses of Pediarix administered concomitantly with either Hiberix (N=1177), ActHIB (N=1173), HibTITER (N=1174), or PedvaxHIB (two doses) (N=1171); a fifth group received Infanrix, oral poliovirus vaccine (OPV; no longer licensed in the U.S.), and ActHIB (N=776). The percentage of subjects reporting a serious adverse event within 31 days after any dose was 1.9% following Pediarix + Hiberix, 1.5% following Pediarix + ActHIB, 1.2% following Pediarix + HibTITER, 1.4% following Pediarix + PedvaxHIB, and 1.8% following Infanrix + ActHIB + OPV. The nature and timing of the serious adverse events raised no particular safety concerns about Hiberix.

In the largest of the booster immunization studies, solicited injection site reactions (pain, redness, and swelling) occurred commonly (15% to 25% of subjects) following Hiberix. Pain that prevented usual activities, redness >20 mm in diameter, and swelling >20 mm in diameter each occurred in approximately 1% to 2% of subjects. The occurrence of fever was actively monitored with daily temperature measurements during the period Days 0-3 after booster vaccination with Hiberix administered concomitantly with Pediarix. Approximately 35% of subjects reported post-vaccination fever $\geq 38^{o}C$ and approximately 4% reported fever $>39.5^{o}C$. Based on the data from this study, it is not possible to draw conclusions about attribution of post-vaccination fever to Hiberix and/or Pediarix, as all subjects received these vaccines concomitantly.

Post-Marketing Safety Experience

The BLA includes a review of the post-marketing safety experience with Hiberix during a 12 year period when approximately -b(4)- million doses of Hiberix were distributed in other countries. The ten most frequent, spontaneously reported adverse events for Hiberix were pyrexia, various local injection site reactions, and drug administration error. There were 27 reports with a fatal outcome (approximately --b(4)--million doses distributed). The disease processes in these cases were consistent with the prevalent causes of death in infants and children in the first two years of life and no unusual patterns were noted. In response to three post-marketing reports, GSK has been closely monitoring leukocytoclastic vasculitis. In addition to medical evaluation and expedited reporting of individual case reports, GSK will follow-up reports of leukocytoclastic vasculitis with a targeted questionnaire to obtain a standardized, detailed description of the cases. In response to one post-marketing report in an adult who received Hiberix, GSK plans to follow-up reports of type III, immune complex-mediated reactions on an individual basis.

Pediatric Research Equity Act (PREA)

Based on clinical studies of booster immunization with Hiberix in children predominantly 15 to 18 months of age, GSK has requested approval of Hiberix for booster immunization in children 15 months through 4 years of age (prior to 5^{th} birthday). It is anticipated that the safety profile of Hiberix, when used for catch-up booster vaccination in children 19 months through 4 years of age, would not meaningfully differ from that observed in clinical studies of children 15 to 18 months of age. Extrapolation of immunogenicity data on booster vaccination with Hiberix from children 15 to 18 months of age to older children 19 months through 4 years of age is supported by previous experience demonstrating robust anti-PRP immune responses following unconjugated Haemophilus b Polysaccharide Vaccine in children 4 to 5 years of age.[7]

A waiver to conduct studies of Hiberix in children 0 to <6 weeks of age and in children 5 to 17 years of age is justified because in these age groups, use of Hiberix is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules and Hiberix is not likely to be

used in a substantial number of patients. In addition, for children 5 to 17 years of age, necessary studies with Hiberix would be impossible or highly impracticable.

Deferral of a study of Hiberix in children 6 weeks to 14 months of age is justified since waiting for results of such a study would unnecessarily delay approval of Hiberix for booster immunization. Availability of Hiberix for booster immunization is expected to help in restoring and maintaining an adequate vaccine supply and in accomplishing catch-up vaccination for children whose booster dose has been deferred because of the shortage of Haemophilus b Conjugate Vaccines. GSK has committed to conduct a study to evaluate the safety and immunogenicity of Hiberix for primary immunization in infants beginning as early as 6 weeks of age, with follow-up through 6 months after the booster dose administered at 15 to 18 months of age. This study is expected to be initiated by September 2009 and the final report submitted by January 2013.

Conclusions and Approval Recommendation

The available immunogenicity data, obtained in generally healthy children who were almost exclusively Caucasian and predominantly 15 to 18 months of age, demonstrate a robust immune response against PRP elicited by a booster dose of Hiberix administered concomitantly with various DTaP combination vaccines that contained components of Pediarix. Although most subjects had been primed with Hiberix, the robust immune response after booster vaccination appeared to be consistent, regardless of the Haemophilus b Conjugate Vaccine used for priming. Data are not available on the effectiveness of Hiberix in children who may be at increased risk for invasive disease due to *H. influenzae* type b, including American Indian/Alaska Native children and children with certain immunosuppressive conditions.

The available safety data on Hiberix raised no particular concerns about the safety of booster vaccination with Hiberix. While much of the booster immunization data were obtained in children previously primed with Hiberix, there is no compelling reason to think that the overall safety profile of Hiberix would differ substantially depending on the particular Haemophilus b Conjugate Vaccine used for priming.

In view of the shortage of Haemophilus b Conjugate Vaccines which resulted in deferral of routine booster vaccination from December 18, 2007 through June 25, 2009, and insufficient supplies to currently support mass catch-up vaccination, the clinical studies immunogenicity and safety data, combined with the post-marketing experience with Hiberix in other countries, support accelerated approval of Hiberix for booster immunization for the prevention of invasive disease due to *H. influenzae* type b. The available clinical data are considered adequate to support use of Hiberix for booster immunization in children 15 months through 4 years of age. The number of children 12 to 14 months of age who were evaluated in clinical studies of booster immunization with Hiberix was not sufficient to support approval for this age group.

Recommendations for Post-Marketing Actions

As required by CBER, GSK has committed to conduct a clinical trial in the U.S. to evaluate the safety and immunogenicity of primary and booster vaccination with Hiberix, relative to a U.S. licensed Haemophilus b Conjugate Vaccine. The trial will be conducted in a study population that is representative of the racial/ethnic composition of U.S. children. In the trial, Hiberix will be administered concomitantly with other vaccines that are recommended for U.S. children. The planned trial is intended to provide confirmatory evidence of the clinical benefit of booster immunization with Hiberix, in accordance with the accelerated approval regulations. The planned trial is also intended to fulfill the PREA requirement for pediatric studies for the age group 6 weeks to 14 months of age and to support approval of Hiberix for a 3-dose primary series. GSK

expects to initiate the study by September 2009 and to submit the final study report by January 2013.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

Hiberix is intended for the prevention of invasive disease caused by *H. influenzae* type b when used as a booster dose in children 15 months through 4 years of age (prior to the 5th birthday) who were previously primed with a Haemophilus b Conjugate Vaccine that is licensed for use as a primary series.

Currently, there are two other manufacturers of licensed Haemophilus b Conjugate Vaccines in the U.S. Merck & Co., Inc. produces PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and COMVAX [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine]. Sanofi Pasteur produces ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], TriHIBit [ActHIB reconstituted with Tripedia (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)], and Pentacel [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine]. All of these vaccines are approved for primary and booster immunization against invasive disease due to *H. influenzae* type b, with the exception of TriHIBit, which is approved for booster immunization only.

In December 2007, Merck & Co., Inc. announced a voluntary recall of certain lots of PedvaxHIB and Comvax and suspended production of both vaccines, disrupting the U.S. supply of Haemophilus b Conjugate Vaccine.[1] To assure that enough vaccine would be available for all U.S. children to complete the primary series, on December 18, 2007, the CDC recommended that providers defer the booster dose of Haemophilus b Conjugate Vaccine (routinely administered in the second year of life) for all children except those at increased risk for invasive disease due to *H. influenzae* type b, temporarily, until restoration of the vaccine supply.[1] On June 26, 2009, coinciding with an increase in the number of doses of ActHIB and Pentacel available in the U.S., the CDC recommended reinstatement of the booster dose for children 12-15 months of age who have completed a primary series with Haemophilus b Conjugate Vaccine.[2] In their June 26, 2009 recommendation, the CDC indicated that older children for whom the booster dose was deferred should receive their booster dose at the next routinely scheduled visit or medical encounter.[2] As of June 26, 2009, although supply is sufficient to reinstate the booster dose and begin catch-up vaccination, supply is not yet ample enough to support a mass notification process to contact all children with deferred booster doses.[2]

4.2 Previous Human Experience with Hiberix

Hiberix was first licensed in Germany in June 1996 and is now registered in 98 countries as a stand-alone vaccine and in more than 100 countries when combined with other vaccines. Generally, Hiberix is administered as a primary series of three doses administered in the first 6 months of life, with the first dose administered as early as 6 weeks of age. The primary series is followed by a booster dose in the second year of life. From launch until November 30, 2008, approximately -b(4)- million doses of Hiberix were distributed. See section 5.1.2 for a review of post-marketing safety surveillance data for Hiberix.

4.3 Regulatory Background Information

4.3.1 Chronology of Review

Below is a chronology of the clinical review of the Hiberix BLA.

2/2/09: Pre-BLA meeting between CBER and GSK

3/17/09: Application received

4/23/09: Information request letter issued regarding proposed post-marketing clinical trial, Study Hib-097, which is designed to evaluate the safety and immunogenicity of primary and booster immunization with Hiberix relative to a U.S. licensed vaccine. This trial is intended to provide confirmatory evidence of the clinical benefit of booster immunization with Hiberix, as required by CBER under the accelerated approval regulations, and to fulfill the requirement, under PREA, for assessment of Hiberix in children 6 weeks to 14 months of age.

6/1/09: Information request letter issued regarding Study Hib-097.

4.3.2 Application of Accelerated Approval Regulations

Although not studied under U.S. IND, Hiberix has been evaluated in clinical studies that supported its first licensure in Germany in 1996 and subsequent licensure in other countries. Prior to submission of this BLA, CBER reviewed clinical studies data on Hiberix provided by GSK. CBER determined that the available data on the effectiveness of Hiberix for primary and/or booster immunization were not sufficient to support traditional approval. Limitations of the studies included lack of racial/ethnic diversity of study populations, lack of concomitant administration data with certain other vaccines that are used on the same schedule in the U.S., limited data comparing Hiberix to a U.S. licensed vaccine, ----------b(4)----------, and limited data on booster vaccination in subjects previously primed with a U.S. licensed vaccine on a U.S. schedule. However, CBER viewed the safety and effectiveness data from available clinical studies, combined with the post-marketing experience with Hiberix, as reasonably predictive of clinical benefit of booster immunization with Hiberix. In view of the shortage of Haemophilus b Conjugate Vaccine, with concurrence from its Office of General Counsel, CBER agreed to consider a BLA for Hiberix for booster immunization under the accelerated approval regulations, 21 CFR Part 601, Subpart E.

Accelerated approval may be granted for certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. CBER stipulated that accelerated approval of Hiberix for booster immunization could only be granted in the context of a shortage in the supply of the existing, licensed Haemophilus b Conjugate Vaccines. CBER also stipulated that accelerated approval of Hiberix for booster immunization would be subject to the requirement that GSK conduct an adequate and well-controlled safety and immunogenicity study to verify the clinical benefit of booster immunization with Hiberix. GSK has committed to conduct such a study, which is described in Section 12.2.1 of this review. Serological correlates of protection against invasive disease due to *H. influenzae* type b are discussed in Section 6 of this review.

5 Clinical Data Sources, Review Strategy and Data Integrity

5.1 Material Reviewed

5.1.1 BLA Sections Reviewed

The following sections of the BLA were reviewed:
m 1.9 Pediatric Administrative Information
m 1.11.2 Safety Information Amendment – Integrated Summary of Safety
m 1.11.3 Efficacy Information Amendment – Concept Protocol
m 1.11.4 Multiple Module Information (Response to CBER letter regarding Study Hib-097)
m 1.13.10 Foreign Marketing History
m 1.14 Labeling
m 2.5 Clinical Overview
m 2.7 Clinical Summary
m 5 Clinical Study Reports

5.1.2 Postmarketing Experience

5.1.2.1 Global Review of Postmarketing Safety Surveillance Data

The BLA included a report of a global review of postmarketing safety surveillance data for Hiberix conducted by GSK. For this report, the GSK worldwide safety database was searched from first approval for marketing of Hiberix in Germany on June 3, 1996, through May 31, 2008. The total patient exposure can be estimated from the number of doses distributed. During this period, approximately ---b(4)-- doses of Hiberix were distributed as a monovalent vaccine (i.e., not distributed as a component of a combination vaccine). However, it is common practice, in many countries, for healthcare providers to mix Hiberix with other vaccines in a single syringe immediately prior to administration. Therefore, the number of patients who received Hiberix as a monovalent vaccine cannot be determined. Hiberix is typically administered to infants as a 3-dose primary series, followed by a single booster dose in the second year of life. The number of persons exposed can be estimated under the assumption that infants and toddlers may receive one to four doses of Hiberix. Therefore, the number of individuals exposed can be estimated to be between 12,948,071 and ---b(4)-----.

For this analysis, spontaneous reports in which Hiberix was reported as a suspect vaccine were considered. To determine whether specific events should be included in the U.S. prescribing information for Hiberix, the following factors were evaluated by GSK: (1) frequency of reporting, (2) time to onset after vaccination, (3) published literature and reference healthcare organization assessment (e.g., Advisory Committee on Immunization Practices [ACIP] guidelines), (4) adverse reactions identified for similar vaccines, (5) specificity (e.g. dyspnea as a symptom of an allergic reaction was not considered to be a separate adverse reaction), (6) distinctness, (7) severity, and (8) occurrence of the event following natural disease.

Based on this evaluation, the following events were identified by GSK for inclusion in the Adverse Reactions section of the U.S. package insert:
• Rash
• Convulsion (with or without fever)
• Hypotonic-hyporesponsive episode
• Syncope or vasovagal responses to injection
• Somnolence
• Apnea
• Urticaria
• Allergic reactions (including anaphylactic and anaphylactoid reactions)
• Angioedema
• Extensive swelling of vaccinated limb
• Injection site induration

5.1.2.2 Most Frequently Reported Events

GSK also provided the Periodic Safety Update Report for Hiberix covering the period from June 1, 2008 through November 30, 2008. This report included an overview of the most frequently reported events for Hiberix, taking into account events reported in all age groups from launch (June 3, 1996) through November 30, 2008 (Table 1). When only children 15 months through 4 years of age were considered, the ten most frequently reported events included peripheral edema and all of the events listed in Table 1, with the exception of crying.

Table 1. Overview of the 10 most frequently reported events for Hiberix, spontaneous post-marketing reports, all age groups (June 3, 1996 through November 30, 2008)

System Organ Class	Preferred term	Number of Events	Reported frequency per 100,000 doses distributed
General disorders and administration site conditions	Pyrexia	235	0.43
General disorders and administration site conditions	Injection site erythema	182	0.33
General disorders and administration site conditions	Injection site oedema	104	0.19
Psychiatric disorders	Crying	95	0.17
General disorders and administration site conditions	Injection site swelling	82	0.15
Injury, poisoning and procedural complications	Drug administration error	80	0.15
General disorders and administration site conditions	Injection site reaction	79	0.14
Skin and subcutaneous tissue disorders	Erythema	79	0.14
General disorders and administration site conditions	Injection site pain	66	0.12
General disorders and administration site conditions	Local reaction	55	0.10

Includes regulatory and consumer reports, but not clinical trials cases; includes serious and non-serious events.
Source: m5.3.6 psur-sum-aes.pdf, pages 28-29

5.1.2.3 Reports of Potential Vaccination Failures

In a search of their worldwide safety database through November 30, 2008 for reports describing potential vaccination failures, GSK identified 20 cases in which the patients had completed the primary vaccination schedule (at least 3 doses) and invasive *H. influenzae* type b infection had been confirmed by laboratory testing.

In 8 (40%) of the 20 cases, the patients were reported to have received at least one priming dose with a DTP-based combination vaccine mixed with Hiberix in the same syringe just prior to administration. Five (63%) of these 8 patients had been administered DTP whole-cell pertussis-based vaccines as part of the primary series. In 11 (55%) of the 20 reports, the patients were more than 18 months of age when they experienced invasive *H. influenzae* type b disease. In 10 (91%) of the 11 reports, the patients had not received a booster dose of Haemophilus b Conjugate Vaccine following the 3 dose primary series. The reporting frequency of lack of efficacy was approximately -b(4)- reports per million doses distributed based on ---b(4)-----doses of Hiberix having been distributed through November 30, 2008.

5.1.2.4 Reports with Fatal Outcomes

Through November 30, 2008, there were 27 reports with fatal outcomes. Twenty (74%) of the 27 reports describe the administration of concomitant vaccines in addition to Hiberix. In 7 (26%) of the 27 reports, Hiberix is the only vaccine reported. The 27 reports originated from the following countries: China (n=7), India (n=4), Kenya (n=3), Korea (n=2), United Kingdom (n=2), Malaysia (n=2); Belgium, Ireland, Jamaica, Sri Lanka, Panama, Spain, and Chile (n=1 each). The

time to onset from vaccination to event ranged from immediately after vaccine administration to 9 days. Twenty-one (78%) of the 27 reports had a time to onset of 1 day or less. In 25 (93%) of the 27 reports, the patients were less than 15 months of age or the age of the patient was not specified. Two (7%) of the 27 reports described patients reported to be 15 months through 4 years of age.

According to GSK, of the 27 reports with fatal outcomes:

- Eight reports contained insufficient information with which to perform a thorough medical review.
- In 5 reports, aspiration of vomitus or respiratory tract obstruction may have contributed to the patients' deaths.
- In 4 reports, congenital anomalies or a concurrent condition contributed to the patients' deaths.
- In 5 reports, acute infectious processes may have contributed to the deaths.
- Two reports describe twins who co-slept with their parents and who died of unexplained causes 1 day after vaccination.
- One report described an infant who died of an unspecified "serious disturbance of ventilation or air-exchange caused by multiple lesions."
- In one report, the postmortem results showed hemophagocytosis in the spleen and bone marrow of unknown etiology.

The reports of death in patients 15 months through 4 years of age included a 2-year-old who experienced *H. influenzae* type b meningitis. The report did not specify whether the patient was fully immunized. The other patient was a 2-year-old who died 21 hours after immunization. The autopsy report described chronic non-specific inflammation of multiple organs along with pulmonary and cerebral edema.

In summary, GSK has received 27 reports with fatal outcomes following the administration of Hiberix. Given that approximately b(4)-million doses of Hiberix have been distributed since launch as a monovalent vaccine, the reporting frequency of fatal cases is 0.049 per --b(4)-- doses (or approximately --b(4)-- million doses) distributed. The disease processes in these reports are consistent with the prevalent causes of death in infants and children in the first two years of life and no unusual patterns were noted.

5.1.2.5 Leukocytoclastic Vasculitis

Through November 30, 2008, GSK has received 3 reports of leukocytoclastic vasculitis in infants, with time to onset since vaccination reported as 1 day, 2 days, and 3 days, respectively. Two of the 3 reports of leukocytoclastic vasculitis had limited clinical data, and in neither patient was the diagnosis confirmed by biopsy. In one of these cases, the treating pediatrician considered the event to be related to concurrent Augmentin. In the third report, a biopsy was performed and the patient was diagnosed with acute hemorrhagic edema of infancy, a form of leukocytoclastic vasculitis. Given that the patient had fever and diarrhea, it is possible that an infectious process was the underlying cause of the vasculitis. Each of the three cases had cutaneous manifestations, with no evidence for visceral involvement. In each case, the event resolved, without any reported sequelae.

Leukocytoclastic vasculitis refers to a spectrum of cutaneous small-vessel vasculitic syndromes, including Henoch-Schönlein Purpura, as well as to specific biopsy findings. The overall annual incidence of Henoch-Schönlein Purpura has been estimated to be 9/100,000 population.[8] Through November 30, 2008, --b(4)---- doses of Hiberix have been distributed, corresponding to a

reporting rate of leukocytoclastic vasculitis of -b(4)- reports per --b(4)-- doses distributed. GSK closely monitors reports of leukocytoclastic vasculitis. In addition to medical evaluation and expedited reporting of individual case reports, GSK will follow-up reports of leukocytoclastic vasculitis with a targeted questionnaire to obtain a standardized, detailed description of the cases.

5.1.2.6 Type III, Immune Complex-Mediated Reactions

GSK has received one report consistent with an antigen-antibody mediated (type III) hypersensitivity reaction in a 26 year old female. The report did not specify why the patient had been administered Hiberix. Based on this report, GSK has identified type III, immune complex-mediated reactions as a potential risk and will closely monitor suspected or confirmed cases of such reactions, with follow-up on an individual basis.

5.2 Tables of Clinical Studies

Data from seven clinical studies of booster immunization with Hiberix (Table 2) and two supportive primary immunization studies (Table 3) were included in the BLA. None of the studies were conducted under U.S. IND.

Across the seven booster immunization studies, the age range of subjects enrolled was 11 to 25 months, with the mean age at the time of receipt of Hiberix ranging from 15.9 to 18.7 months. Of the 1,008 subjects who received Hiberix, 172 (17.1%) were 11 to 14 months of age, 642 (63.7%) were 15 to 18 months of age, and 194 (19.2%) were 19 to 25 months of age at the time of vaccination. Across the six booster immunization studies in which the immune response to Hiberix was evaluated, a total of 415 subjects were included in the per protocol immunogenicity cohorts. Of these 415 subjects, 30 (7.2%) were 11 to 14 months of age, 316 (76.1%) were 15 to 18 months of age, and 69 (16.6%) were 19 to 25 months of age.

Table 2. Hiberix Booster Immunization Studies

Study [No.] Country	Study Start/ End	Priming History	Relevant Booster Study Groups	Mean Age at Booster Dose (Months)	Number of subjects	
					Total Cohort	Per Protocol Immunogenicity Cohort
DTPa-HBV-032 [208140/032] Argentina Brazil	June 1997/ May 1999	2, 4, 6 months: DTPa-HBV + Hiberix	DTPa-HBV + Hiberix	16.7	146	85[1]
DTPa-IPV-013p [213503/013] Canada	Nov 1995/ March1996	2, 4, 6 months: Kinrix + Hiberix	Kinrix + Hiberix	17.9	64	64
DTPa-HBV-020 [208140/020] Germany	June 1995/ Feb 1996	3, 4, 5 months: DTPa-HBV + Hiberix	DTPa-HBV + Hiberix	18.7	138	108
DTPa-IPV-026 [213503/026] Lithuania	March 1997/ July 1997	3, 4.5, 6 months: Pediarix + Hiberix or Pediarix + ActHIB (~2/3 Hiberix primed)	Infanrix + Hiberix + OPV	17.4	92	60
DTPa-HBV-IPV-010 [217744/010] Canada	Sep 1995/ Nov 1995	2, 4, 6 months: Pediarix + ActHIB	Pediarix + Hiberix	16.9	43	42
DTPa-HBV-IPV-035 [21744/035] Germany	Dec 1997/ Dec 1998	3, 4, 5 months: Pediarix + Hiberix or Pediarix + ActHIB or Pediarix + HibTITER or Pediarix + PedvaxHIB or Infanrix + ORIMUNE + ActHIB	Pediarix + Hiberix	15.9	150	56
DTPa-HBV-IPV-028 [21744/028] Germany	Apr 1997/ Nov 1998	3, 4, 5 months: Pediarix + Hiberix or Pediarix + ActHIB or Pediarix + HibTITER or Pediarix + PedvaxHIB or Infanrix + ORIMUNE + ActHIB	Pediarix + Hiberix	16.4	375	NA
			Total Hiberix		1008	415

Total cohort = all vaccinated subjects
The symbol "+" is used to indicate that two vaccines are administered concomitantly in two separate injections.
DTPa-HBV = diphtheria-tetanus acellular pertussis hepatitis B virus vaccine, same antigens as in Pediarix
Kinrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine, GSK (licensed in U.S. for use in children 4-6 years of age following 4 previous doses of DTaP using Infanrix and/or Pediarix for the first 3 doses and Infanrix for the fourth dose).
Infanrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, GSK (licensed in U.S. for 5 dose DTaP series in children 6 weeks to 7 years of age)
Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, GSK (licensed in U.S. as a 3-dose primary series in children 6 weeks to 7 years of age)
ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
OPV (oral poliovirus vaccine) used in Study DTPa-IPV-026 was manufactured by GSK; not licensed in U.S.
ORIMUNE = oral poliovirus vaccine (no longer licensed in U.S.), Lederle Laboratories
HibTITER = Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in U.S.), Wyeth Pharmaceuticals, Inc.
PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co, Inc.
[1]For one subject, immunogenicity data were available pre-vaccination, but not post-vaccination.
Source: m 2.5 clinical-overview.pdf, pages 17-19 and m 2.5 summary-clin-safety.pdf, page 28

Table 3. Hiberix Supportive, Primary Immunization Studies

Study [No.] Country	Study Start/ Study End	Study Groups	Vaccination Schedule	Number of subjects	
				Safety cohort (all vaccinated subjects)	Per Protocol Immunogenicity Cohort
DTPa-HBV-IPV-011 [21744/011] Germany	Nov 1995/ Dec 1997	Hiberix + Pediarix ActHIB + Pediarix HibTITER + Pediarix PedvaxHIB + Pediarix Infanrix + ActHIB + ORIMUNE	3, 4, 5 months (PedvaxHIB: 3 and 5 months)	1177 1174 1174 1171 776	NA
DTPa-HBV-IPV-012 [21744/012] Lithuania	Nov 1995/ July 1996	Hiberix + DTPa-HBV-IPV ActHIB + DTPa-HBV-IPV HibTITER + DTPa-HBV-IPV PedvaxHIB + DTPa-HBV-IPV	3, 4.5, 6 months (PedvaxHIB: 3 and 6 months)	219 110 110 110	202 102 100 105
		TOTAL Hiberix		1396	202

Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, GSK (licensed in U.S. as a 3-dose primary series in children 6 weeks to 7 years of age)
ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER = Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co., Inc.
Infanrix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, GSK (licensed in U.S. for 5 dose DTaP series in children 6 weeks to 7 years of age)
ORIMUNE = oral poliovirus vaccine (no longer licensed in the U.S.), Lederle Laboratories
Source: m 2.5 clinical-overview.pdf, page 20 and m 2.5 summary-clin-safety.pdf, page 15

5.3 Review Strategy

All of the clinical studies submitted with the BLA (Table 2 and Table 3) were reviewed and considered in the evaluation of the safety of Hiberix. For the two supportive primary immunization studies, as agreed upon between CBER and GSK, safety analyses included in the BLA were limited to serious adverse events. Post-marketing safety surveillance data were also considered in the evaluation of the safety of Hiberix for booster immunization.

Six of the seven booster immunization studies included an assessment of the immunogenicity of Hiberix, and were considered in the evaluation of effectiveness. In addition, one of the primary immunization studies included immunogenicity data that were considered supportive in the evaluation of the effectiveness of Hiberix for booster immunization. In E-mail correspondence June 30, 2009, CBER's assay reviewer for the Hiberix BLA indicated that the anti-PRP assays used in the clinical studies of Hiberix were acceptable.

5.4 Good Clinical Practices and Data Integrity

As per recommendation from Dr. Norman Baylor, Director, Office of Vaccines Research and Review, CBER (Email correspondence, March 27, 2009), bioresearch monitoring inspections for studies included in the Hiberix BLA were waived. This recommendation was based, in part, on the expectation that such inspections may not yield useful information for studies that were conducted in the mid- to late-1990s.

For one of the booster immunization studies, Study DTPa-IPV-026 (Section 7.1.4), GSK suspected fraud in data collection at one of the study sites. The site was closed and subjects from

the site were excluded from the According to Protocol analyses. With this exception, no other concerns regarding data integrity were identified for the clinical studies included in the BLA.

6 Human Pharmacology (Immunogenicity)

Specific levels of antibody to PRP have been shown to correlate with protection against invasive disease due to *H. influenzae* type b. Based on an efficacy study with an unconjugated Haemophilus b Polysaccharide Vaccine[3] and data from passive antibody studies[4], an anti-PRP level of 0.15 mcg/mL has been accepted as a minimum protective level. An anti-PRP level of 1.0 mcg/mL has been accepted as predicting long-term (at least one year) protection[5,6]. Use of these levels of anti-PRP to evaluate the effectiveness of Haemophilus b Conjugate Vaccines has been previously accepted by CBER. These levels of anti-PRP antibody were evaluated in studies of Hiberix that were submitted with the Hiberix BLA.

7 Clinical Studies

7.1 Booster Immunization Studies

7.1.1 Trial # 1

7.1.1.1 Applicant's Protocol # and Protocol Title

Study DTPa-HBV-032 [208140/032]: Open clinical study of the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV vaccine, when co-administered with SB Biologicals' Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course in healthy infants aged 2, 4 and 6 months, followed by a booster administered according to local Expanded Program on Immunization schedule.

7.1.1.2 Primary Objective/Rationale

To establish the immunogenicity and reactogenicity of GSK's combined diphtheria-tetanus-acellular pertussis-hepatitis B vaccine (DTPa-HBV) and Hiberix when administered concomitantly.

7.1.1.3 Design Overview

The study was an open-label, single group clinical study conducted at three sites in Argentina and Brazil. The study investigated the immunogenicity and reactogenicity of GSK's DTPa-HBV vaccine co-administered with Hiberix in two concomitant injections into opposite limbs, as a primary vaccination course in healthy infants aged 2, 4 and 6 months, followed by booster vaccination at 15-18 months of age.

7.1.1.4 Population

Inclusion Criteria

- Between 6 and 10 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parents or guardians.

Exclusion Criteria

- Evidence of previous diphtheria, tetanus, pertussis, hepatitis B or *H. influenza* type b vaccination(s) or disease.
- History of allergic disease likely to be stimulated by vaccination.
- History of progressive neurological disease.
- Acute severe febrile illness at the time of planned vaccination.
- Immunosuppressive therapy (with the exception of topical corticosteroids).
- Any suspected or confirmed immunosuppressive or immunodeficient condition.
- Immunoglobulin therapy or administration of any blood product since birth or during the study period.
- Administration of an investigational or non-registered drug or vaccine during the study period or within 30 days prior to the start of the study.
- Simultaneous administration of a non-protocol vaccine, with the exception of oral poliovirus vaccine.

Concomitant Products

Concomitant administration of any non-study vaccine by the parenteral route was not permitted.

7.1.1.5 Products Mandated by the Protocol

Hiberix was administered intramuscularly into the left anterolateral thigh. Hiberix lots Hib039A47/M, Hib016A47/M and Hib076A44 were used in the study. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	12.6 mg

DTPa-HBV (not licensed in the U.S.) was administered intramuscularly into the right anterolateral thigh. DTPa-HBV lots 16730A2, 16729A2 and 16718A2 were used. Each dose of DTPa-HBV contained:

Inactivated Pertussis toxin (PT)	-b(4)- mcg
Filamentous haemagglutinin (FHA)	-b(4)- mcg
Pertactin (PRN)	-b(4)- mcg
Diphtheria toxoid	-b(4)- IU
Tetanus toxoid	-b(4)- IU
Recombinant DNA Hepatitis B Surface Antigen (HbsAg)	-b(4)- mcg
Aluminium (as salts)	-b(4)- mg
Phenoxyethanol	-b(4)- mg

7.1.1.6 Endpoints

Some of the endpoints pertained to the evaluation of Hiberix administered as a primary series and to the evaluation of GSK's DTPa-HBV vaccine. Only the endpoints that pertained to the evaluation of booster immunization with Hiberix will be presented in this review. There were no pre-defined acceptance criteria for any of the endpoints.

7.1.1.6.1 Primary Endpoints

- Percentage of subjects with post-vaccination anti-PRP antibody $\geq$0.15 mcg/ml

7.1.1.6.2 Secondary Endpoints

- Percentage of subjects with post-vaccination anti-PRP antibody ≥1.0 mcg/ml
- Post-vaccination anti-PRP GMCs
- Occurrence of solicited symptoms during the 4-day post-vaccination period
- Occurrence of unsolicited symptoms within 30 days post-vaccination
- Occurrence of serious adverse events within 30 days post-vaccination

7.1.1.7 Surveillance/Monitoring

7.1.1.7.1 Immunogenicity Monitoring

Serum samples (from a minimum of 3 ml of whole blood) were collected from all vaccinees at the following time points:

- at the time of the first dose of Hiberix;
- one month following the third dose of Hiberix;
- at the time of the booster dose of Hiberix; and
- one month following the booster dose of Hiberix.

Serum samples were tested for antibodies to PRP using an --b(4)-- performed by GSK.

7.1.1.7.2 Safety Surveillance/Monitoring

Safety monitoring following the booster dose of study vaccines is described below.

- Vaccinees were observed closely at the study site for at least 15 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record axillary body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and fussiness. Parents/guardians were instructed to return the completed diary card at the next visit, and to contact the investigator for any signs or symptoms perceived as severe.
- Between day 4 and day 7 post-vaccination, the investigator or a nurse was to contact the parents/guardians once by telephone to check on completion of the diary card and the presence of any adverse events. If the parents/guardians had no telephone, the investigator was to arrange for a contact between day 4 and day 7 post-vaccination.
- At the one-month post-vaccination visit for collecting serum samples, the parents/guardians were queried about the occurrence of unsolicited adverse events, both non-serious and serious.

7.1.1.8 Statistical Considerations

7.1.1.8.1 Sample Size/Statistical Power

Initially, the planned enrollment was 300 infants, in order to obtain 250 evaluable subjects following the third dose of study vaccines. The sample size was based on considerations for the evaluation of post-dose 3 antibodies to PRP and HbsAg. The protocol was subsequently amended for a target enrollment of 240 infants, in order to obtain 190 evaluable subjects following the third dose of study vaccines.

7.1.1.8.2 Study Cohorts Analyzed

The protocol specified that both per-protocol and intent-to-treat analyses of immunogenicity would be performed. The per-protocol immunogenicity cohort was defined as “subjects corresponding to criteria defined in the protocol”. The protocol specified that the intent-to-treat immunogenicity analyses “will include all data available from all subjects”.

In the study report, the cohorts analyzed were defined as follows:

Total Cohort
The Total Cohort included all vaccinated subjects with available data.

According-To-Protocol (ATP) Cohort for Safety
The ATP cohort for analysis of safety included all subjects:
- who received at least one dose of study vaccine,
- with sufficient data to perform an analysis of safety,
- with documented vaccination site,
- who had not received a vaccine not specified or forbidden in the study protocol.

ATP Cohort for Immunogenicity
The ATP Cohort for Immunogenicity included all subjects:
- who met all eligibility criteria,
- who complied with protocol procedures,
- with assay results for antibody against at least one vaccine antigen after vaccination.

The ATP cohort analyses of immunogenicity were initially specified as the primary immunogenicity analyses. However, because the number of evaluable subjects was below the planned evaluable population, the principal immunogenicity analysis was based on the Total Cohort.

7.1.1.8.3 Statistical Analyses
The percentage of subjects with anti-PRP levels $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml and the corresponding 95% confidence intervals were calculated. Anti-PRP GMCs with 95% confidence intervals were calculated by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay (i.e., -b(4)- mcg/ml) were given an arbitrary value of half the cut-off for the GMT calculation.

The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.1.9 Results

7.1.1.9.1 Populations Enrolled/Analyzed
Three centers (two in Argentina and one in Brazil) enrolled a total of 199 subjects. The first subject was enrolled in the study on June 19, 1997. The last study visit was on May 28, 1999.

Of the 199 subjects enrolled in the study, 146 (73.4%) received the fourth dose of study vaccines and are most relevant to this review. Table 4 presents a summary of subjects who were enrolled and completed the study, covering the entire study period, from Dose 1 of study vaccines through the end of the study (one month post-dose 4). Fifty-eight subjects dropped out of the study for reasons detailed in Table 4, resulting in a study completion rate of 71%. Seven subjects were terminated ('Other' in Table 4) due to lack of compliance, particularly lack of adherence to dosing intervals. The four protocol violations involved subjects who received whole-cell pertussis DTP vaccine.

Table 4. Study DTPa-HBV-032: Subjects entered, completed, dropped, and reason for drop-out*

	Total
Number of subjects planned	240
Number of subjects entered	199
Number of subjects completed	141
Reasons for drop-out:	
Adverse event	0
Protocol violation	4
Consent withdrawal	10
Migrated/moved from the study area	0
Lost to follow-up for the full vaccination course/for final blood sample	37
Other	7

*This table covers the entire study period, from Dose 1 through 1 month post-Dose 4.
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 30.

Table 5 details reasons for exclusion from study analyses. The information in Table 5 covers the entire study period, from Dose 1 of study vaccines through one month post-Dose 4. Subjects eligible for safety analysis received at least one dose of study vaccine and had documentation of the presence/absence of signs and symptoms post-vaccination. Nine of the 199 enrolled subjects were not eligible for analysis of reactogenicity due to reasons detailed in Table 5. Subjects eligible for the ATP analysis of immunogenicity complied with all protocol requirements and assay results were available for at least one study vaccine antigen. A further 88 subjects were eliminated from the ATP analysis of immunogenicity due to reasons detailed in Table 5.

Table 5. Study DTPa-HBV-032: The Number of Subjects Entered, Completed, Dropped, and Reason for Drop-out

	TOTAL	Percent
Number of subjects planned	240	
Subject or vaccine number not allocated	101	
*Number of subjects enrolled	199	(100 %)
Administration of vaccine(s) forbidden in the protocol	2	
Study vaccine dose not administered according to protocol	1	
Essential data missing	6	
**Number of subjects included in the analysis of reactogenicity	190	(95.5 %)
Protocol violation (too young/old, unknown age or gender)	9	
Non-compliance with vaccination schedule (including wrong and unknown dates)	34	
Non-compliance with blood sampling schedule (including wrong and unknown date)	45	
***Number of subjects included in the analysis of immunogenicity	102	(51.3 %)

This table covers the entire study period, from Dose 1 through 1 month post-Dose 4.
*: Pertains to Total cohort
**: Pertains to ATP analysis of reactogenicity (safety)
***: Pertains to ATP analysis of immunogenicity
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 31.

7.1.1.9.2 Subject Demographics

Of the 146 subjects who received a booster dose of Hiberix, 75 (51.4%) were male. Age at receipt of the fourth dose ranged from 14 to 19 months (mean age 16.7 months). Information on race/ethnicity was provided, overall, for the 199 subjects enrolled: 192 (96.5%) were Caucasian, 4 were classified as Black, and 3 were classified as mixed race. Information on race/ethnicity specific to the subgroup of subjects who received a booster dose of Hiberix was not provided.

7.1.1.9.3 Immunogenicity Outcomes

Table 6 and Table 7 present anti-PRP seroprotection rates and GMCs, respectively, prior to and one month after receipt of the fourth dose of Hiberix for the total cohort. The corresponding results for the ATP cohort are presented in Tables 8 and 9.

Table 6. Study DTPa-HBV-032 Anti-PRP levels ≥0.15 mcg/ml and ≥1.0 mcg/ml, total cohort

Timing	N	≥0.15 mcg/ml				≥1.0 mcg/ml			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
pre-dose 4	147	143	97.3	93.2	99.3	98	66.7	58.4	74.2
post-dose 4	141	141	100.0	97.4	100.0	141	100.0	97.4	100.0

N = number of subjects tested
n= number with titers within the specified range
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 34

Table 7. Study DTPa-HBV-032 Anti-PRP GMCs, total cohort

Timing	**N**	GMT (mcg/ml)		
		value	**95% CI**	
			LL	**UL**
pre-dose 4	147	2.007	1.579	2.551
post-dose 4	141	129.690	104.665	160.698

N = number of subjects tested
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 34

Table 8. Study DTPa-HBV-032 Anti-PRP levels ≥0.15 mcg/ml and ≥1.0 mcg/ml, ATP immunogenicity cohort

Timing	N	≥0.15 mcg/ml				≥1.0 mcg/ml			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
pre-dose 4	85	83	97.6	91.8	99.7	56	65.9	54.8	75.8
post-dose 4	84	84	100.0	95.7	100.0	84	100.0	95.7	100.0

N = number of subjects tested
n= number with titers within the specified range
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 42

Table 9. Study DTPa-HBV-032 Anti-PRP GMCs, ATP immunogenicity cohort

Timing	N	GMT (mcg/ml)		
		value	95% CI	
			LL	UL
pre-dose 4	85	1.944	1.403	2.694
post-dose 4	84	137.128	103.486	181.706

N = number of subjects tested
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, page 42

7.1.1.9.4 Safety Outcomes

7.1.1.9.4.1 Solicited Adverse Events

Safety results for solicited adverse events were reported for the ATP cohort for reactogenicity. Of the 146 subjects who received a booster dose of Hiberix, 140 were included in the ATP cohort for reactogenicity. Two subjects were excluded from the ATP cohort for reasons of: administration of vaccine not specified, or forbidden, in the protocol and study vaccine administration site unknown. Four subjects were excluded from the ATP cohort because their diary cards were not returned. Table 10 presents the incidence of solicited local and general adverse events reported in the 4-day period (Day 0 to 3) following the booster dose of Hiberix. Data on solicited adverse events, categorized by intensity, were not provided for the booster dose specifically. However, across Doses 1-4 of Hiberix, there were 2 reports of Grade 3 pain defined as cries when the limb is moved/spontaneously painful (prevents normal activity); 1 report of injection site redness >20 mm; 2 reports of injection site swelling >20 mm; 3 reports of fever $\geq 39^{o}$C, and 7 reports of Grade 3 irritability/fussiness (persistent crying and cannot be comforted).

Table 10. Study DTPa-HBV-032 Incidence of solicited adverse events within the 4-day period (Day 0 to 3) following the fourth dose of Hiberix administered concomitantly with GSK's DTPa-HBV*, ATP analysis of safety

			95% CI	
	n	%	LL	UL
Number of Symptom Sheets Returned	140			
Local Reactions at the Hiberix Injection Site				
Pain	35	25.0	18.1	33.0
Redness	23	16.4	10.7	23.6
Swelling	20	14.3	8.9	21.2
General Symptoms				
Fever* $\geq 37.5^{o}$C	22	15.7	10.1	22.8
Fussiness	46	32.9	25.2	41.3

*GSK's DTPa-HBV vaccine is not licensed in the U.S.
n = number of reports of a given symptom
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
*Axillary temperature was recorded in the evening
Source: m 5.3.5.4.3 dtpa-hbv-032-report-body.pdf, pages 44 and 46

7.1.1.9.4.2 Unsolicited Adverse Events

Of the 146 subjects who received a booster dose of Hiberix, 6 (4.1%) reported an unsolicited adverse event within the 31 day (Days 0-30) period following the booster dose. There were two reports of urticaria and one each of vomiting, bronchitis, pneumonia, and rhinitis. None of these events were considered Grade 3 (prevents normal, everyday activities) in intensity and none were serious adverse events.

In the primary vaccination phase of the study, one serious adverse event was reported—a case of meningococcal meningitis 28 days following the second dose of DTPa-HBV and Hiberix.

7.1.1.10 Comments and Conclusions

The anti-PRP immunogenicity data, obtained using GSK's -b(4)-, suggest maintenance of a minimum seroprotective level (i.e., anti-PRP $\geq$0.15 mcg/ml) through 15-18 months of age following priming with Hiberix at 2, 4, and 6 months of age, in a high proportion (i.e., approximately 97%) of subjects. Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix, as evidenced by a 65-fold increase in GMCs from pre- to post-vaccination. In addition, the proportion of subjects with anti-PRP $\geq$1.0 mcg/ml increased substantially from pre-vaccination (approximately two-thirds) to post-vaccination (100%).

Local injection site reactions, fever $\geq$37.5^{o}C, and fussiness were reported commonly following the booster dose of Hiberix (approximately 15-30% of subjects) administered concomitantly with GSK's DTPa-HBV vaccine.

7.1.2 Trial # 2

7.1.2.1 Applicant's Protocol # and Protocol Title

Study DTPa-IPV-013p [213503/013] Open randomized clinical study to assess the immunogenicity and reactogenicity of coadministration of SmithKline Beecham Biologicals' DTPa-IPV vaccine, and SmithKline Beecham Biologicals' Hib vaccine, either mixed in one syringe and given in one single injection or given in two simultaneous injections into opposite limbs, as a booster vaccination at the age of 15 to 19 months to healthy children, previously primed with a three dose primary vaccination course using the same vaccines in study DTPa-IPV 004.

7.1.2.2 Primary Objective/Rationale

The primary objective of this study was to evaluate the immunological memory induced by the study vaccines during primary vaccination, as assessed through a booster response to all antigens contained in GSK's combined DTPa-IPV and Hiberix, following a fourth dose in the second year of life.

7.1.2.3 Design Overview

The study was an open-label, randomized (1:1), multi-center study (4 Canadian sites) with two groups: booster vaccination with GSK's combined DTPa-IPV/Hib or booster vaccination with GSK's separately administered DTPa-IPV + Hiberix.

7.1.2.4 Population

Inclusion Criteria

- participation in GSK's study DTPa-IPV-004 (pilot phase) and receipt of complete primary vaccination course of three doses of Hiberix and GSK's DTPa-IPV vaccine
- age between 15 and 19 months at the time of entry to the study
- good physical condition established by medical history and physical examination
- written informed consent obtained from parents or guardians

Exclusion Criteria

- history of allergic disease likely to be stimulated by any vaccine component as well as allergic reactions to neomycin, streptomycin and polymyxin B.
- evidence of previous polio, diphtheria, tetanus, pertussis and/or *H. influenzae* type b booster vaccination or disease
- major congenital defects or serious chronic illness
- history of progressive neurological disease
- episode of acute febrile illness at the time of planned vaccination
- any suspected or confirmed immunosuppressive condition
- immunosuppressive therapy (except topical corticosteroids)
- any chronic drug therapy continuing during the study period (except vitamins, minerals or other dietary supplements).
- immunoglobulin therapy or any blood products within the previous two months or planned during the study period
- simultaneous administration of a vaccine not included in the study protocol
- administration of an investigational or non registered drug or vaccine during the study period or within 30 days prior to the start of the study
- Evidence of one of the following events after previous DTP vaccine
  - Fever ≥ 40.5°C (rectal temperature) or ≥ 40.0°C (axillary temperature) within 48 hours after vaccination
  - Seizures
  - Encephalopathy
  - Hypersensitivity reaction to the vaccine

7.1.2.5 Products Mandated by the Protocol

Study Group 1 received DTPa-IPV vaccine mixed in the same syringe with Hiberix. Results for this group were not included in the Hiberix BLA.

Study Group 2 received GSK's DTPa-IPV vaccine intramuscularly in the left deltoid and Hiberix intramuscularly in the right deltoid. Subjects in Study Group 2 had previously received separate administration of GSK's DTPa-IPV and Hiberix in the primary immunization study, Study DTPa-IPV-004.

Hiberix lot Hib008A44/Diluent lot 95A31/4 was used in Study DTPa-IPV-013p. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	12.6 mg

DTPa-IPV lot 20704A2 was used. Each dose of DTPa-IPV contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin (PRN)	8 mcg
Diphtheria toxoid	-b(4)- IU
Tetanus toxoid	-b(4)- IU
Inactivated poliovirus type 1 (Mahoney)	40 D antigen units
Inactivated poliovirus type 2 (MEF-1)	8 D antigen units
Inactivated poliovirus type 3 (Saukett)	32 D antigen units
Aluminum (as salts)	0.5 mg
Phenoxyethanol	2.5 mg

The formulation of GSK's DTPa-IPV used in this study is the same as that of U.S. licensed Kinrix, except that Kinrix marketed in the U.S. does not contain phenoxyethanol. In the U.S., Kinrix is approved for use as the fifth dose of DTaP and the fourth dose of IPV in children 4-6 years of age previously vaccinated with approved regimens of Infanrix and/or Pediarix.

7.1.2.6 Endpoints

Some of the endpoints pertained to the evaluation of GSK's DTPa-IPV vaccine. Only the endpoints that pertained to the evaluation of booster immunization with Hiberix will be presented in this review. In the protocol, primary and secondary endpoints were listed as "Immunogenicity, Persistence of antibodies, Reactogenicity". The protocol specified that anti-PRP levels (GMCs and percentage of subjects $\geq$0.15 mcg/ml, $\geq$0.5 mcg/ml, and $\geq$1.0 mcg/ml) would be assessed before and after booster vaccination and that reactogenicity would be assessed by description of local and general adverse experiences reported during a 4-day solicited follow-up period. There were no pre-defined acceptance criteria for any study endpoints.

7.1.2.7 Surveillance/Monitoring

Only the study procedures that pertained to the evaluation of booster immunization with Hiberix will be presented in this review.

7.1.2.7.1 Immunogenicity Monitoring

A minimum of 3 ml whole blood was obtained from vaccinees at the time of the booster dose of Hiberix and one month later. The protocol allowed for an interval of 30-35 days between the booster dose and blood sampling. Serum samples were tested by GSK for antibodies to PRP using a------- ----------b(4)----------.

7.1.2.7.2 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 30 minutes following vaccination.
- Diary cards were distributed to the parents/guardians to record axillary body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included local reactions (pain, redness, and swelling) at the injection site and general symptoms (fever, unusual crying lasting more than one hour, vomiting, diarrhea, loss of appetite, and restlessness). Parents/guardians were instructed to contact the investigator immediately for any severe signs or symptoms.
- On days 1 and 4 post-vaccination, the investigator or a nurse contacted the parents/guardians by telephone to check on the occurrence of adverse events and to review the diary cards.
- At the one-month post-vaccination visit for collecting serum samples, the parents/guardians were queried about the occurrence of adverse events since Day 4 post-vaccination.

7.1.2.8 Statistical Considerations

7.1.2.8.1 Sample Size/Statistical Power

Since the study was a follow-up of a primary vaccination study, no sample size/statistical power calculations were performed.

7.1.2.8.2 Study Cohorts Analyzed

The protocol specified that both per-protocol and intent-to-treat analyses of immunogenicity would be performed. The per-protocol immunogenicity cohort was defined as "subjects corresponding to criteria defined in the protocol". The protocol specified that the intent-to-treat immunogenicity analyses "will include all data available from all subjects except those eliminated from reactogenicity analysis".

7.1.2.8.3 Statistical Analyses

The percentage of subjects with anti-PRP levels $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml and the corresponding 95% confidence intervals were calculated. In addition, anti-PRP GMCs with 95% confidence intervals were calculated. Antibody titers below the cut-off of the assay (i.e., -b(4)- mcg/ml) were given an arbitrary value of half the cut-off value for the purpose of GMT calculation.

The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.2.9 Results

7.1.2.9.1 Populations Enrolled/Analyzed

Four Canadian study sites enrolled a total of 64 subjects in Study Group 2 (separate administration of GSK's DTPa-IPV and Hiberix). The study period was November 18, 1995 through March 17, 1996. All 64 subjects in Group 2 completed the study and were eligible for per protocol analyses of immunogenicity.

7.1.2.9.2 Subject Demographics

All 64 subjects in Group 2 were between 16 and 19 months of age at the time of vaccination. The mean age was 17.9 months. Thirty-four of the 64 subjects were female.

7.1.2.9.3 Immunogenicity Outcomes

The protocol allowed for an interval of 30-35 days between the booster dose and blood sampling. However, for analyses, this interval was extended to 21-42 days to maximize inclusion into the analysis of immunogenicity. Table 11 and Table 12 present anti-PRP seroprotection rates and GMCs, respectively, prior to and one month after receipt of the fourth dose of Hiberix.

Table 11. Study DTPa-IPV-013p Anti-PRP levels ≥0.15 mcg/ml and ≥1.0 mcg/ml, Study Group 2*

Timing	N	≥0.15 mcg/ml				≥1.0 mcg/ml			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
pre-dose 4	63	45	71.4	58.7	82.1	8	12.7	5.6	23.5
post-dose 4	64	64	100.0	94.4	100.0	64	100.0	94.4	100.0

*Study Group 2 received Hiberix concomitantly with Kinrix (DTaP-IPV, GSK). In the U.S., Kinrix is licensed for use in children 4-6 years of age for the fifth dose of DTaP and the fourth dose of IPV following an approved series using Infanrix (DTaP, GSK) and/or Pediarix (DTaP-HBV-IPV, GSK).
N = number of subjects tested
n= number with titers within the specified range
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-ipv-013p-report-body.pdf, page 19 and summary-clin-efficacy-hib-immunization.pdf, page 25

Table 12. Study DTPa-IPV-013p Anti-PRP GMCs, Study Group 2*

Timing	**N**	GMT (mcg/ml)		
		value	**95% CI**	
			LL	**UL**
pre-dose 4	63	0.254	0.196	0.330
post-dose 4	64	47.779	36.891	61.881

*Study Group 2 received Hiberix concomitantly with Kinrix (DTaP-IPV, GSK). In the U.S., Kinrix is licensed for use in children 4-6 years of age for the fifth dose of DTaP and the fourth dose of IPV following an approved series using Infanrix (DTaP, GSK) and/or Pediarix (DTaP-HBV-IPV, GSK).
N = number of subjects tested
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 dtpa-ipv-013p-report-body.pdf, page 21

7.1.2.9.4 Safety Outcomes

7.1.2.9.4.1 Solicited Adverse Events

Symptom sheets were returned for all vaccinated subjects. Table 13 presents the incidence of solicited local and general adverse events reported in the 4-day period (Day 0 to 3) following the fourth dose of Hiberix.

Table 13. Study DTPa-IPV-013p Incidence of solicited local reactions and general symptoms within the 4-day period (Day 0 to 3) following the fourth dose of Hiberix administered concomitantly with GSK's DTPa-IPV, Study Group 2[*], all vaccinated subjects†

	n	%	95% Confidence Interval
Number of Symptom Sheets Returned	64		
Local Reactions at the Hiberix Injection Site			
Pain, any	16	25.0	(15.0, 37.4)
Pain, grade 3	0	-	(0.0, 5.6)
Redness, any	7	10.9	(4.5, 21.2)
Redness >20 mm	1	1.6	(0.0, 8.4)
Redness >30 mm	0	-	(0.0, 5.6)
Swelling, any	8	12.5	(5.6, 23.2)
Swelling >20 mm	0	0	(0.0, 5.6)
General Symptoms			
Fever[§] ≥38.0°C	16	25.0	(15.0, 37.4)
Fever >39.5 °C	4	6.3	(1.7, 15.2)
Unusual crying, any	11	17.2	(8.9, 28.7)
Unusual crying grade 3	1	1.6	(0.0, 8.4)
Restlessness, any	23	35.9	(24.3, 48.9)
Restlessness grade 3	2	3.1	(0.4, 10.8)
Loss of appetite, any	18	28.1	(17.6, 40.8)
Loss of appetite grade 3	2	3.1	(0.4, 10.8)

n = number of reports of a given symptom
Grade 3: preventing normal everyday activities
[*]Study Group 2 received Hiberix concomitantly with Kinrix (DTaP-IPV, GSK). In the U.S., Kinrix is licensed for use in children 4-6 years of age for the fifth dose of DTaP and the fourth dose of IPV following an approved series using Infanrix (DTaP, GSK) and/or Pediarix (DTaP-HBV-IPV, GSK).
[†]All vaccinated subjects had solicited symptom follow-up documented; the ATP cohort included all vaccinated subjects.
[§]In general, temperatures were measured by the axillary route. For 4 subjects both axillary and rectal temperatures were taken. For one subject, temperature was taken by the tympanic route.
Source: m 5.3.5.4.3 dtpa-ipv-013p-report-body.pdf, pages 17-18 and m 2.7.3 summary-clin-safety.pdf, pages 34-37

7.1.2.9.4.2 Unsolicited Adverse Events

Of the 64 subjects who received a booster dose of Hiberix, 37 (57.8%) reported an unsolicited adverse event within the 31 day (Days 0-30) period following the booster dose. The most commonly reported events were upper respiratory tract infection (15 subjects), otitis media (9 subjects), and injection site reaction (7 subjects). One event, a case of otitis media, was considered Grade 3 in intensity.

There were no serious adverse events within the 31 day period following booster vaccination with Hiberix.

7.1.2.10 Comments and Conclusions

The anti-PRP immunogenicity data, obtained using GSK's --b(4)--, indicate that approximately 70% of subjects had a minimum protective level of anti-PRP (i.e., anti-PRP ≥0.15 mcg/ml)

through approximately 18 months of age following priming with Hiberix at 2, 4, and 6 months of age. Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix. Of 56 subjects with an anti-PRP level <1.0 mcg/ml prior to Dose 4 of Hiberix, all achieved this level after booster vaccination. Anti-PRP GMCs increased 188-fold from pre- to post-vaccination.

Local injection site reactions, fever $\geq$38.0^{o}C, unusual crying, restlessness, and loss of appetite were reported commonly following the booster dose of Hiberix (approximately 10-35% of subjects) administered concomitantly with GSK's DTPa-IPV.

7.1.3 Trial # 3

7.1.3.1 Applicant's Protocol # and Protocol Title

208140/020 (DTPa-HBV-020): Open clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV and dtpa-HBV vaccines when administered with SB Biologicals' Hib vaccine, either mixed in one syringe and given in one single injection or given in two simultaneous injections into opposite limbs, as a booster vaccination at the age of 15 to 22 months to healthy children, previously primed with a three-dose primary vaccination course using the DTPa-HBV vaccine.

7.1.3.2 Primary Objective/Rationale

To assess the immunogenicity of GSK's combined DTPa-HBV, dtpa-HBV and Hiberix when given as a fourth dose, either in one injection or given separately in opposite limbs. Neither DTPa-HBV nor dtpa-HBV is licensed in the U.S.

7.1.3.3 Design Overview

The study was an open-label, randomized multicenter booster study with 4 groups:
Group 1: received a separate dose of DTPa-HBV + Hiberix (subjects received primary vaccination of DTPa-HBV + Hiberix in study DTPa-HBV-004)

Group 2: received a separate dose of dtpa-HBV + Hiberix (subjects received primary vaccination of DTPa-HBV + Hiberix in study DTPa-HBV-004)

Group 3: received a mixed dose of DTPa-HBV/Hib (subjects received primary vaccination of DTPa-HBV/Hib in study DTPa-HBV-007c)

Group 4: received a mixed dose of dtpa-HBV/Hib (subjects received primary vaccination of DTPa-HBV/Hib in study DTPa-HBV-007c)

As agreed between GSK and CBER, the Hiberix BLA included only results for Study Group 1.

7.1.3.4 Population

Children who had previously participated in Study DTPa-HBV-004 (enrolled in booster study as groups 1 and 2) or Study DTPa-HBV-007c (enrolled in booster study as groups 3 and 4) and had received a complete primary vaccination course of three consecutive doses of GSK's DTPa-HBV and Hiberix (at 3, 4, and 5 months of age) were to be enrolled in Study DTPa-HBV-020 according to the following criteria:

Inclusion Criteria

- Subjects to have received a complete primary vaccination course of three consecutive doses of GSK's DTPa-HBV and Hiberix.
- Age: between 15 and 22 months of age at the time of vaccination.
- Free of obvious health problems as established by medical history and examination before entering into the study.
- Written informed consent obtained from the parents/guardians of the infant

Exclusion Criteria

- Evidence of previous diphtheria, tetanus, pertussis, hepatitis B or *H. influenzae* type b booster vaccination(s) or disease.
- History of allergic disease likely to be stimulated by the vaccination.
- History of significant and persisting hematologic, hepatic, renal, cardiac, or respiratory disease.
- History of convulsions, epilepsy, or any signs of central nervous system disease.
- Acute febrile illness at the time of planned vaccination.
- Immunosuppressive therapy (with the exception of topical corticosteroids).
- Any suspected or confirmed immune disorder.
- Immunoglobulin therapy or administration of any blood product within the previous two months or during the study period.
- Any chronic drug therapy to be continued during the study period (with the exception of vitamins, minerals or other dietary supplements).
- Administration of an investigational or non-registered drug or vaccine during the study period or within 30 days prior to the start of the study.
- Simultaneous administration of a vaccine not foreseen by the study protocol, with the exception of oral poliovirus vaccine.
- Evidence of one of the following events after previous DTP vaccine
  - Fever ≥40.5°C (rectal temperature) within 48 hours after vaccination
  - Seizures
  - Encephalopathy
  - Hypersensitivity reaction

Concomitant vaccines

Concomitant administration of any other vaccine by the parenteral route was not permitted.

7.1.3.5 Products Mandated by the Protocol

Hiberix, administered as a separate injection in Study Group 1, was given intramuscularly into the left anterolateral thigh. Hiberix lot Hib007A44 was used. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

DTPa-HBV, administered as a separate injection in Study Group 1, was given intramuscularly into the right anterolateral thigh. DTPa-HBV lot 16717A2 was used. Each dose of DTPa-HBV contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin (PRN)	8 mcg
Diphtheria toxoid	-b(4)- IU
Tetanus toxoid	-b(4)- IU
Recombinant DNA Hepatitis B Surface Antigen (HbsAg)	10 mcg
Aluminium (as salts)	0.7 mg
Phenoxyethanol	2.5 mg

The active ingredients in DTPa-HBV (not licensed in the U.S.) used in this study are the same as the DTaP and Hepatitis B vaccine components of U.S. licensed Pediarix.

7.1.3.6 Endpoints

Some of the endpoints pertained to the evaluation of GSK's DTPa-HBV and dTpa-HBV vaccines, which are not licensed in the U.S. Only the endpoints that pertained to the evaluation of booster immunization with Hiberix will be presented in this review. In the protocol, primary and secondary endpoints were listed as "Immunogenicity" and "Reactogenicity". The protocol specified that anti-PRP levels (GMCs and percentage of subjects $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml) would be assessed before and after booster vaccination and that reactogenicity would be assessed by description of local and general adverse experiences reported during a 4-day solicited follow-up of study subjects. There were no pre-defined acceptance criteria for any study endpoints.

7.1.3.7 Surveillance/Monitoring

Only the study procedures that pertained to the evaluation of booster immunization with Hiberix will be presented in this review.

7.1.3.7.1 Immunogenicity Monitoring

A blood sample (2 to 4 ml) was obtained from all vaccinees at the time of the booster dose of Hiberix and one month later. Serum samples were tested for antibodies to PRP using a -b(4)- performed by GSK.

7.1.3.7.2 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 30 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record rectal body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and general events (fever, unusual crying lasting more than one hour, vomiting, diarrhea, loss of appetite, and restlessness). Parents/guardians were instructed to return the completed diary card at the one-month post-vaccination visit and to contact the investigator for any signs or symptoms perceived as severe.

7.1.3.8 Statistical Considerations

7.1.3.8.1 Sample Size/Statistical Power

This study was a follow-up of a primary vaccination study. No sample size calculation was performed for the booster vaccination study.

7.1.3.8.2 Study Cohorts Analyzed

The protocol specified that both per-protocol and intent-to-treat analyses of immunogenicity would be performed. The per-protocol immunogenicity cohort was defined as "subjects corresponding to criteria defined in the protocol". The protocol specified that the intent-to-treat immunogenicity analyses "will include all data available for all subjects except those eliminated from the analysis of reactogenicity".

7.1.3.8.3 Statistical Analyses

The percentage of subjects with anti-PRP levels $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml and the corresponding 95% confidence intervals were calculated. In addition, anti-PRP GMCs with 95% confidence intervals were calculated. Antibody titers below the cut-off of the assay (i.e., -b(4)-mcg/ml) were given an arbitrary value of half the cut-off value for the purpose of GMT calculation.

The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.3.9 Results

7.1.3.9.1 Populations Enrolled/Analyzed

The study was conducted at a single site in Mainz, Germany. The study began June 28, 1995 and was completed February 28, 1996. Considering all four study groups, the planned enrollment was 600 subjects; 553 subjects were enrolled. Considering only Group 1, the planned enrollment was 150 subjects; 138 subjects were enrolled. Table 14 presents a summary of subject disposition for Group 1.

Table 14. Study DTPa-HBV-020: Study Group 1 subjects with data available for analysis and eligibility for inclusion

Number of subjects planned	**150**
Subjects or vaccine number not allocated	12
Number of subjects enrolled	**138**
Administration of vaccine not specified or forbidden in the protocol	2
Randomization failure	7
Number of subjects included in the analysis of reactogenicity	**129**
Initially seropositive or unknown antibody status	1
Non compliance with blood sampling schedule	16
Blood sample lost or unable to test (e.g. hemolysis, insufficient volume)	4
Number of subjects included in the analysis of immunogenicity	**108**

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
Source: m 5.3.5.4.3 dtpa-hbv-020-report-body.pdf, page 17

7.1.3.9.2 Subject Demographics

Of the 138 subjects enrolled in Group 1, 68 (49.3%) were female. Age at receipt of the fourth dose of Hiberix ranged from 16 to 23 months (mean age 18.7 months). Information on race/ethnicity was not provided.

7.1.3.9.3 Immunogenicity Outcomes

Table 15 and Table 16 present ATP analyses of anti-PRP seroprotection rates and GMCs, respectively, prior to and one month after receipt of the fourth dose of Hiberix for Study Group 1. The corresponding results for the total cohort are presented in Tables 17 and 18.

Table 15. Study DTPa-HBV-020 Group 1 anti-PRP levels ≥0.15 mcg/ml and ≥1.0 mcg/ml, ATP analysis of immunogenicity

Timing	N	≥0.15 mcg/ml				≥1.0 mcg/ml			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
pre-dose 4	108	84	77.8	68.6	85.0	35	32.4	23.9	42.2
post-dose 4	108	108	100.0	95.7	100.0	108	100.0	95.7	100

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
N = number of subjects tested
n= number with titers within the specified range
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 DTPa-HBV-020-report-body.pdf, pages 19 and 24 and summary-clin-efficacy-hib-immunization.pdf, page 26

Table 16. Study DTPa-HBV-020 Group 1 anti-PRP GMCs, ATP analysis of immunogenicity

Timing	**N**	GMT (mcg/ml)		
		value	**95% CI**	
			LL	**UL**
pre-dose 4	108	0.585	0.430	0.797
post-dose 4	108	96.119	74.074	124.726

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
N = number of subjects tested
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 DTPa-HBV-020-report-body.pdf, page 19

Table 17. Study DTPa-HBV-020 Group 1 anti-PRP levels ≥0.15 mcg/ml and ≥1.0 mcg/ml, Total cohort

Timing	N	≥0.15 mcg/ml				≥1.0 mcg/ml			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
pre-dose 4	132	102	77.3	69.0	83.9	44	33.3	24.9	41.8
post-dose 4	127	127	100.0	96.3	100.0	127	100.0	96.3	100.0

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
N = number of subjects with available data
n= number with titers within the specified range
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 DTPa-HBV-020-report-body.pdf, page 25

Table 18. Study DTPa-HBV-020 Group 1 anti-PRP GMCs, Total cohort

Timing	N	GMT (mcg/ml)		
		value	95% CI	
			LL	UL
pre-dose 4	132	0.59	0.44	0.78
post-dose 4	127	89.45	69.96	114.36

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
N = number of subjects with available data
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
Source: m 5.3.5.4.3 DTPa-HBV-020-report-body.pdf, page 25

7.1.3.9.4 Safety Outcomes

7.1.3.9.4.1 Solicited Adverse Events

For the 129 subjects in Group 1 included in the reactogenicity analysis, 128 subjects returned a symptom sheet. Of the 129 doses of Hiberix administered to the subjects included in the analysis of reactogenicity, 116 were injected in the anterolateral thigh (as per protocol) and 13 were injected in the buttock or gluteal muscle.

Safety results for solicited adverse events were reported for the ATP cohort for reactogenicity. Table 19 presents the incidence of solicited local and general adverse events reported in the 4-day period (Day 0 to 3) following the fourth dose of Hiberix for Group 1 subjects.

Table 19. Study DTPa-HBV-020 Group 1 Incidence of selected solicited adverse events within the 4-day period (Day 0 to 3) following the fourth dose of Hiberix administered concomitantly with GSK's DTPa-HBV, ATP analysis of reactogenicity

	N=128		
	n	%	95% CI
Local Reactions at the Hiberix Injection Site			
Pain, any	16	12.5	7.3, 19.5
Pain, Grade 3	0	0.0	0.0, 2.8
Redness, any	29	22.7	15.7, 30.9
Redness >20 mm	4	3.1	0.9, 7.8
Swelling, any	24	18.8	12.4, 26.6
Swelling >20 mm	1	0.8	0.0, 4.3
General Symptoms			
Fever* ≥38.0°C	37	28.9	21.2, 37.6
Fever ≥39.5 °C	2	1.6	0.2, 5.5
Unusual crying, any	11	8.6	4.4, 14.9
Unusual crying grade 3	0	0.0	0.0, 2.8
Restlessness, any	27	21.1	14.4, 29.2
Restlessness grade 3	2	1.6	0.2, 5.5
Loss of appetite, any	23	18.0	11.7, 25.7
Loss of appetite grade 3	0	0.0	0.0, 2.8

Group 1 subjects received a booster dose of Hiberix concomitantly with GSK's DTPa-HBV (not licensed in the U.S.)
n = number of reports of a given symptom
Grade 3 pain = cries when limb is moved/spontaneously painful (prevents normal activities)
Grade 3 for other events = prevents everyday activities
95% CI, LL and UL = 95% confidence intervals, lower and upper limit
*Rectal temperatures
Source: m 5.3.5.4.3 DTPa-HBV-020-report-body.pdf, pages 20-21 and m 2.7.4 Summary of Clinical Safety pages 34-37

7.1.3.9.4.2 Unsolicited Adverse Events

Of the 129 subjects in Group 1 included in the reactogenicity analysis, 24 subjects reported a total of 31 unsolicited symptoms within 30 days post-vaccination. The most frequently reported unsolicited event was upper respiratory tract infection (4 reports), followed by diarrhea (3 reports) and gastroenteritis (3 reports). An analysis of unsolicited adverse events within 30 days post-vaccination was also performed for the total vaccinated cohort of 138 subjects in Group 1. Twenty-six of the 138 subjects reported at least one unsolicited event. None of the unsolicited events were graded as severe (preventing everyday activities). There were no serious adverse events reported in Group 1.

7.1.3.10 Comments and Conclusions

The anti-PRP immunogenicity data, obtained using a -b(4)-, indicate that approximately 80% of subjects had a minimum protective anti-PRP level (i.e., anti-PRP ≥0.15 mcg/ml) through approximately 19 months of age following priming with Hiberix at 3, 4, and 5 months of age. Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix. Approximately two-thirds of subjects had an anti-PRP level <1.0 mcg/ml prior to Dose 4 of Hiberix; all subjects achieved this level after booster vaccination. Anti-PRP GMCs increased 164-fold from pre- to post-vaccination.

Local injection site reactions, fever ≥38.0°C, unusual crying, restlessness, and loss of appetite were reported commonly (approximately 10-20% of subjects) following the booster dose of Hiberix administered concomitantly with GSK's DTPa-HBV vaccine.

7.1.4 Trial # 4

7.1.4.1 Applicant's Protocol # and Protocol Title

213503/026 (DTPa-IPV-026): Open, randomized clinical study to assess the reactogenicity and immunogenicity of SB Biologicals' DTPa vaccine co-administered with SB Biologicals' Hib vaccine in two concomitant injections into opposite limbs, as compared to SB Biologicals' DTPa vaccine mixed with SB Biologicals' Hib vaccine and to SB Biologicals' DTPa-IPV vaccine mixed with SB Biologicals' Hib vaccine, administered as a booster dose to healthy children in their second year of life, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine.

7.1.4.2 Primary Objective/Rationale

The primary objective of the study was to evaluate and compare the local reactogenicity of three booster regimens (DTaP + Hiberix administered separately, DTaP mixed with Hiberix, and DTaP-IPV mixed with Hiberix).

7.1.4.3 Design Overview

The study was an open-label, randomized multicenter booster study with 3 groups. Subjects previously primed with Pediarix and PRP-T conjugate vaccine (Hiberix or ActHIB) underwent a randomization in a 1:1:1 ratio to three study groups:
Group 1: received DTaP + Hiberix + OPV
Group 2: received DtaP/Hiberix (mixed) + OPV
Group 3: received DtaP-IPV/Hiberix (mixed).

As agreed between GSK and CBER, the BLA included only results for Study Group 1.

7.1.4.4 Population

In a previously conducted study, Study DTPa-HBV-IPV-012, 330 children received three doses of Pediarix and Haemophilus b Conjugate vaccine (either Hiberix or ActHIB) at 3, 4.5 and 6 months of age. These children were eligible for enrollment according to the following criteria:

Inclusion Criteria

- Subjects must have participated in Study DTPa-HBV-IPV-012 and have received three doses of Pediarix and PRP-T (Hiberix or ActHIB) according to protocol.
- Age: between 15 and 24 months of age at the time of booster vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Written informed consent obtained from the parents/guardians of the infant.
- Absence of previous diphtheria, tetanus, pertussis and/or polio booster vaccination or disease.

Exclusion Criteria

- History of allergic disease likely to be stimulated by the vaccination, including allergic reactions to neomycin and polymyxin B.
- Intercurrent diphtheria, tetanus, pertussis, poliomyelitis and/or *H. influenza* type b disease.
- Major congenital defects or serious chronic illness.
- Progressive neurological disease.
- Acute febrile illness at the time of planned vaccination.
- Immunosuppressive therapy (with the exception of topical corticosteroids).
- Any suspected or confirmed immune disorder.
- Immunoglobulin therapy or administration of any blood product within three months before study entry or during the study period.
- Administration of an investigational or non-registered drug or vaccine during the study period or within 30 days prior to the start of the study.
- Simultaneous administration of a vaccine not foreseen by the study protocol at the same visit as the study vaccine.
- One of the following events after previous DTP vaccine
  - Fever ≥ 40.5°C (rectal temperature) or ≥40.0°C (axillary temperature) within 48 hours after vaccination
  - Hypotonic-hyporesponsive episode within 48 hours after vaccination
  - Seizures within 3 days after vaccination
  - Encephalopathy within 7 days of vaccination
  - Hypersensitivity reaction due to the vaccine
  - Persistent, inconsolable crying for more than 3 hours within 48 hours of vaccination.

Concomitant administration of non-study vaccines was not permitted.

7.1.4.5 Products Mandated by the Protocol

Hiberix, administered as a separate injection in Study Group 1, was given intramuscularly into the right anterolateral thigh. Hiberix lot Hib039A47/M was used. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

GSK's DTaP, Infanrix, administered as a separate injection in Study Group 1, was given intramuscularly into the left anterolateral thigh. Infanrix lot DTPa811B9/M was used. The formulation of Infanrix used in this study is the same as that licensed in the U.S. except that it also contained 2-phenoxyethanol as a preservative. Each 0.5 ml dose of Infanrix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin (PRN)	8 mcg
Diphtheria toxoid	-b(4)- IU
Tetanus toxoid	-b(4)- IU
Aluminum (as salts)	0.5 mg
Phenoxyethanol	2.5 mg

Oral poliovirus vaccine manufactured by GSK (not licensed in the U.S.) was given orally. Lot S2273A3/A was used. Each 0.5 ml dose contained:

Poliovirus type 1 ---b(4)---	-----b(4)---------
Poliovirus type 2 -----b(4)---------	------b(4)--------
Poliovirus type 3 ---b(4)----------	-----b(4)---------

7.1.4.6 Endpoints

The protocol specified the endpoints as follows:

Primary endpoint:

Incidence and intensity of solicited local reactions (swelling, redness, pain) at the injection site(s) of the study vaccines.

Secondary endpoints:

- incidence, intensity and relationship to vaccination of solicited general symptoms.
- incidence, nature, intensity and relationship to vaccination of unsolicited adverse experiences.
- incidence, nature, intensity and relationship to vaccination of serious adverse experiences.
- for antibodies to the three pertussis antigens PT, FHA and pertactin: percentage of vaccine response and percentage of subjects eliciting titers ≥ 5 EU/ml and GMTs before and one month after the booster dose.
- for anti-PRP: percentages of subjects eliciting levels ≥0.15 mcg/ml, ≥0.5 mcg/ml and ≥1.0 mcg/ml, and GMCs before and one month after the booster dose.
- for antibodies to diphtheria and tetanus toxoid: percentage of subjects eliciting levels ≥ 0.1 IU/ml and GMTs before and one month after the booster dose.
- for anti-Hepatitis B surface antigen: percentage of subjects with levels ≥10 mIU/ml and GMCs before the booster dose.

For the pertussis antigens, vaccine response was defined as:

- the appearance of antibodies (titer ≥cut-off) when the titer is undetectable prior to vaccination
- at least a 2-fold increase from pre- to post-vaccination titers in initially seropositive subjects.

There were no pre-defined acceptance criteria for any study endpoints.

7.1.4.7 Surveillance/Monitoring

Only the study procedures that pertained to the evaluation of Study Group 1 will be presented in this review.

7.1.4.7.1 Immunogenicity Monitoring

A 3 ml blood sample was obtained from all vaccinees at the time of the booster dose of Hiberix and one month (day 30-35 per protocol) later. Serum samples were tested by GSK for antibodies to PRP using a -b(4)-, for antibodies to PT, FHA, and pertactin using an -b(4)----, for antibodies to diphtheria and tetanus using an -b(4)-, and for antibodies to polioviruses (not presented in this review) using a -------b(4)- --------- assay.

7.1.4.7.2 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 15 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record rectal body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and general events (fever, unusual crying lasting more than one hour, vomiting, diarrhea, loss of appetite, and restlessness). Parents/guardians were instructed to return the completed diary card at the one-month post-vaccination visit and to contact the investigator for any signs or symptoms perceived as severe.
- Between Day 4 and Day 7 post-vaccination, an investigator or nurse contacted the parents/guardians once by telephone to check on completion of the diary card and the presence of any adverse events. For families without a telephone, the investigator arranged for a contact between Day 4 and Day 7 post-vaccination.
- Information on unsolicited adverse events through one month post-vaccination was obtained at the second study visit.

7.1.4.8 Statistical Considerations

7.1.4.8.1 Sample Size/Statistical Power

Statistical power considerations were limited to comparisons of local injection site reactions between groups. These considerations assumed 80 evaluable subjects per group.

7.1.4.8.2 Study Cohorts Analyzed

The protocol specified that both per-protocol and intent-to-treat analyses of immunogenicity would be performed. The per-protocol immunogenicity cohort was defined as “subjects corresponding to criteria defined in the protocol”. The protocol specified that the intent-to-treat immunogenicity analyses “will include all data available from all subjects”.

In the study report, the cohorts analyzed were defined as follows:

Total Cohort

The Total Cohort included all enrolled subjects with available data. For immunogenicity, this included all subjects for whom immunogenicity data were available.

According-To-Protocol (ATP) Cohort for Safety

The ATP cohort for analysis of safety included all subjects:

- who received at least one dose of study vaccine according to their random assignment,
- with sufficient data to perform an analysis of safety,
- for whom the administration site was according to protocol,
- who had not received a vaccine not specified or forbidden in the study protocol.

ATP Cohort for Immunogenicity

The ATP Cohort for Immunogenicity included all evaluable subjects (i.e., those meeting all inclusion/exclusion criteria, and complying with protocol procedures, for whom assay results were available for antibodies against at least one study vaccine antigen).

7.1.4.8.3 Statistical Analyses

For the immunogenicity endpoints listed in Section 7.1.4.6, the percent of subjects achieving specified levels of antibodies and antibody GMCs or GMTs were calculated, with corresponding

95% confidence intervals. For antibody GMT calculations, antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off value.

Although the protocol-defined window for collection of post-vaccination blood samples was 30-35 days, the protocol indicated that deviation from this window may not necessarily lead to the exclusion of subjects from the analyses. The actual interval for inclusion in the immunogenicity analyses was expanded to 21 to 42 days.

The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.4.9 Results

7.1.4.9.1 Populations Enrolled/Analyzed

The study was conducted at five sites in Lithuania. The study began March 4, 1997 and was completed July 8, 1997. Two hundred and seventy-three children, previously primed in study DTPa-HBV-IPV-012, were enrolled in Study DTPa-IPV-026. The allocation of subjects in Group 1 is presented in Table 20.

Table 20. Study DTPa-IPV-026: Allocation of subjects to Group 1, based on priming vaccines

Primary Phase (DTPa-HBV-IPV-012)	Booster Phase (DTPa-IPV-026) Group 1 Infanrix + Hiberix + OPV (N= 92) n
Pediarix + Hiberix (N = 219)	64
Pediarix + ActHIB (N = 110)	28

Infanrix = DTaP, GSK
OPV = oral poliovirus vaccine (not licensed in the U.S.)
Pediarix = DTaP-HBV-IPV, GSK
ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
N = number of subjects enrolled
n = number of subjects enrolled in booster study according to primary groups
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 25

All but one subject from one of the study centers (Center 3) (27 from Group 1) were eliminated from analyses due to a suspected fraud in data collection. The GSK monitor noticed that several diary cards from subjects at this center were filled in with the same pen and the same handwriting. Therefore, in agreement with the principal investigator, it was decided to close this center and exclude all subjects from the ATP analyses. An additional 5 subjects from Group 1 were eliminated from the ATP immunogenicity analysis because of non-compliance with blood sampling schedule (no post-vaccination blood sample for one subject and samples obtained more than 42 days post-vaccination for four subjects). Thus, as shown in Table 21, 60 subjects from Group 1 were included in the ATP analysis of immunogenicity.

Table 21. Study DTPa-IPV-026 Subject inclusion and eligibility for analysis, Group 1

Number of subjects enrolled	**92**
Excluded because of suspected fraud at study site	27
Number of subjects included in the analysis of reactogenicity	**65**
Non compliance with blood sampling schedule	5
Number of subjects included in the ATP analysis of immunogenicity	**60**

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 26

Of the 92 subjects enrolled in Group 1, 90 completed the study. One subject dropped out because of consent withdrawal and one subject was lost to follow-up at the final blood sampling.

7.1.4.9.2 Subject Demographics

Of the 92 subjects enrolled in Group 1, 56 (60.9%) were male. The mean age at the booster dose was 17.4 months (range 15-19 months). Age and gender characteristics for the Group 1 ATP cohort for reactogenicity and the Group 1 ATP cohort for immunogenicity were similar to that of the total cohort enrolled in Group 1. Information on race/ethnicity was not provided.

7.1.4.9.3 Immunogenicity Outcomes

Table 22 presents ATP analyses of anti-PRP seroprotection rates and GMCs prior to and one month after receipt of Hiberix for Study Group 1, irrespective of receipt of Hiberix or ActHIB for priming. The corresponding results for the total cohort are presented in Table 23.

Table 22. Study DTPa-IPV-026 Anti-PRP seroprotection rates and GMCs prior to and one month after the receipt of Hiberix, Group 1 subjects, ATP analysis of immunogenicity

Timing	N	≥0.15 mcg/ml		95% CI		≥1.0 mcg/ml		95% CI		GMC (mcg/ml)	95% CI	
		n*	%	LL	UL	n**	%	LL	UL		LL	UL
Pre	60	56	93.3	83.0	97.8	19	31.7	19.1	44.3	0.73	0.52	1.02
Post	60	60	100.0	92.5	100.0	60	100.0	92.5	100.0	80.02	59.38	107.83

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = total number of subjects tested
n* = total number of subjects with levels ≥0.15 mcg/ml
n** = total number of subjects with levels ≥1.0 mcg/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 37

Table 23. Study DTPa-IPV-026 Anti-PRP seroprotection rates and GMCs prior to and one month after the receipt of Hiberix, Group 1 subjects, Total cohort

Timing	N	≥0.15 mcg/ml		95% CI		≥1.0 mcg/ml		95% CI		GMC (mcg/ml)	95% CI	
		n*	%	LL	UL	n**	%	LL	UL		LL	UL
Pre	92	86	93.5	85.8	97.3	32	34.8	24.5	45.1	0.76	0.58	1.01
Post	90	90	100.0	94.9	100.0	90	100.0	94.9	100.0	90.83	72.09	114.53

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = total number of subjects tested
n* = total number of subjects with levels ≥0.15 mcg/ml
n** = total number of subjects with levels ≥1.0 mcg/ml
95% CI, L.L. and U.L. = 95% Confidence Interval, Lower and Upper limits
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 47

Table 24 presents ATP analyses of anti-PRP seroprotection rates and GMCs prior to and one month after receipt of Hiberix for Study Group 1, stratified by priming with Hiberix or ActHIB.

Table 24. Study DTPa-IPV-026 Anti-PRP seroprotection rates and GMCs prior to and one month after the receipt of Hiberix, Group 1 subjects, stratified by Haemophilus b Conjugate Vaccine received for primary series, ATP cohort for immunogenicity

Priming vaccine	Timing	N	≥0.15 mcg/ml		95% CI		≥1 mcg/ml		95% CI		GMC	95% CI	
			n	%	LL	UL	n	%	LL	UL	value	LL	UL
Hiberix	Pre	40	38	95.0	83.1	99.4	15	37.5	22.7	54.2	0.8	0.5	1.2
	Post	40	40	100	91.2	100	40	100	91.2	100	78.1	54.4	112.0
ActHIB	Pre	20	18	90.0	68.3	98.8	4	20.0	5.7	43.7	0.6	0.3	1.2
	Post	20	20	100	83.2	100	20	100	83.2	100	84.0	47.2	149.8

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: m 5.3.5.4.3 DTPa-IPV-026 addendum.pdf, page 4

Table 25 presents ATP analyses of anti-diphtheria seropositivity rates and GMTs, as measured by -b(4)-, prior to and one month after receipt of Infanrix for Study Group 1. Anti-diphtheria antibody levels below the -b(4)- cut-off -b(4)- IU/ml) were re-tested with the more sensitive -b(4)- test (cut off -b(4)- IU/ml). When the -b(4)- cell results were considered, more than 98.3% of subjects were seropositive for anti-diphtheria antibodies prior to booster vaccination.

Table 25. Study DTPa-IPV-026 Anti-diphtheria seropositivity rates and GMTs, by -b(4)-, prior to and month after the receipt of Infanrix administered concomitantly with Hiberix, Group 1 subjects, ATP analysis of immunogenicity

Timing	N	% ≥0.1 IU/ml		95%CI		GMT (IU/ml)	95%CI	
		n	%	LL	UL		LL	UL
Pre	60	39	65.0	52.1	77.9	0.146	0.114	0.185
Post	60	60	100.0	92.5	100.0	5.415	4.296	6.825

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 33

Table 26 presents ATP analyses of anti-tetanus seropositivity rates and GMTs, prior to and one month after receipt of Infanrix for Study Group 1.

Table 26 Study DTPa-IPV-026 Anti-tetanus seropositivity rates and GMTs, by -b(4)-, prior to and month after the receipt of Infanrix administered concomitantly with Hiberix and OPV, Group 1 subjects, ATP analysis of immunogenicity

Timing	N	% ≥0.1 IU/ml		95%CI		GMT (IU/ml)	95%CI	
		n	%	LL	UL		LL	UL
Pre	60	57	95.0	85.2	98.7	0.397	0.321	0.491
Post	60	60	100.0	92.5	100.0	10.872	8.802	13.429

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = number of subjects with available results
n (%) = number (percentage) of subjects with concentration within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 34

Table 27 presents booster response rates for each pertussis antigen for Group 1 subjects included in the ATP analysis of immunogenicity, categorized according to pre-booster vaccination status.

Table 27 Study DTPa-IPV-026 Pertussis antibody booster response rates, Group 1 subjects, ATP analysis of immunogenicity

Antibody	Pre-vaccination status	N	n	Vaccine Response % [95% CI]
Anti-PT	S-	8	8	100.0
	S+	52	51	98.1
	Total	60	59	98.3
				[89.9 , 99.9]
Anti-FHA	S+	57	54	95.0
	Total	57	54	95.0
				[84.5 , 98.6]
Anti-pertactin	S-	3	3	100.0
	S+	57	54	94.7
	Total	60	57	95.0
				[85.2 , 98.7]

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = total number of subjects tested
n = number of subjects with a vaccine response
95% CI = 95% Confidence Interval
S+ = titers ≥5 EU/ml , S- = titers <5 EU/ml
Vaccine response definition:
For pre-booster seronegative subjects (S-): Appearance of titer (≥ 5 EU/ml)
For pre-booster seropositive subjects (S+): At least two-fold increase in pre-vaccination titer
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 35

Table 28 presents GMTs of antibodies to the pertussis antigens, prior to and one month after receipt of Infanrix for Study Group 1.

Table 28 Study DTPa-IPV-026 Pertussis antibody GMTs, Group 1 subjects, ATP analysis of immunogenicity

Antibody	Timing	N	GMT (EU/ml)	95% CI	
				UL	LL
Anti-PT	Pre	60	10.8	8.7	13.4
	Post	60	127.3	108.4	149.6
Anti-FHA	Pre	57	40.1	30.0	53.5
	Post	60	597.4	483.4	738.2
Anti-pertactin	Pre	60	26.7	20.5	34.9
	Post	60	814.9	634.5	1046.6

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = total number of subjects tested
95% CI, LL and UL = 95% Confidence Interval, Lower and Upper limits
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 35

7.1.4.9.4 Safety Outcomes

7.1.4.9.4.1 Solicited Adverse Events

Safety results for solicited adverse events were reported for the ATP cohort for reactogenicity. Table 29 presents the incidence of solicited local reactions at the Infanrix and Hiberix injection sites that occurred in the 4-day period (Day 0 to 3) following vaccination for Group 1 subjects.

Table 29. Study DTPa-IPV-026 Group 1 Incidence of solicited local reactions at the Infanrix and Hiberix injection sites that occurred in the 4-day period (Day 0 to 3) following vaccination, ATP analysis of reactogenicity

		N = 65			
		Infanrix site	Hiberix site		
		%	n	%	95% CI
Pain	Any	12.3	8	12.3	5.5, 22.8
	grade 3	0.0	0	0	0.0, 5.5
Redness	Any	52.3	28	43.1	30.8, 56.0
	>20 mm	12.3	4	6.2	1.7, 15.0
Swelling	Any	33.8	13	20.0	11.1, 31.8
	>20 mm	16.9	3	4.6	1.0, 12.9

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = total number of doses administered with a symptom sheet returned
Any = all specified symptoms, regardless of intensity
n/% = number/percentage of subjects reporting the specified solicited local symptom
pain graded 3 in intensity: pain preventing everyday activities
95% CI = 95% Confidence Interval, Lower Limit, Upper Limit
n and 95% CI not provided for Infanrix site
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 28 and m 2.7.4 Summary of Clinical Safety, page 34

Table 30 presents the incidence of selected solicited general symptoms that occurred in the 4-day period (Day 0 to 3) following vaccination for Group 1 subjects.

Table 30. Study DTPa-IPV-026 Group 1 Incidence of selected solicited general symptoms that occurred in the 4-day period (Day 0 to 3) following vaccination with Hiberix, Infanrix and OPV, ATP analysis of reactogenicity

		N = 65		
Symptom	Intensity	n	%	95 % CI
Fever	Any	5	7.7	2.5, 17.0
	Grade 3	0	0.0	0.0, 5.5
Loss of appetite	Any	14	21.5	12.3, 33.5
	Grade 3	0	0.0	0.0, 5.5
Sleeping less than usual	Any	20	30.8	19.9, 43.4
	Grade 3	1	1.5	0.0, 8.3
Unusual crying	Any	12	18.5	9.9, 30.0
	Grade 3	0	0.0	0.0, 5.5

Group 1 subjects received a booster dose of Hiberix concomitantly with Infanrix (DTaP, GSK) and oral poliovirus vaccine (OPV). OPV is not licensed in the U.S.
N = total number of doses administered with a symptom sheet returned
n = total number of documented doses followed by the specific symptom
Any Fever = axillary/oral temperatures ≥37.5°C or rectal temperatures ≥38.0°C
Grade 3 Fever = ≥39.1°C (axillary/oral) or ≥39.6°C (rectal)
Grade 3 loss of appetite, sleeping more than usual, unusual crying = symptom preventing everyday activity
Source: m 5.3.5.4.3 DTPa-IPV-026-report-body.pdf, page 29 and m 2.7.4 Summary of Clinical Safety, pages 36-37

7.1.4.9.4.2 Unsolicited Adverse Events

Considering the total vaccinated cohort of 92 subjects in Group 1, 17 unsolicited adverse events were reported during the 0-30 day period following vaccination. The most frequently reported unsolicited symptom was upper respiratory tract infection (4 cases), followed by pharyngitis and atopic dermatitis (3 cases each), and allergic dermatitis (2 cases). There was one case each of dyspepsia, enteritis, gastritis, bronchitis, and rhinitis. None of these were reported as grade 3 in intensity (preventing normal everyday activities).

One subject in Group 1 reported a serious adverse event, with onset 39 days post-vaccination. This subject was hospitalized for fever, vomiting and diarrhea. The events resolved after seven days.

7.1.4.10 Comments and Conclusions

In this study, 92 subjects previously primed with Hiberix (N = 64) or ActHIB (N = 28) at 3, 4.5, and 6 months of age received a booster dose with Hiberix administered concomitantly with Infanrix and OPV. Subjects enrolled at one of the study sites were excluded from analyses because of suspected fraud in data collection at that site. In the study report submitted with the BLA, GSK did not raise concerns about the integrity of the data from the other study sites.

Of the 60 subjects included in the ATP analyses of immunogenicity, 90-95% of subjects had a minimum protective anti-PRP level (i.e., anti-PRP $\geq$0.15 mcg/ml) prior to booster vaccination at approximately 17 months of age. Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix. Prior to booster vaccination, approximately 60-80% of subjects had an anti-PRP level <1 mcg/ml; all achieved this level after a booster dose of Hiberix. Anti-PRP GMCs increased approximately 100-fold from pre- to post-vaccination, regardless of priming vaccine.

The sponsor submitted data on the immune responses to Infanrix (following priming with Pediarix) administered concomitantly with a booster dose of Hiberix. The data suggest robust booster responses to the pertussis antigens contained in Infanrix, as evidenced by the pre- to post-vaccination GMTs and booster response rates. However, the definitions used for pertussis booster response were not evaluated by CBER for appropriateness, taking into consideration the assays used. Most subjects had seroprotective levels of tetanus and diphtheria antibody prior to vaccination and analyses of tetanus and diphtheria booster responses were not provided. The data provided on the immune responses to Infanrix raise no concerns, but are not sufficient to make claims of non-interference in diphtheria, tetanus or pertussis immune responses when Infanrix is administered concomitantly with Hiberix.

The most commonly reported solicited adverse event following booster vaccination with Hiberix was injection site redness, which was reported in approximately 40% of subjects. Other commonly reported solicited adverse events were injection site pain, swelling, fever $\geq$38.0^{o}C, loss of appetite, unusual crying, and sleeping less than usual (approximately 10-30% of subjects, depending on symptom). Local injection site swelling or redness >20 mm and other solicited events of Grade 3 in intensity (prevented everyday activities) were reported uncommonly.

7.1.5 Trial # 5

7.1.5.1 Applicant's Protocol # and Protocol Title

217744/010 (DTPa-HBV-IPV-010): Open clinical study to evaluate the immunogenicity and reactogenicity of SmithKline Beecham Biologicals' DTPa-HBV-IPV vaccine, co-administered with SmithKline Beecham Biologicals' Hib vaccine as two separate injections and given as a booster vaccination at the age of 15 to 18 months to healthy children, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine and a commercially available Hib vaccine.

7.1.5.2 Primary Objective/Rationale

The primary objective of the study was to evaluate the persistence of antibodies to all vaccine antigens contained in Pediarix approximately one year after the primary vaccination course.

7.1.5.3 Design Overview

Study DTPa-HBV-IPV-010 was an open study with one group.

7.1.5.4 Population

In a previous study, Study DTPa-HBV-IPV-004, 50 subjects received a primary vaccination course of Pediarix co-administered with ActHIB as two separate injections in opposite limbs at 2, 4 and 6 months of age. Subjects from Study DTPa-HBV-IPV-004 were eligible for enrollment in Study DTPa-HBV-IPV-010 according to the following criteria.

Inclusion Criteria

- Subjects must have participated in Study DTPa-HBV-IPV-004 and have received three doses of Pediarix.
- Age: between 15 and 18 months of age at the time of booster vaccination.
- Good clinical condition as determined by the investigator.
- Written informed consent obtained from the parents/guardians.

Exclusion Criteria

- History of allergic disease likely to be stimulated by the vaccination, including allergic reactions to neomycin, streptomycin and polymyxin B.
- Previous diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenza* type b booster vaccination or disease.
- History of any significant, persisting hematologic, hepatic, renal, cardiac, or respiratory disease.
- History of convulsions, epilepsy or other signs of central nervous system disease.
- Acute febrile illness at the time of planned vaccination.
- Immunosuppressive therapy (with the exception of topical corticosteroids).
- Any suspected or confirmed immune disorder.
- Immunoglobulin therapy or administration of any blood product within the previous two months or during the study period.
- Any chronic drug therapy to be continued during the study with the exception of vitamins, minerals, other dietary supplements.
- Administration of an investigational or non-registered drug or vaccine during the study period or within 30 days prior to the start of the study.
- Simultaneous administration of a vaccine not foreseen by the study protocol.
- Any of the following events after previous DTP vaccine
  - Fever ≥ 40.5°C (rectal temperature) within 48 hours after vaccination
  - Seizures
  - Encephalopathy
  - Hypersensitivity reaction.

Concomitant administration of non-study vaccines was not permitted.

7.1.5.5 Products Mandated by the Protocol

Hiberix, administered as a separate injection, was given intramuscularly into the left deltoid. Hiberix lot Hib 008 A44 was used. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

Pediarix, administered as a separate injection, was given intramuscularly into the right deltoid. Pediarix lot DTPa-HBV-IPV 21701 A2 was used. Each 0.5 ml dose of Pediarix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin	8 mcg
Diphtheria toxoid	-b(4)- IU
Tetanus toxoid	-b(4)- IU
Hepatitis B surface antigen	10 mcg
Poliovirus type 1 (Mahoney)	40 D antigen units
Poliovirus type 2 (MEF-1)	8 D antigen units
Poliovirus type 2 (Saukett)	32 D antigen units

7.1.5.6 Endpoints

Endpoints specified in the protocol included GMTs of antibodies to all vaccine antigens pre- and post-vaccination, anti-HbsAg ≥10 IU/ml, vaccine response to pertussis antigens, anti-tetanus and anti-diphtheria levels ≥0.1 IU/ml, and anti-poliovirus antibodies ≥1:8. None of the endpoints were

specifically classified as primary endpoints. There were no pre-defined acceptance criteria for any study endpoints.

7.1.5.7 Surveillance/Monitoring

7.1.5.7.1 Immunogenicity Monitoring

The protocol specified that the prevaccination blood sample (2 ml) be obtained at the first visit. Blood samples taken for other purposes up to 7 days before visit 1 were analyzed as pre-vaccination samples when appropriate in terms of volume, serum separation and storage conditions. The interval between visits 1 and 2 specified in the protocol was 30 to 35 days. However, the interval for inclusion in the immunogenicity analysis was expanded to 21 to 42 days. The volume of the post-vaccination blood sample was specified as a minimum of 2 ml.

Serum samples were tested by GSK for antibodies to PRP using a --b(4)--. Serum samples were also tested for antibodies to the antigens contained in Pediarix. Since Pediarix is not approved in the U.S. for a fourth consecutive dose, the data on immune responses to Pediarix will not be presented in this review.

7.1.5.7.2 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 15 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record rectal body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and general events (fever, unusual crying lasting more than one hour, vomiting, diarrhea, loss of appetite, and restlessness). Parents/guardians were instructed to return the completed diary card at the one-month post-vaccination visit and to contact the investigator for any signs or symptoms perceived as severe.
- Twenty-four hours after vaccination, a research nurse visited the subjects at home. The nurse examined the child and interviewed the parents/guardians for assessment of adverse events. Additional calls on subsequent days were made until signs/symptoms resolved.
- Information on unsolicited adverse events through one month post-vaccination was obtained at the second study visit.

7.1.5.8 Statistical Considerations

7.1.5.8.1 Sample Size/Statistical Power

The target sample size was 30 evaluable subjects out of the 50 subjects who had previously participated in Study DTPa-HBV-IPV-004.

7.1.5.8.2 Study Cohorts Analyzed

The protocol specified that both per-protocol and intent-to-treat analyses of immunogenicity would be performed. The per-protocol immunogenicity cohort was defined as “subjects corresponding to criteria defined in the protocol”. The protocol specified that the intent-to-treat immunogenicity analyses “will include all data available from all subjects except those eliminated from reactogenicity analysis”.

7.1.5.8.3 Statistical Analyses

The percentage of subjects with anti-PRP levels $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml and the corresponding 95% confidence intervals were calculated. In addition, anti-PRP GMCs with 95%

confidence intervals were calculated. For antibody GMT calculations, antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off value.

Although the protocol-defined window for collection of post-vaccination blood samples was 30-35 days post-vaccination, the actual interval for inclusion in the immunogenicity analyses was expanded to 21 to 42 days.

The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.5.9 Results

7.1.5.9.1 Populations Enrolled/Analyzed

The study was conducted at one site in Canada. The study began September 5, 1995 and was completed November 23, 1995. Forty-three of the 50 subjects who had previously received three doses of Pediarix and ActHIB in Study DTPa-HBV-IPV-004 were enrolled in Study DTPa-HBV-IPV-010. All 43 enrolled subjects were included in the analyses of reactogenicity. One subject was excluded from the ATP analysis of immunogenicity because of non-compliance with the blood sampling schedule. Forty-two of the 43 enrolled subjects completed Study DTPa-HBV-IPV-010. There was one drop out due to consent withdrawal.

7.1.5.9.2 Subject Demographics

Of the 43 subjects enrolled, 24 (55.8%) were female. The mean age of subjects at the time of booster vaccination was 16.9 months (range 16-18 months). Information on race/ethnicity was not provided.

7.1.5.9.3 Immunogenicity Outcomes

Table 31 presents ATP analyses of anti-PRP seroprotection rates and GMCs prior to and approximately one month after receipt of Hiberix at 16-18 months of age in Study DTPa-HBV-IPV-010. Subjects had previously received three doses of ActHIB at 2, 4, and 6 months of age. Results of intent-to-treat analyses of anti-PRP seroprotection rates and GMTs were similar to those for the ATP analyses.

Table 31. Study DTPa-HBV-IPV-010 Anti-PRP seroprotection rates and GMCs prior to and month after receipt of Hiberix at 16-18 months of age in subjects previously vaccinated with ActHIB at 2, 4, and 6 months of age, ATP analysis of immunogenicity

Timing	N	≥0.15 mcg/ml		95% CI		≥1.0 mcg/ml		95% CI		GMC (mcg/ml)	95% CI	
		n	%	LL	UL	n	%	LL	UL		LL	UL
Pre	42	32	76.2	60.5	87.9	15	35.7	21.6	52.0	0.46	0.31	0.68
Post	42	42	100.0	91.6	100	41	97.6	87.4	99.9	59.07	35.94	97.07

Subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK) administered as a fourth consecutive dose. In the U.S., Pediarix is approved for use as a 3-dose primary series.
ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur.
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = total number of subjects
n = number of subjects within given range
95% CI, LL and UL = 95% Confidence Interval, Lower and Upper limits
Source: m 5.3.5.4.3 dtpa-hbv-ipv-010-report-body.pdf, page 26 and m 2.7.3 summary-clin-efficacy-hib-immunization.pdf, page 30

7.1.5.9.4 Safety Outcomes

7.1.5.9.4.1 Solicited Adverse Events

Table 32 presents the incidence of solicited local reactions (Hiberix injection site) and selected solicited general events that occurred in the 4-day period (Day 0 to 3) following vaccination with Hiberix administered concomitantly with Pediarix.

Table 32. Study DTPa-HBV-IPV-010 Incidence of solicited local reactions at the Hiberix injection site and selected solicited general symptoms that occurred in the 4-day period (Day 0 to 3) following receipt of Hiberix and Pediarix, total vaccinated cohort

		N = 43		
Symptom	Intensity	n	%	(95% CI)
Local reactions at Hiberix injection site				
Pain	Any	13	30.2	(17.2, 46.1)
	Grade 3*	0	0.0	(0.0, 8.2)
Redness	Any	1	2.3	(0.1, 12.3)
	>20 mm	1	2.3	(0.1, 12.3)
	>30 mm	1	2.3	(0.1, 12.3)
	>40 mm	0	0.0	(0.0, 8.2)
Swelling	Any	4	9.3	(2.6, 22.1)
	>20 mm	3	7.0	(1.5, 19.1)
	>40 mm	0	0.0	(0.0, 8.2)
General events				
Fever	≥38.0°C**	7	16.3	(6.8, 30.7)
	>39.5°C**	1	2.3	(0.1, 12.3)
Loss of appetite	Any	17	39.5	(25.0, 55.6)
	Grade 3*	0	0.0	(0.0, 8.2)
Unusual crying	Any	6	14.0	(5.3, 27.9)
	Grade 3*	0	0.0	(0.0, 8.2)
Restlessness	Any Grade 3*	23	53.5	(37.7, 68.8)
		2	4.7	(0.6, 15.8)

Subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK) administered as a fourth consecutive dose. In the U.S., Pediarix is approved for use as a 3-dose primary series.
All vaccinated subjects had solicited symptom follow-up documented. The total vaccinated cohort is the same as the ATP cohort for safety
N = number of symptom sheets returned
n = total number of documented doses followed by the specific symptom
*Grade 3 prevents normal, everyday activities
**Rectal temperatures
Source: m 5.3.5.4.3 dtpa-hbv-ipv-010-report-body.pdf, pages 28-29 and m 2.7.4 Summary of Clinical Safety, pages 34-37

7.1.5.9.4.2 Unsolicited Adverse Events

There were 24 reports of unsolicited symptoms in 13 subjects; none were considered severe. The most frequently reported unsolicited symptom was injection site reaction (8 reports). These were all cases of redness and swelling which had begun during the four day follow-up period but had not resolved within that period, except one case of bruising around the injection site. Other unsolicited events included three reports of upper respiratory tract infection, two reports of

nervousness, two reports of anorexia, and one report each of fatigue, fever, diarrhea, somnolence, and otitis media.

No serious adverse events were reported during the course of the study.

7.1.5.10 Comments and Conclusions

Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix in subjects previously primed with three doses of ActHIB. Twenty-six of 27 subjects who had an anti-PRP level <1 mcg/ml prior to booster vaccination, achieved this level following a booster dose with Hiberix. Anti-PRP GMCs increased 128-fold from pre- to post-vaccination.

Injection site pain was reported commonly after receipt of Hiberix (30% of subjects). Solicited general adverse events of restlessness and loss of appetite were reported in approximately 50% and 40% of subjects, respectively; fever and unusual crying were each reported in approximately 15% of subjects. Subjects in this study received a fourth consecutive dose of Pediarix concomitantly with Hiberix. In the U.S., Pediarix is approved for use as a three dose primary series, but is not approved for booster vaccination. From this study, is not possible to draw conclusions about potential attribution of general adverse events to either Hiberix or Pediarix.

7.1.6 Trial # 6

7.1.6.1 Applicant's Protocol # and Protocol Title

217744/035 (DTPa-HBV-IPV-035): A phase II randomized booster vaccination study of one dose of SB Biologicals' DTPa-HBV-IPV vaccine, co-administered with two formulations of SB Biologicals' Hib conjugate vaccine, either mixed in one syringe or injected simultaneously in two concomitant injections into opposite limbs at the same visit, in healthy children who previously participated in Study 217744/011 (DTPa-HBV-IPV- 011) or Groups 1, *2* and 3 of Study 217744/016 (DTPa-HBV-IPV-016).

7.1.6.2 Primary Objective/Rationale

The primary objective of the study was to evaluate and compare the safety and reactogenicity of Pediarix mixed with two formulations of GSK's Haemophilus b Conjugate Vaccine.

7.1.6.3 Design Overview

Study DTPa-HBV-IPV-035 was a randomized, parallel group, multi-site booster study with 4 groups with unbalanced allocation (5:5:1:1). Blood samples were taken prior to and one month after the booster dose in a randomized subset of subjects (1:1:1:1). The study was performed in a double-blind manner for the two Haemophilus b Conjugate Vaccine formulations. The study groups were as follows:
Group 1: DTPa-HBV-IPV/Hib (formulation B);
Group 2: DTPa-HBV-IPV/Hib (formulation A);
Group 3: DTPa-HBV-IPV + Hib (formulation A);
Group 4: DTPa-HBV-IPV + Hib (formulation B)

As per agreement between CBER and GSK, the Hiberix BLA includes results only for Group 3, as the data for the other study groups were not considered as contributing substantially to the evaluation of Hiberix intended for licensure in the U.S.

7.1.6.4 Population

The study was conducted at 70 sites in Germany. Healthy children were eligible for enrollment in the study according to the following criteria.

Inclusion Criteria

- Between 13 and 24 months of age at the time of the booster vaccination.
- Free of obvious health problems as established by physical exam before entering into the study.
- Previously participated in Study 217744/011 (DTPa-HBV-IPV-011) or Groups 1, 2 and 3 of Study 217744/016 (DTPa-HBV-IPV-016) and completed the three-dose primary vaccination course.
- Written informed consent obtained from parents/guardians of the child.

Exclusion Criteria

- Use of any investigational or non-registered drug or vaccine other than study vaccines during the study period or within 30 days prior to booster vaccination in the study.
- Chronic immunosuppressive therapy (with the exception of topical corticosteroids).
- Administration of a non-protocol vaccine during the period starting one week before the study vaccine dose and ending 30 days after.
- Previous booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenzae* type b.
- Intercurrent diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenzae* type b disease.
- Any suspected or confirmed immunosuppressive or immunodeficient disorder.
- History of allergic disease likely to be exacerbated by any component of the vaccine, including allergic reactions to neomycin and polymyxin B.
- Major congenital defects or serious chronic illness.
- Progressive neurological disease.
- Acute febrile illness at the time of planned vaccination.
- Administration of immunoglobulins and/or any blood product within the previous two months or during the study period.
- One of the following events after previous DTP vaccine
  - Fever ≥ 40.5°C (rectal temperature) within 48 hours after vaccination
  - Seizures
  - Encephalopathy
  - Hypersensitivity reaction.

Concomitant administration of non-study vaccines was not permitted.

7.1.6.5 Products Mandated by the Protocol

Vaccines received by subjects in Study Group 3 were Hiberix (Formulation A) and Pediarix.

Hiberix (Formulation A), administered as a separate injection in Study Group 3, was given intramuscularly into the right anterolateral thigh. Hiberix (Formulation A) lot Hib087A47/M was used. Each 0.5 ml dose of Hiberix (Formulation A) contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

Pediarix, administered as a separate injection in Study Group 3, was given intramuscularly into the left anterolateral thigh. Pediarix lot D21724A2 was used. The formulation of Pediarix used in this study is the same as that licensed in the U.S. except that it also contained 2-phenoxyethanol. Each 0.5 ml dose of Pediarix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin	8 mcg
Diphtheria toxoid	-b(4)- (25 Lf)
Tetanus toxoid	-b(4)- (10 Lf)
Hepatitis B surface antigen	10 mcg
Poliovirus type 1 (Mahoney)	40 D antigen units
Poliovirus type 2 (MEF-1)	8 D antigen units
Poliovirus type 2 (Saukett)	32 D antigen units
Aluminum	0.7 mg
Phenoxyethanol	2.5 mg

7.1.6.6 Endpoints

The protocol-specified primary and secondary endpoints relevant to the evaluation of booster vaccination with Hiberix were stated as follows:

7.1.6.6.1 Primary Endpoint

- Occurrence, nature and relationship to vaccination of solicited symptoms

7.1.6.6.2 Secondary Endpoints

- Occurrence of any local symptoms within 4 days after vaccination
- Occurrence of any general symptoms within 4 days after vaccination
- Occurrence of any symptoms within 4 days after vaccination
- Occurrence of unsolicited symptoms within 30 days after vaccination
- Occurrence of serious adverse events throughout the entire study up to and including 30 days post-vaccination
- Anti-PRP antibody concentrations before and one month after a booster dose of Hiberix
- Percent of subjects with anti-PRP $\geq$ 0.15 mcg/ml and $\geq$ 1.0 mcg/ml before and one month after a booster dose of Hiberix

There were no pre-defined acceptance criteria for any study endpoints.

Additional secondary endpoints that pertained to the evaluation of immune responses to a booster dose of Pediarix or a booster dose of Pediarix mixed with GSK's Haemophilus b Conjugate Vaccine in the same syringe are not presented in this review. In the U.S., Pediarix is licensed for use as a three-dose primary series, but is not licensed for a fourth consecutive (booster) dose.

7.1.6.7 Surveillance/Monitoring

7.1.6.7.1 Immunogenicity Monitoring

The protocol specified that pre- and post-vaccination blood samples (3 ml) would be obtained from a subset of subjects. Blood samples taken for other purposes up to 7 days before visit 1 were analyzed as pre-vaccination samples when appropriate in terms of volume, serum separation and storage conditions. The interval between visits 1 and 2 specified in the protocol was 30 to 35 days. However, the interval for inclusion in the ATP immunogenicity analysis was expanded to 21 to 42 days.

Serum samples were tested for antibodies to PRP using an -b(4)--- at the laboratory of -----b(4)----------. Serum samples were also tested for antibodies to the antigens contained in Pediarix, but those results will not be presented in this review.

7.1.6.7.2 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 15 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record rectal body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and general events (fever, fussiness/irritability, vomiting, diarrhea, restlessness/sleeping less than usual, loss of appetite, and sleepiness). Parents/guardians were instructed to take temperatures rectally, but if another route was used, the route was to be recorded. Parents/guardians were instructed to return the completed diary card at the post-vaccination visit and to contact the investigator for any signs or symptoms perceived as severe.
- Information on unsolicited adverse events through one month post-vaccination was obtained at the second study visit.

7.1.6.8 Statistical Considerations

7.1.6.8.1 Sample Size/Statistical Power

The protocol indicated that the target sample size was a total of 2,400 evaluable subjects, randomized 5:5:1:1 (thus, 200 evaluable subjects targeted for Group 3). The target sample size was determined based on statistical power to detect differences in rates of specified adverse events between Study Groups 1 and 2 (irrelevant to this review).

7.1.6.8.2 Study Cohorts Analyzed

Although subjects from two previous primary immunization studies, Study DTPa-HBV-IPV-011 and Study DTPa-HBV-IPV-016 may have been eligible for enrollment in Study DTPa-HBV-IPV-035, a protocol amendment specified that an interim analysis would be performed and limited to subjects primed in Study DTPa-HBV-IPV-011 and having completed the booster vaccination before January 1, 1999. The Hiberix BLA included the interim study report that was limited to these subjects.

Subject cohorts analyzed were as follows:
ATP cohort for reactogenicity analysis: This included all subjects
• who have received at least one dose of study vaccine according to randomization
• with sufficient data to perform an analysis of safety
• for whom the administration site of study vaccine is known
• who have not received a vaccine not specified or forbidden in the protocol

ATP cohort for post-booster immunogenicity analysis**:** The protocol-defined cohort for analysis of post-booster immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, and fulfilling requirements for analysis) for whom data concerning immunogenicity were available. This included subjects for whom assay results were available for antibodies against at least one study vaccine antigen component at, at least, one blood-sampling time point.

***ITT cohort for reactogenicity analysis*:** This included all subjects enrolled in the study for whom reactogenicity data were available.

***ITT cohort for immunogenicity analysis*:** This included all subjects enrolled in the study for whom immunogenicity data were available.

The protocol specified that the primary analyses would be based on the ATP cohorts.

7.1.6.8.3 Statistical Analyses

All analyses of safety and immunogenicity presented in the interim study report submitted in the Hiberix BLA were descriptive.

For anti-PRP GMC calculations, antibody concentrations below the cut-off of the assay were given an arbitrary value of half the cut-off value.

Although the protocol-defined window for collection of post-vaccination blood samples was 28-35 days post-vaccination, the actual interval for inclusion in the immunogenicity analyses was expanded to 21 to 42 days.

7.1.6.9 Results

7.1.6.9.1 Populations Enrolled/Analyzed

The study began December 22, 1997. The date of the last visit for the interim analysis was December 31, 1998. A total of 1701 subjects (all study groups) who were enrolled from 70 study sites in Germany were included in the interim analysis. Of these, 150 subjects were randomized to Study Group 3. Of the Group 3 subjects, 149 completed the study and one was lost to follow-up. The number of Group 3 subjects eligible for interim analysis is presented in Table 33.

Table 33. Study DTPa-HBV-IPV-035 Eligibility for interim analysis, Study Group 3

Number of subjects available for interim analysis (Total cohort)	150
Administration of vaccine(s) forbidden in the protocol Randomization failure Essential data missing	2 2 1
Number of subjects in the protocol defined analysis of safety	145
Protocol violation (vaccinated outside of analysis age range 12-25 months) Non compliance with blood sampling schedule Essential serological data missing Subject not planned to be bled for serological analysis	1 4 7 77
Number of subjects in the protocol defined analysis of immunogenicity	56

Group 3 subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK). In this study, Pediarix was administered following either three previous doses of Pediarix or three previous doses of Infanrix (DTaP, GSK) + oral poliovirus vaccine. In the U.S., Pediarix is approved for use as a 3-dose primary series.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-035-report-body.pdf, page 36

7.1.6.9.2 Subject Demographics

Of the 150 subjects enrolled in Group 3, 78 (52%) were female. The mean age at the booster dose was 15.9 months (range 11-24 months). One subject was 11 months of age, 51 subjects were 12-14 months of age, 74 subjects were 15-18 months of age, and 24 subjects were 19-24 months of

age. Race was reported as White for 144 (96%) subjects, Oriental for 4 (2.7%) subjects, Black for 1 subject, and Other for 1 subject.

7.1.6.9.3 Primary Vaccination

Subjects in Study DTPa-HBV-IPV-035 were primed with one of five different vaccine combinations in study DTPa-HBV-IPV-011. Primary Study Groups 1 to 4 received Pediarix co-administered with a commercially available Haemophilus b Conjugate Vaccine from one of four different manufacturers in separate injections, while Primary Study Group 5 was primed with separate administration of Infanrix + ActHIB + OPV. In Study DTPa-HBV-IPV-011, the priming vaccine doses were administered at 3, 4, and 5 months of age.

Redistribution of the subjects from the primary study DTPa-HBV-IPV-011 into booster study groups are presented in Tables 34 and 35 for the ITT analyses of safety and the ATP analyses of immunogenicity, respectively.

Table 34. Study DTPa-HBV-IPV-035 Group 3 study cohort composition according to primary immunization (ITT cohort)

DTPa-HBV-IPV-011 primary study (N = 1701)	Study DTPa-HBV-IPV-035 – Booster phase *Group 3* Pediarix + Hiberix N = 150
Group 1 Pediarix + Hiberix n=322	n=26
Group 2 Pediarix + ActHIB n=315	n=27
Group 3 Pediarix + HibTITER n=316	n=31
Group 4 Pediarix + PedvaxHIB n=346	n=26
Group 5 Infanrix + OPV + ActHIB n=402	n=40

Group 3 subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK). In this study, Pediarix was administered following either three previous doses of Pediarix or three previous doses of Infanrix (DTaP, GSK) + OPV. In the U.S., Pediarix is approved for use as a 3-dose primary series.
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc..
PedvaxHIB: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co., Inc.
OPV: Oral poliovirus vaccine (no longer licensed in the U.S.)
Source: m 5.3.5.4.3 dtpa-hbv-ipv-035-report-body.pdf, page 52

Table 35. Study DTPa-HBV-IPV-035 Group 3 study cohort composition according to primary immunization (ATP immunogenicity cohort)

DTPa-HBV-IPV-011 primary study	Study DTPa-HBV-IPV-035 – Booster phase *Group 3* Pediarix + Hiberix N = 56
Group 1 Pediarix + Hiberix n=41	n=9
Group 2 Pediarix + ActHIB n=39	n=9
Group 3 Pediarix + HibTITER n=39	n=11
Group 4 Pediarix + PedvaxHIB n=44	n=9
Group 5 Infanrix + OPV + ActHIB n=80	n=18

Group 3 subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV). In this study, Pediarix was administered following either three previous doses of Pediarix or three previous doses of Infanrix (DTaP, GSK) + OPV. In the U.S., Pediarix is approved for use as a 3-dose primary series.
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
PedvaxHIB: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co., Inc.
OPV: Oral poliovirus vaccine (no longer licensed in the U.S.)
Source: m 5.3.5.4.3 dtpa-hbv-ipv-035-report-body.pdf, page 38

7.1.6.9.4 Immunogenicity Outcomes

Table 36 presents ATP analyses of anti-PRP seroprotection rates and GMCs prior to and one month after receipt of Hiberix administered as a booster dose concomitantly with Pediarix in Study DTPa-HBV-IPV-035. Subjects had previously received a primary series with one of four Haemophilus b Conjugate Vaccines and either Pediarix or Infanrix + OPV, as shown in Table 35. The results presented in Table 36 are for all priming groups combined. Of the two subjects who did not have an anti-PRP level $\geq$1.0 mcg/ml following booster vaccination with Hiberix, one had been primed with Hiberix and one had been primed with ActHIB. Results of ITT analyses of anti-PRP seroprotection rates and GMCs were similar to those obtained for the ATP analyses.

Table 36. Study DTPa-HBV-IPV-035 Anti-PRP seroprotection rates and GMCs prior to and month after receipt of Hiberix as a booster dose in subjects previously vaccinated with Haemophilus b Conjugate Vaccine at 3, 4 and 5 months of age[1], Study Group 3, ATP analysis of immunogenicity

Timing	N	≥0.15 mcg/ml		95% CI		≥1.0 mcg/ml		95% CI		GMC (mcg/ml)	95% CI	
		n	%	LL	UL	n	%	LL	UL		LL	UL
Pre	56	54	96.4	87.7	99.6	29	51.8	38.0	65.3	1.189	0.882	1.603
Post	56	56	100.0	93.6	100	54	96.4	87.7	99.6	53.642	35.730	80.533

[1]Priming Haemophilus b Conjugate Vaccines included: Hiberix (n=9); ActHIB (Tetanus Toxoid Conjugate), Sanofi Pasteur (n=27); HibTITER (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc. (n=11); and PedvaxHIB (Meningococcal Protein Conjugate), Merck & Co. (n=9). Priming doses of PedvaxHIB were administered at 3 and 5 months of age.
Group 3 subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK). In this study, Pediarix was administered following either three previous doses of Pediarix or three previous doses of Infanrix (DTaP, GSK) + oral poliovirus vaccine. In the U.S., Pediarix is approved for use as a 3-dose primary series.
Pre = pre-booster vaccination, Post = approximately one month after the booster dose
N = total number of subjects
n = number of subjects within given range
95% CI, LL and UL = 95% Confidence Interval, Lower and Upper limits
Source: m 5.3.5.4.3 dtpa-hbv-ipv-035-report-body.pdf, page 48

7.1.6.9.5 Safety Outcomes

7.1.6.9.5.1 Solicited Adverse Events

Table 37 presents the incidence of solicited local reactions (Hiberix injection site) and selected solicited general events that occurred in the 4-day period (Day 0 to 3) following vaccination for subjects in Study Group 3. Analyses of solicited events for Study Group 3, stratified by priming vaccine—Hiberix, ActHIB, PedvaxHIB, or HibTITER, were also provided in the BLA. However, the numbers of subjects per priming group were too small to draw conclusions about comparative reactogenicity of Hiberix in subjects primed with different vaccines.

Table 37. Study DTPa-HBV-IPV-035 Incidence of solicited local reactions at the Hiberix injection site and selected solicited general symptoms that occurred in the 4-day period (Day 0 to 3) following receipt of Hiberix and Pediarix, Study Group 3, total vaccinated cohort

		N = 148-150	
Symptom	Intensity	n	% (95% CI)
Local reactions at Hiberix injection site			
Pain	Any	47	31.8 (24.4, 39.9)
	Grade 3*	7	4.7 (1.9, 9.5)
Redness	Any	56	37.8 (30.0, 46.2)
	>20 mm	10	6.8 (3.3, 12.1)
Swelling	Any	35	23.6 (17.1, 31.3)
	>20 mm	6	4.1 (1.5, 8.6)
General events			
Fever*	≥38.0°C	64	42.7 (34.6, 51.0)
	>38.5 °C	24	16.0 (10.5, 22.9)
	>39.0°C	13	8.7 (4.7, 14.4)
	>39.5°C	4	2.7 (0.7, 6.7)
	>40.0 °C	0	0.0 (0.0, 2.4)
Fussiness	Any	57	38.0 (30.2, 46.3)
	Grade 3	4	2.7 (0.7, 6.7)
Loss of appetite	Any	44	29.3 (22.2, 37.3)
	Grade 3	1	0.7 (0.0, 3.7)
Sleeping more than usual	Any	31	20.7 (14.5, 28.0)
	Grade 3	0	0.0 (0.0, 2.4)
Restlessness	Any Grade 3	30	20.0 (13.9, 27.3)
		2	1.3 (0.2, 4.7)

Group 3 subjects received a booster dose of Hiberix concomitantly with Pediarix (DTaP-HBV-IPV, GSK). In this study, Pediarix was administered following either three previous doses of Pediarix or three previous doses of Infanrix (DTaP, GSK) + oral poliovirus vaccine. In the U.S., Pediarix is approved for use as a 3-dose primary series.
N = number of subjects vaccinated
n = total number of documented doses followed by the specific symptom
*Rectal temperatures or 0.5°C added to axillary, oral, or tympanic temperatures
Grade 3 pain = cried when limb was moved; Grade 3 fussiness = persistent crying and could not be comforted; Grade 3 for other symptoms = preventing normal daily activities
Source: m 5.3.5.4.3 dtpa-hbv-ipv-035 addendum.pdf, pages 5-8

7.1.6.9.5.2 Unsolicited Adverse Events

Of the 150 subjects in Study Group 3, 61 reported at least one unsolicited adverse event within the 31 day period post-vaccination. The most frequently reported event was bronchitis (14 reports), followed by pyrexia and otitis media (7 reports each). One unsolicited event, a viral infection (not further specified) was considered Grade 3 in intensity (i.e., prevented normal everyday activities). No serious adverse events were reported in Study Group 3 subjects.

7.1.6.10 Comments and Conclusions

Of the 56 subjects evaluated prior to booster vaccination, 96.4% had an anti-PRP level ≥0.15 mcg/ml and 51.8% had an anti-PRP level ≥1.0 mcg/ml. Despite the lack of pre-defined acceptance criteria, the data demonstrate a robust immune response to a booster dose of Hiberix in subjects previously primed with Haemophilus b Conjugate Vaccine (either Hiberix or vaccines

from other manufacturers, including ActHIB and PedvaxHIB, both of which are licensed in the U.S.). Following booster vaccination with Hiberix, 96.4% of subjects had an anti-PRP level ≥1.0 mcg/ml. Anti-PRP GMCs increased 45-fold from pre- to post-vaccination.

Injection site reactions were reported commonly after receipt of Hiberix (approximately 20-40% of subjects, depending on reaction). Solicited general adverse events were also reported commonly following receipt of Hiberix administered concomitantly with Pediarix (approximately 20-40% of subjects, depending on event). In the U.S., Pediarix is approved for use as a three dose primary series, but is not approved for booster vaccination. From this study, it is not possible to draw conclusions about potential attribution of general adverse events to either Hiberix or Pediarix.

7.1.7 Trial # 7

7.1.7.1 Applicant's Protocol # and Protocol Title

217744/028 (DTPa-HBV-IPV-028): Open clinical study to assess the safety and reactogenicity of SB Biologicals DTPa vaccine, co-administered with commercial Hib vaccine into opposite limbs, as compared to SB Biologicals' DTPa vaccine mixed with SB Biologicals' Hib vaccine, to SB Biologicals' DTPa-IPV vaccine mixed with SB Biologicals' Hib vaccine, and to SB Biologicals' DTPa-HBV-IPV vaccine co-administered with SB Biologicals' Hib vaccine into opposite limbs, when given as a booster dose to healthy children in their second year of life, previously primed with three doses of SB Biologicals' DTPa-HBV-IPV vaccine.

7.1.7.2 Primary Objective/Rationale

The original objective in the study protocol was to assess and compare the safety and reactogenicity of the four booster vaccination regimens. Prior to analysis the primary objective was modified as follows: to demonstrate that Pediarix co-administered in separate injections with Hiberix is not clinically significantly more reactogenic than Infanrix, HibTITER, and OPV in terms of grade 3 solicited symptoms.

7.1.7.3 Design Overview

Study DTPa-HBV-IPV-028 was an open, randomized, multi-site booster study with 4 parallel groups with unbalanced allocation (1:3:2:2). The study groups were as follows:
Group 1 (control): Infanrix + HibTITER (separate injections) + OPV;
Group 2: GSK's DTPa/Hib (single injection) + OPV;
Group 3: GSK's DTPa-IPV/Hib (single injection);
Group 4: Pediarix + Hiberix (separate injections)

As per agreement between CBER and GSK, the Hiberix BLA includes results only for Group 4, as the data for the other study groups were not considered as contributing substantially to the evaluation of Hiberix intended for licensure in the U.S.

7.1.7.4 Population

The study was conducted at 45 sites in Germany. Healthy children were eligible for enrollment according to the following criteria:

Inclusion Criteria

- Between 13 and 24 months of age at the time of booster vaccination.
- Free of obvious health problems as established by physical and clinical examination before entering into the study.
- Previously participated in Study 217744/011 (DTPa-HBV-IPV-011) and completed the three-dose primary vaccination course of Pediarix and Haemophilus b Conjugate Vaccine according to protocol.
- Absence of previous diphtheria, tetanus, pertussis, hepatitis B and/or polio booster vaccination or disease
- Written informed consent obtained from parents/guardians of the child.

Exclusion Criteria

- Allergic disease likely to be exacerbated by vaccination, including allergic reactions to neomycin and polymyxin B.
- Intercurrent diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenzae* type b disease.
- Acute febrile illness at the time of planned vaccination.
- Major congenital defects or serious chronic illness.
- Progressive neurological disease.
- Any suspected or confirmed immunosuppressive condition.
- Use of any investigational or non-registered drug or vaccine other than study vaccines during the study period or within 30 days prior to booster vaccination in the study.
- Simultaneous administration of a non-protocol vaccine at the same visit as the study vaccine.
- One of the following events after previous DTP vaccine
  - Fever ≥ 40.5°C (rectal temperature) or ≥ 40.0°C (axillary temperature) within 48 hours after vaccination
  - Seizures within 3 days after vaccination
  - Encephalopathy within 7 days after vaccination
  - Hypersensitivity reaction
  - Hypotonic-hyporesponsive episode within 48 hours after vaccination
  - Persistent inconsolable screaming or crying for more than 3 hours within 48 hours after vaccination.

7.1.7.5 Products Mandated by the Protocol

Vaccines received by subjects in Study Group 4 were Hiberix and Pediarix.

Hiberix, administered as a separate injection in Study Group 4, was given intramuscularly into the right anterolateral thigh. Hiberix lot Hib039A47/M1 was used. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

Pediarix, administered as a separate injection in Study Group 4, was given intramuscularly into the left anterolateral thigh. Pediarix lot 21708/C2 was used. The formulation of Pediarix used in

this study is the same as that licensed in the U.S. except that it also contained 2-phenoxyethanol. Each 0.5 ml dose of Pediarix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin	8 mcg
Diphtheria toxoid	-b(4)- IU (25 Lf)
Tetanus toxoid	-b(4)- IU (10 Lf)
Hepatitis B surface antigen	10 mcg
Poliovirus type 1 (Mahoney)	40 D antigen units
Poliovirus type 2 (MEF-1)	8 D antigen units
Poliovirus type 2 (Saukett)	32 D antigen units
Aluminum as salts	0.7 mg
Phenoxyethanol	2.5 mg

7.1.7.6 Endpoints

The protocol-specified primary and secondary endpoints relevant to the evaluation of booster vaccination with Hiberix were as follows:

7.1.7.6.1 Primary Endpoint

- Proportion of subjects reporting any solicited symptoms graded 3 in intensity during the 4 day follow-up period after vaccination.

7.1.7.6.2 Secondary Endpoints

- Proportions of subjects reporting any symptom (local or general, solicited or unsolicited) during the 4 day follow-up period after vaccination.
- Proportions of subjects reporting any local symptom (solicited or unsolicited) during the 4 day follow-up period after vaccination.
- Proportions of subjects reporting any general symptom (solicited or unsolicited) during the 4 day follow-up period after vaccination.
- Incidence of each solicited local symptom during the 4 day follow-up period after vaccination (any intensity and grade 3 intensity, respectively).
- Incidence of each solicited general symptom during the 4 day follow-up period after vaccination (any intensity, grade 3 intensity, and with probable or suspected relationship to vaccination, respectively).
- Incidence of unsolicited symptoms counted and classified by WHO preferred terms, during the 30 day follow-up period after the vaccination.

7.1.7.7 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 15 minutes following vaccination.
- On the day of vaccination, diary cards were distributed to the parents/guardians to record rectal body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period days 0 to 3 post-vaccination. Solicited events included injection site reactions (pain, redness, and swelling) and general events (fever, fussiness/irritability, vomiting, diarrhea, restlessness/sleeping less than usual, loss of appetite, and sleepiness). Parents/guardians were instructed to take temperatures rectally, but if another route was used, the route was to be recorded. Parents/guardians were instructed to return the completed diary card at the second visit (Day 30-35 post-vaccination) and to contact the investigator for any signs or symptoms perceived as severe.
- Information on unsolicited adverse events through one month post-vaccination was obtained at the second study visit.

7.1.7.8 Statistical Considerations

7.1.7.8.1 Treatment Allocation and Randomization

The booster regimen administered was determined by the primary vaccination course. In the primary vaccination study, DTPa-HBV-IPV-011, a total of 5600 subjects were planned for enrollment and randomly allocated to five study groups. Of these, 2400 subjects who received a primary vaccination course with Pediarix and Haemophilus b Conjugate Vaccine (groups 1 to 4 from the primary vaccination study) were eligible for enrollment in Study DTPa-HBV-IPV-028. Of the 2400 subjects who were eligible for enrollment, 600 were randomized to Study Group 4, as shown in Table 38.

Table 38. Study DTPa-HBV-IPV-028 Subjects randomized to Study Group 4, according to vaccine priming history

Primary Vaccination	Booster Vaccination Study DTPa-HBV-IPV-028
Study DTPa-HBV-IPV-011	*Group 4:* Pediarix + Hiberix
Group 1 or 2: Pediarix + (Hiberix or ActHIB)	Subgroup 14 (n = 300)
Group 3 Pediarix + HibTITER	Subgroup 34 (n = 300)
Group 4: Pediarix + PedvaxHIB	—

In Study DTPa-HBV-IPV-028, Pediarix (DTaP-HBV-IPV, GSK) was administered as a fourth consecutive dose. In the U.S., Pediarix is approved for use as a 3-dose primary series.
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
PedvaxHIB: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co., Inc.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-028-report-body.pdf, page 26

7.1.7.8.2 Sample Size/Statistical Power

Of the overall 2400 subjects eligible for enrollment, the target sample size was 1600 subjects to be randomized 1:3:2:2 to Groups 1, 2, 3, and 4, respectively. Statistical power calculations were provided for analyses to detect differences in rates of specified adverse events between the four booster vaccination study groups (irrelevant to this review).

7.1.7.8.3 Study Cohorts Analyzed

Two subject cohorts were analyzed:
• ITT cohort: all subjects enrolled in this study for whom reactogenicity data were available.
• ATP cohort for analysis of reactogenicity: all subjects
- who had received the study vaccine(s) according to their random assignment,
- with sufficient data to perform reactogenicity analysis,
- who had not received a vaccine(s) not specified or forbidden in the protocol.

The ATP analysis was specified as primary.

7.1.7.8.4 Statistical Analyses

All analyses presented in the study report submitted in the Hiberix BLA were descriptive. The percentage of subjects reporting specific adverse events and the corresponding 95% confidence intervals were calculated.

7.1.7.9 Results

7.1.7.9.1 Populations Enrolled/Analyzed

The study period was April 29, 1997 through November 6, 1998. Overall (all four study groups), 1513 subjects were enrolled, including 375 subjects enrolled in Group 4. Of the 375 Group 4 subjects, 368 subjects completed the study and 7 subjects were lost to follow-up. There were no drop outs due to adverse events. The number of Group 4 subjects eligible for analysis is presented in Table 39.

Table 39. Study DTPa-HBV-IPV-028 Eligibility for analysis, Study Group 4

Number of subjects randomized	600
Target number of subjects for enrollment	400
Subject or vaccine number not allocated	225
Number of subjects enrolled	375
Administration of vaccine(s) forbidden in the protocol	1
Randomization failure	6
Did not complete primary vaccination according to primary study protocol	6
Essential data missing	3
Number of subjects included in the ATP analysis of reactogenicity	359

Study Group 4 received a booster dose of Hiberix administered concomitantly with a fourth consecutive dose of Pediarix (DTaP-HBV-IPV, GSK). In the U.S., Pediarix is approved for use as a 3-dose primary series.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-028-report-body.pdf, page 38

7.1.7.9.2 Subject Demographics

Of the 359 subjects in Group 4 included in the ATP analysis of reactogenicity, 193 (53.8%) were male. The mean age at the booster dose of Hiberix was 16.4 months (range 12-23 months). Race was reported as White for 337 (93.9%) subjects, Oriental for 12 (3.3%) subjects, Black for 5 subjects (1.4%) and Other for 5 (1.4%) subjects.

7.1.7.9.3 Primary Vaccination

The distribution of the participants in Study DTPa-HBV-IPV-028, Group 4 according to the primary vaccination groups is shown in Table 40.

Table 40. Study DTPa-HBV-IPV-028 Group 4 study cohort composition according to vaccine priming history

Primary Vaccination Study DTPa-HBV-IPV-011 (3, 4, 5 months)	Booster Vaccination Study DTPa-HBV-IPV-028 (12-28 months) *Group 4:* Pediarix + Hiberix
Group 1 or 2 Pediarix + (Hiberix or ActHIB)	n = 189‡ (subgroup 14)
Group 3 Pediarix + HibTITER	n = 186 (subgroup 34)
Group 4: Pediarix + PedvaxHIB	—

In Study DTPa-HBV-IPV-028, Study Group 4 subjects received a booster dose of Hiberix administered concomitantly with a fourth consecutive dose of Pediarix (DTaP-HBV-IPV, GSK). In the U.S., Pediarix is approved for use as a 3-dose primary series.
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
PedvaxHIB: Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co., Inc.
n: number of subjects enrolled
‡ Of the 189 subjects in subgroup 14, 92 subjects were primed with Hiberix and 97 subjects were primed with ActHIB in primary study DTPa-HBV-IPV-011
Source: m 5.3.5.4.3 dtpa-hbv-ipv-028-report-body.pdf, page 39

7.1.7.9.4 Compliance with Protocol Specified Procedures

Subjects identified with major protocol violations were eliminated from the ATP analysis as shown in Table 39. In addition, for two subjects in Group 4, the procedure for obtaining informed consent was not followed (form signed after vaccination or form for another study was signed). A total of 39 subjects in group 4 were not vaccinated according to the sites and sides specified in the protocol:

• 4 subjects were vaccinated in the deltoid instead of the thigh.
• 32 subjects were vaccinated in the buttock instead of the thigh.
• For 3 subjects vaccinated in the thigh, the sides specified in the protocol were not respected.

None of these subjects were eliminated from the ATP analysis.

None of the subjects were eliminated for not respecting the protocol specified age for booster vaccination, or the interval between visits 1 and 2. The mean duration of the follow-up period was 36 days, notable variability was observed. Twelve subjects in group 4 were followed for less then 28 days (the shortest period being 7 days).

7.1.7.9.5 Safety Outcomes

7.1.7.9.5.1 Solicited Adverse Events

Table 41 presents the incidence of solicited local reactions (Hiberix injection site) and selected solicited general events that occurred in the 4-day period (Day 0 to 3) following vaccination for subjects in Study Group 4. The study report also included analyses of solicited events for Study Group 4, stratified by priming vaccine—Hiberix, ActHIB, or HibTITER. There did not appear to be any consistent, clinically relevant differences in the occurrence of solicited adverse events following Hiberix based on priming vaccine.

Table 41. Study DTPa-HBV-IPV-028 Incidence of solicited local reactions at the Hiberix injection site and selected solicited general symptoms that occurred in the 4-day period (Day 0 to 3) following receipt of Hiberix and Pediarix, Study Group 4, total vaccinated cohort

Symptom	Intensity	N = 371			
		n	%	95% CI	
				LL	UL
Local reactions at Hiberix injection site					
Pain	Any	76	20.5	16.5	25.0
	Grade 3	4	1.1	0.3	2.7
Redness	Any	91	24.5	20.2	29.2
	>20 mm	9	2.4	1.1	4.6
Swelling	Any	55	14.8	11.4	18.9
	>20 mm	8	2.2	0.9	4.2
General events					
Fever*	≥38.0°C	129	34.8	29.9	39.9
	>39.5 °C	14	3.8	2.1	6.3
Fussiness	Any	96	25.9	21.5	30.6
	Grade 3	3	0.8	0.2	2.3
Loss of appetite	Any	85	22.9	18.7	27.5
	Grade 3	3	0.8	0.2	2.3
Sleeping more than usual	Any	74	19.9	16.0	24.4
	Grade 3	4	1.1	0.3	2.7
Restlessness	Any	81	21.8	17.7	26.4
	Grade 3	2	0.5	0.1	1.9

Study Group 4 received a booster dose of Hiberix administered concomitantly with a fourth consecutive dose of Pediarix (DTaP-HBV-IPV, GSK). In the U.S., Pediarix is approved for use as a 3-dose primary series.
N = number of documented doses
n = total number of documented doses followed by the specific symptom
*Rectal temperatures or 0.5°C added to axillary, oral, or tympanic temperatures
Grade 3 pain = causing child to cry when limb was moved. Grade 3 fussiness = persistent crying and the child could not be comforted; Grade 3 for other symptoms = preventing normal daily activities
Source: m 5.3.5.4.3 dtpa-hbv-ipv-028.pdf, pages 71-74

Table 42 and Table 43 present the incidence of solicited local and general adverse events, respectively, that were reported during the 4 days following Hiberix as a booster dose, stratified by priming vaccines.

Table 42. Study DTPa-HBV-IPV-028 Incidence of solicited local reactions at the Hiberix injection site that occurred in the 4-day period (Day 0 to 3) following receipt of Hiberix and Pediarix as booster doses, stratified by priming vaccines, Study Group 4, total vaccinated cohort

Primary vaccination group	N	Any				Grade 3			
		n	%	95%CI		n	%	95%CI	
				LL	UL			LL	UL
	Pain								
Pediarix + Hiberix	91†	15	16.5	9.5	25.7	2	2.2	0.3	7.7
Pediarix + ActHIB	95‡	19	20.0	12.5	29.5	1	1.1	0.0	5.7
Pediarix + HibTITER	181φ	42	23.2	17.3	30.0	1	0.6	0.0	3.0
	Redness								
Pediarix + Hiberix	91†	25	27.5	18.6	37.8	2	2.2	0.3	7.7
Pediarix + ActHIB	95‡	24	25.3	16.9	35.2	1	1.1	0.0	5.7
Pediarix + HibTITER	181φ	42	23.2	17.3	30.0	6	3.3	1.2	7.1
	Swelling								
Pediarix + Hiberix	91†	17	18.7	11.3	28.2	1	1.1	0.0	6.0
Pediarix + ActHIB	95‡	12	12.6	6.7	21.0	0	0.0	0.0	3.8
Pediarix + HibTITER	181φ	26	14.4	9.6	20.3	7	3.9	1.6	7.8

Study Group 4 received a booster dose of Hiberix administered concomitantly with a fourth consecutive dose of Pediarix (DTaP-HBV-IPV, GSK). In the U.S., Pediarix is approved for use as a 3-dose primary series.
N= number of subjects with the documented dose;
n/%= number/percentage of subjects reporting at least once the symptom;
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit;
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.).
Grade 3 pain : cried when limb was moved;
Grade 3 redness and swelling: >20 mm;
† 1 subject who received DTaP and Haemophilus b Conjugate Vaccine mixed in the same syringe was excluded from the analyses.
‡ 1 subject who did not return symptom sheet documentation and 1 subject who received DTaP and Haemophilus b Conjugate Vaccine mixed in the same syringe were excluded from the analyses.
φ 3 subjects who did not return symptom sheet documentation and 2 subjects who received DTaP and Haemophilus b Conjugate Vaccine mixed in the same syringe were excluded from the analyses.
Source: m2.4.4 summary-clin-safety.pdf, page 43

Table 43. Study DTPa-HBV-IPV-028 Incidence of selected solicited general adverse events that occurred in the 4-day period (Day 0 to 3) following receipt of Hiberix and Pediarix as booster doses, stratified by priming vaccines, Study Group 4, total vaccinated cohort

Primary vaccination group	N	Any				Grade 3			
		n	%	95%CI		n	%	95%CI	
				LL	UL			LL	UL
	Fever								
Pediarix + Hiberix	92	32	34.8	25.1	45.4	3	3.3	0.7	9.2
Pediarix + ActHIB	96‡	38	39.6	29.7	50.1	5	5.2	1.7	11.7
Pediarix + HibTITER	183φ	59	32.2	25.5	39.5	6	3.3	1.2	7.0
	Loss of appetite								
Pediarix + Hiberix	92	24	26.1	17.5	36.3	1	1.1	0.0	5.9
Pediarix + ActHIB	96‡	26	27.1	18.5	37.1	0	0.0	0.0	3.8
Pediarix + HibTITER	183φ	35	19.1	13.7	25.6	2	1.1	0.1	3.9
	Irritability / fussiness								
Pediarix + Hiberix	92	25	27.2	18.4	37.4	0	0.0	0.0	3.9
Pediarix + ActHIB	96‡	29	30.2	21.3	40.4	2	2.1	0.3	7.3
Pediarix + HibTITER	183φ	42	23.0	17.1	29.7	1	0.5	0.0	3.0
	Restlessness / sleeping less than usual								
Pediarix + Hiberix	92	20	21.7	13.8	31.6	1	1.1	0.0	5.9
Pediarix + ActHIB	96‡	25	26.0	17.6	36.0	1	1.0	0.0	5.7
Pediarix + HibTITER	183φ	36	19.7	14.2	26.2	0	0.0	0.0	2.0
	Sleepiness / sleeping more than usual								
Pediarix + Hiberix	92	18	19.6	12.0	29.1	2	2.2	0.3	7.6
Pediarix + ActHIB	96‡	23	24.0	15.8	33.7	0	0.0	0.0	3.8
Pediarix + HibTITER	183φ	33	18.0	12.8	24.4	2	1.1	0.1	3.9

Study Group 4 received a booster dose of Hiberix administered concomitantly with a fourth consecutive dose of Pediarix (DTaP-HBV-IPV, GSK). In the U.S., Pediarix is approved for use as a 3-dose primary series.
N= number of subjects with the documented dose
n/%= number/percentage of subjects reporting at least once the symptom
95%CI= Exact 95% confidence interval; LL = lower limit, UL = upper limit
ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur
HibTITER: Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate) (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Grade 3 fever: >39.5°C (rectally)
Grade 3 loss of appetite: Not eating at all/ loss of appetite that prevented normal daily activities
Grade 3 irritability: Persistent crying and could not be comforted
Grade 3 restlessness/sleeping less than usual: Restlessness that prevented normal daily activities
Grade 3 sleepiness/sleeping more than usual: Sleepiness that prevented normal daily activities
‡ 1 subject who did not return symptom sheet documentation was excluded from the analyses.
φ 3 subjects who did not return symptom sheet documentation were excluded from the analyses.
Source: m2.4.4 summary-clin-safety.pdf, page 44

7.1.7.9.5.2 Unsolicited Adverse Events

Of the 375 subjects in Study Group 4, 127 reported at least one unsolicited adverse event (224 reports) within the 31 day period post-vaccination. The most frequently reported event was upper respiratory tract infection (31 reports), followed by bronchitis (25 reports) and pyrexia (22 reports). Three unsolicited events (one each of injection site reaction, pyrexia, and croup) were considered Grade 3 in intensity (i.e., prevented normal everyday activities). Serious adverse events occurring within 30 days following vaccination were reported for two subjects in Group 4. One subject was hospitalized after accidental intoxication with haloperidol and biperiden 18 days

after vaccination. One child was hospitalized for pneumonia 12 days after vaccination. Both subjects recovered.

7.1.7.10 Comments and Conclusions

Among the available booster vaccination studies, this study provides the largest sample size (N=375) for the evaluation of the safety of booster vaccination with Hiberix. As with the other booster vaccination studies, this study did not include a control group that received a booster dose of a U.S. licensed Haemophilus b Conjugate Vaccine.

In this study, injection site reactions were reported commonly after receipt of Hiberix (approximately 20% of subjects). Fever and other solicited general adverse events were also reported commonly following receipt of Hiberix (approximately 20-35% of subjects, depending on event). Few subjects (i.e., approximately 0.5%-4%) had adverse events that were considered Grade 3 in intensity (i.e., local redness or swelling >20 mm, fever >39.5^{o}C, persistent crying with inability to comfort, or other general adverse events that prevented everyday activities). With regard to solicited adverse events, the safety profile of Hiberix was generally similar in subjects who had been previously primed with Hiberix, ActHIB, or HibTITER.

The solicited general adverse events observed in this study reflect administration of Hiberix concomitantly with a fourth consecutive (booster) dose of Pediarix. In the U.S., Pediarix is approved for use as a three dose primary series, but is not approved for booster vaccination. In the U.S., Hiberix administered as a booster dose, would more likely be given concomitantly with a DTaP vaccine that is not combined with other antigens. Previous clinical trials experience comparing primary immunization with Pediarix relative to separately administered vaccines (Infanrix + U.S. licensed IPV + Engerix B) suggest that rates of some solicited general adverse events (e.g., fever) observed in Study DTPa-HBV-IPV-028, may overestimate the incidence that would be observed following Hiberix administered concomitantly with Infanrix.[9]

The nature and timing of the two reported serious adverse events did not raise concerns about the safety of Hiberix.

7.2 Supportive Primary Immunization Studies

7.2.1 Trial # 8

7.2.1.1 Applicant's Protocol # and Protocol Title

217744/011 (DTPa-HBV-IPV-011) Randomised clinical study to assess the safety and reactogenicity of SB Biologicals' DTPa-HBV-IPV vaccine, when co-administered with Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course to healthy infants at the age of 3, 4 and 5 months.

7.2.1.2 Primary Objective/Rationale

To assess the safety and reactogenicity of Pediarix co-administered with either Hiberix or a commercially available Haemophilus b Conjugate Vaccine, compared to co-administration of Infanrix, ActHIB and OPV.

7.2.1.3 Design Overview

Initially, Study DTPa-HBV-IPV-011 was an open, randomized, multi-site study with four parallel study groups.
Group 1: Pediarix + Hiberix
Group 2: Pediarix + ActHIB
Group 3: Pediarix + HibTITER
Group 4: Pediarix + PedvaxHIB

During the course of the study, the protocol was amended to include a fifth, control group that received Infanrix + ActHIB + OPV.

Due to the differences in physical presentation, dose regimens and mode of administration of the vaccines, the study was performed in an open manner. In order to minimize observer bias, during the study, parents/guardians were not informed about the specific Haemophilus b Conjugate Vaccine administered to their infant.

The vaccination schedule was three doses of study vaccines, administered at 3, 4, and 5 months of age. Subjects in Group 4 received PedvaxHIB only at Visits 1 and 3 (i.e., 3 and 5 months of age). A fourth, follow-up visit was also scheduled one month following the third dose of study vaccines (i.e., at 6 months of age).

7.2.1.4 Population

The study was conducted at 90 sites in Germany. Healthy children were eligible for enrollment in the study according to the following criteria.

Inclusion Criteria

- Between 8 and 16 weeks of age at the time of the first vaccination.
- Free of obvious health problems as established by physical and clinical examination before entering into the study.
- Written informed consent obtained from parents/guardians of the infant.

Exclusion Criteria

- Allergic disease likely to be exacerbated by vaccination, including allergic reactions to neomycin, streptomycin and polymyxin B.
- Previous diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and/or *H. influenzae* type b vaccination or disease.
- Acute febrile illness at the time of planned vaccination.
- Major congenital defects or serious chronic illness.
- Progressive neurological disease.
- Any suspected or confirmed immunosuppressive condition.
- Immunosuppressive therapy (with the exception of topical corticosteroids).
- Administration of any other experimental or non-registered drug or vaccine during the study period or within the preceding 30 days.
- Simultaneous administration of a non-protocol vaccine.
- Immunoglobulin therapy or administration of any blood product within the previous two months or during the study period.

Contraindications to Vaccination

The following adverse events associated with vaccine administration constituted absolute

contraindications to further administration of DTaP vaccine. If any of these adverse events occurred during the study, the subject was to be withdrawn and followed until resolution or stabilization of the event.

- Fever ≥ 40.5°C (rectal temperature) within 48 hours after vaccination
- Seizures
- Encephalopathy
- Hypersensitivity reaction due to vaccination
- Hypotonic-hyporesponsive episode within 48 hours after vaccination
- Persistent inconsolable screaming or crying for more than 3 hours within 48 hours after vaccination.

7.2.1.5 Products Mandated by the Protocol

Hiberix lots Hib016A47/M and Hib007A44 were used. Each 0.5 ml dose of Hiberix contained:

PRP	10 mcg
Tetanus toxoid	-b(4)- mcg
Lactose	10 mg

ActHIB lots 95H25 and 95E15J were used. Each 0.5 ml dose of ActHIB contained:

PRP	10 mcg
Tetanus toxoid	24 mcg
Sucrose	42.5 mg

HibTITER lots 95I22D, 95D06A and 032012 were used. Each 0.5 ml dose of HibTITER contained:

PRP	10 mcg
CRM_{197} protein	25 mcg
NaCl	0.9%

PedvaxHIB lots 032012 and 05004 were used. Each 0.5 ml dose of HibTITER contained:

PRP	15 mcg
Group B meningococcal outer membrane protein complex	250 mcg
Lactose	2 mg
Aluminum as $Al(OH)_3$	225 mcg

Pediarix lots 21701A2, 21702A2, 21703A2, 21705A2, 21706A2 and 21708C2 were used. Each 0.5 ml dose of Pediarix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin	8 mcg
Diphtheria toxoid	-b(4)- IU (25 Lf)
Tetanus toxoid	-b(4)- IU (10 Lf)
Hepatitis B surface antigen	10 mcg
Poliovirus type 1 (Mahoney)	40 D antigen units
Poliovirus type 2 (MEF-1)	8 D antigen units
Poliovirus type 2 (Saukett)	32 D antigen units
Aluminum as salts	0.7 mg
Phenoxyethanol	2.5 mg

Infanrix lot DTPa812A2/M was used. Each 0.5 ml dose of Infanrix contained:

Inactivated Pertussis toxin (PT)	25 mcg
Filamentous haemagglutinin (FHA)	25 mcg
Pertactin	8 mcg
Diphtheria toxoid	-b(4)- IU (25 Lf)
Tetanus toxoid	-b(4)- IU (10 Lf)
Aluminum as salts	0.7 mg
Phenoxyethanol	2.5 mg

ORIMUNE (OPV manufactured by Lederle) lots 0765C and 0755F were used. Each 0.5 ml dose of ORIMUNE contained:

Poliovirus type 1	-----b(4)----------
Poliovirus type 2	-----b(4)----------
Poliovirus type 2	-----b(4)----------

All Haemophilus b Conjugate Vaccines were administered in the left anterolateral thigh. Pediarix or Infanrix was administered in the right anterolateral thigh. ORIMUNE was administered orally.

7.2.1.6 Endpoints

The protocol-specified primary endpoints of local and general adverse events including hospital and emergency room utilization and sudden infant death syndrome. As per agreement between CBER and GSK, the study report submitted with the Hiberix BLA for booster immunization included only results for serious adverse events.

7.2.1.7 Safety Surveillance/Monitoring

- Vaccinees were observed closely at the study site for 30 minutes following each vaccination.
- Parents/guardians used diary cards provided by the study site to record body temperature and local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the period 0-3 days following each vaccination. Parents/guardians were instructed to return the completed diary card at subsequent visits and to contact the investigator for any signs or symptoms perceived as severe.
- The occurrence of unsolicited adverse events, including serious adverse events, was monitored through one month following the third dose of study vaccines.

7.2.1.8 Statistical Considerations

Analyses of serious adverse events submitted in the Hiberix BLA were based on the total vaccinated cohort.

7.2.1.9 Results

7.2.1.9.1 Populations Enrolled/Analyzed

The study period was November 16, 1995 through December 18, 1997.

Pre-amendment period:
During the pre-amendment period of the study, 1569 subjects were enrolled and randomly allocated to four study groups.

Post-amendment period:
During the post-amendment period of the study, 3903 subjects were enrolled and randomly allocated to five study groups.

Data obtained from all subjects vaccinated during the pre- and post-amendment periods were included in the analyses of serious adverse events.

Table 44 provides information on subject enrollment and reasons for drop out.

Table 44. Study DTPa-HBV-IPV-011 Reasons for drop out

	Group					
	1	2	3	4	5	All
Number of subjects planned*	1200	1200	1200	1201	800	5601
Number of subjects entered	1177	1174	1174	1171	776	5472
Number of subjects completed	1150	1142	1143	1133	750	5318
Number of subjects dropped out	27	32	31	38	26	154
Reasons for drop-out:						
Serious adverse event	3	2	2	2	2	11
Non-serious adverse event	1	0	0	0	0	1
Protocol violation (subject should not have been enrolled in the study and asked to withdraw when this became apparent)	1	1	1	3	1	7
Consent withdrawal	9	10	6	8	9	42
Migration (moved) from the study area	1	0	1	2	0	4
Lost to follow-up for the full vaccination course	4	8	4	9	3	28
Lost to follow-up for the final visit	6	10	15	13	11	55
Other	2	1	2	1	0	6

*5600 were planned but one subject was given the vaccine supply from another patient
Group 1: received Pediarix + Hiberix
Group 2: received Pediarix+ ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur
Group 3: received Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Group 4: received Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.)
Group 5: received Infanrix (DTaP, GSK) + ActHIB + ORIMUNE (oral poliovirus vaccine, no longer licensed in the U.S.)
Entered: received a study vaccine dose (note: one subject who was enrolled did not receive vaccine, but was included here).
Completed: returned for the last study visit
Dropout: did not return for the last study visit.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-011.pdf, page 28 and m 2.7.4 Summary of Clinical Safety, page 69

Eleven subjects dropped out due to a serious adverse event, as described below.

In Group 1, withdrawals due to a serious adverse event included:

Subject 6038: This subject had epilepsy with onset one day post-dose 2. Diagnostic evaluation showed cerebral atrophy and hypsarthythmia on EEG. The subject was diagnosed with Idiopathic West Syndrome.

Subject 6860: This subject died due to SIDS 18 days post-dose 2

Subject 1030: This subject died 36 days post-dose 1. Death was thought to be due to a convulsive disorder, with onset of symptoms 4 days post-dose 1.

In Group 2, withdrawals due to a serious adverse event included:

Subject 5430: This subject developed cyanosis and peripheral edema at an unspecified time after vaccination.

Subject 6317: This subject developed anxiety on the day of the first vaccination that led to overnight hospitalization for observation.

In Group 3, withdrawals due to a serious adverse event included:

Subject 133: This subject developed fever 40^{o}C the same day as Dose 2.

Subject 1377: This subject died 23 days post-dose 3, following hypoxic encephalopathy thought to be due to a viral infection. Underlying immunodeficiency was suspected.

In Group 4, withdrawals due to a serious adverse event included:

Subject 4985: This subject developed neonatal convulsions 29 days post-dose 2.

Subject 7321: This subject developed fever 40^{o}C four days post-dose 2.

In Group 5, withdrawals due to a serious adverse event included:

Subject 4377: This subject developed bronchitis 6 days post-dose 1 and was discontinued by parent's decision.

Subject 6208: This subject died of SIDS 21 days post-dose 2.

7.2.1.9.2 Subject Demographics

Among all subjects who entered into the study, the mean age at the first dose was 12.8 weeks (range 1-29 weeks), 48.5% were female and 51.5% were male. Age at first dose and the proportion of male and female subjects were similar between the study groups. The study cohort was predominantly white (>95%).

7.2.1.9.3 Serious Adverse Events

Table 45 presents the incidence of specific serious adverse events, according to vaccine group, for the period Days 0-30 after any vaccine dose. None of the serious adverse events reported in Study Group 1 subjects were considered by the investigator to be related or possibly related to vaccination.

Table 45. Study DTPa-HBV-IPV-011 Percentage of subjects reporting the occurrence of serious adverse events within the 31 day (Days 0-30) post-vaccination period following any vaccine dose, Total Vaccinated Cohort

		Group 1 N = 1177				Group 2 N = 1173				Group 3 N = 1174				Group 4 N = 1171				Group 5 N = 776			
				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		22	1.9	1.2	2.8	18	1.5	0.9	2.4	14	1.2	0.7	2.0	16	1.4	0.8	2.2	14	1.8	1.0	3.0
Blood and lymphatic system disorders	Lymphadenitis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Cardiac disorders	Cyanosis	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Myocarditis	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Tachycardia	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Congenital, familial and genetic disorders	Haemangioma congenital	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Hernia congenital	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Talipes	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Gastrointestinal disorders	Diarrhoea	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	2	0.2	0.0	0.6	1	0.1	0.0	0.7
	Enteritis	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Ileus paralytic	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Intestinal ischaemia	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	obstruction	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	hypersecretion	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Vomiting	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5

Table continued on next page

Intestinal

Salivary

		Group 1 N = 1177				Group 2 N = 1173				Group 3 N = 1174				Group 4 N = 1171				Group 5 N = 776			
				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
General disorders and administration site conditions	Death neonatal	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Hyperpyrexia	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Injection site pain	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Injection site reaction	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Oedema peripheral	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Pyrexia	1	0.1	0.0	0.5	3	0.3	0.1	0.7	3	0.3	0.1	0.7	3	0.3	0.1	0.7	0	0.0	0.0	0.5
	Sudden infant death syndrome	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
Hepatobiliary disorders	Hepatitis	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Infections and infestations	Abscess	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Bacterial infection	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	2	0.3	0.0	0.9
	Bronchitis	3	0.3	0.1	0.7	2	0.2	0.0	0.6	0	0.0	0.0	0.3	3	0.3	0.1	0.7	3	0.4	0.1	1.1
	Broncho-pneumonia	3	0.3	0.1	0.7	2	0.2	0.0	0.6	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Croup infectious	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Gastroenteritis	2	0.2	0.0	0.6	4	0.3	0.1	0.9	5	0.4	0.1	1.0	2	0.2	0.0	0.6	2	0.3	0.0	0.9
	Herpes zoster	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Infection	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Otitis media	1	0.1	0.0	0.5	2	0.2	0.0	0.6	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Pharyngitis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Pneumonia	2	0.2	0.0	0.6	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.1	0.0	0.5	1	0.1	0.0	0.7
	Pyelonephritis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Respiratory tract infection	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Rhinitis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Urinary tract infection	2	0.2	0.0	0.6	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Viral infection	1	0.1	0.0	0.5	1	0.1	0.0	0.5	3	0.3	0.1	0.7	2	0.2	0.0	0.6	0	0.0	0.0	0.5

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		Group 1 N = 1177				Group 2 N = 1173				Group 3 N = 1174				Group 4 N = 1171				Group 5 N = 776			
				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Injury, poisoning and procedural complications	Injury	3	0.3	0.1	0.7	1	0.1	0.0	0.5	0	0.0	0.0	0.3	2	0.2	0.0	0.6	2	0.3	0.0	0.9
Metabolism and nutrition disorders	Anorexia	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Dehydration	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
Nervous system disorders	Convulsion	2	0.2	0.0	0.6	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	neonatal	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	2	0.2	0.0	0.6	0	0.0	0.0	0.5
	Epilepsy	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Mental impairment	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Muscle spasticity	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Psychiatric disorders	Anxiety	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Crying	1	0.1	0.0	0.5	1	0.1	0.0	0.5	0	0.0	0.0	0.3	2	0.2	0.0	0.6	0	0.0	0.0	0.5
	Nervousness	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Renal and urinary disorders	Hydronephrosis	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Renal impairment	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
Reproductive system and breast disorders	Testicular disorder	1	0.1	0.0	0.5	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.5
Respiratory, thoracic and mediastinal disorders	Apnea	1	0.1	0.0	0.5	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Asthma	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5
	Dysnpea	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.7
	Stridor	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
Skin and subcutaneous tissue disorders	Dermatitis contact	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	1	0.1	0.0	0.5	0	0.0	0.0	0.5
	Urticaria	1	0.1	0.0	0.5	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.3	0	0.0	0.0	0.5

Convulsion

Group 1: received Pediarix (DTaP-HBV-IPV, GSK) + Hiberix

Group 2: received Pediarix+ ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur

Group 3: received Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.

Group 4: received Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.

Group 5: received Infanrix (DTaP, GSK) + ActHIB + ORIMUNE (oral poliovirus vaccine, no longer licensed in the U.S.)

Table footnotes continued on next page

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: m 5.3.5.4.3 DTPa-HBV-IPV-011 Additional Statistical Report.pdf, pages 6-10

Four deaths were reported in this study, 2 in Group 1 (pre- and post-amendment), 1 in Group 3 (pre- and post-amendment), and 1 in Group 5 (post-amendment). All deaths were considered by the investigator to be unrelated to vaccination. A case narrative for each death is provided below.

• Subject 1030 (Group 1), was found atonic with eyes deviated to one side four days after her first vaccination. Upon hospital admission, she was somnolent and had a temperature of 38.3^{o}C, but recovered within an hour. Two days later, she had recurrent episodes of atonic convulsions without fever, and was found to have elevated SGOT, SGPT, CK and CK_MB. Despite extensive diagnostic evaluation, the etiology of the convulsions was not determined. Myocarditis was suspected, but EKG and cardiac echography were normal. After approximately three weeks, she was discharged from the hospital. Subsequently, 36 days after the first vaccination, the child developed fever and restlessness. Later that day, she was found inanimated and cyanotic. Resuscitation en route to the hospital was unsuccessful. Death was thought to be causally related to the infant's convulsive disorder. An autopsy was not performed.

• Subject 6860 (Group 1) died of SIDS 18 days after the second vaccination.

• Subject 1377 (Group 3) had a history of premature birth (birth weight 1490g), apnea, cerebral bleeding, transitional hyperparathyroidism, and sleep apnea. At the time of enrollment, the child met all study entry criteria. Twenty-three days after the third dose, the child developed fever up to 38.7° C and convulsions. He was hospitalized and found to have hypoxic cerebral damage and sepsis. He had a respiratory arrest and died. The autopsy indicated that the child had a congenital immunodeficiency (not further specified).

• Subject 6208 (Group 5) died of SIDS 21 days after the second vaccination.

In addition to convulsions reported in Subject 1030 (described above), two other subjects reported seizures within 31 days following Hiberix (Table 45). Subject 6038, previously described in Section 7.2.1.9.1, was diagnosed with Idiopathic West Syndrome. Another subject, Subject 5852, developed suspected convulsions 23 days after the third dose of Hiberix. Concurrently, she had nasopharyngitis. She was hospitalized for evaluation and found to have a normal EEG and no evidence for a seizure disorder.

The case of urticaria following Hiberix and included in Table 45 occurred 3 days post-vaccination. A reaction to Paracetamol was suspected. The case of apnea following Hiberix and included in Table 45 occurred 12 days post-vaccination, in association with a moderate upper respiratory viral infection.

7.2.1.10 Comments and Conclusions

In this study, infants received a primary series of Pediarix administered concomitantly with one of four Haemophilus b Conjugate Vaccines—Hiberix, ActHIB, HibTITER, or PedvaxHIB. Approximately 1,170 infants were enrolled in each of these four study groups. An additional 776 infants received a primary series of ActHIB administered concomitantly with Infanrix and OPV. In the absence of substantial comparative safety data on booster vaccination with Hiberix relative to other U.S. licensed Haemophilus b Conjugate Vaccines, this study provides useful comparative data on serious adverse events that are considered supportive in the evaluation of the safety of Hiberix for booster immunization. The data on serious adverse events from this study raised no particular safety concerns about Hiberix.

7.2.2 Trial # 9

7.2.2.1 Applicant's Protocol # and Protocol Title
217744/012 (DTPa-HBV-IPV-012) Randomised clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV-IPV vaccine, when co-administered with Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course to healthy infants at the age of 3, 4-1/2 and 6 months.

7.2.2.2 Primary Objective/Rationale
To assess the immunogenicity of Pediarix when co-administered with either Hiberix or with commercially available Haemophilus b Conjugate Vaccines.

7.2.2.3 Design Overview
Study DTPa-HBV-IPV-012 was an open, randomized, multi-site study with four study groups.
Group 1: Pediarix + Hiberix
Group 2: Pediarix + ActHIB
Group 3: Pediarix + HibTITER
Group 4: Pediarix + PedvaxHIB

The vaccination schedule was three doses of study vaccines, administered at 3, 4.5, and 6 months of age. Subjects in Group 4 received PedvaxHIB only at 3 and 6 months of age. A fourth, follow-up visit was scheduled one month following the third dose of study vaccines (i.e., at 7 months of age) for blood sampling and safety follow-up.

7.2.2.4 Population
The study was conducted at multiple sites in Lithuania. The inclusion and exclusion criteria were the same as those used in Study DTPa-HBV-IPV-011 (section 7.2.1.4) except that in this study infants were to be between 12 and 16 weeks of age at the time of the first vaccination. Contraindications to further doses of DTaP vaccine were as previously outlined for Study DTPa-HBV-IPV-011 (section 7.2.1.4).

7.2.2.5 Products Mandated by the Protocol
The composition of Hiberix, ActHIB, HibTITER, PedvaxHIB, and Pediarix used in this study was the same as that used in Study DTPa-HBV-IPV-011 (section 7.2.1.5).

Lots of vaccines used were as follows: Hiberix lot HIB007A44, ActHIB lot 95D05, HibTITER lot 95D06A, PedvaxHIB lot 034011, and Pediarix lot 21704A2.

All Haemophilus b Conjugate Vaccines were administered in the left anterolateral thigh. Pediarix was administered in the right anterolateral thigh.

7.2.2.6 Endpoints
Endpoints included local and general adverse events, serious adverse events, and the evaluation of immune response to both Pediarix and the Haemophilus b Conjugate Vaccines. As per agreement between CBER and GSK, the study report submitted with the Hiberix BLA for booster immunization included only results for serious adverse events and the anti-PRP immune responses (anti-PRP $\geq$0.15 mcg/ml, anti-PRP $\geq$1.0 mcg/ml, and anti-PRP GMCs).

7.2.2.7 Immunogenicity Monitoring
On the day of the first vaccination (visit 1) and at visit 4 (approximately 30 to 35 days after the last vaccine dose), blood samples (minimum of 3 ml) were obtained. The interval recommended

in the protocol between the third vaccine dose and final blood sampling was 30 to 35 days. This range served as a target and not as an absolute criterion for inclusion or exclusion from analysis. The interval between the third vaccine dose and final blood sampling was expanded to 21 to 42 days for inclusion in the immunogenicity analysis. Antibodies to PRP were measured by -b(4)- performed by GSK.

7.2.2.8 Safety Surveillance/Monitoring

Safety monitoring procedures described for Study DTPa-HBV-IPV-011 (section 7.2.1.7) were also followed in this study. In addition, in this study, once during the period Days 4-7 following each vaccination, the investigator or nurse contacted the parents, by telephone or visit, to monitor completion of the diary cards and the occurrence of adverse events.

7.2.2.9 Statistical Considerations

Pre- and post-vaccination seroprotection rates for antibodies to PRP were compared using Fisher's exact test. In case a statistically significant difference was detected between groups, pair-wise comparisons were performed.

Two analyses were performed: a first one included only subjects corresponding to criteria defined in the protocol (ATP), and a second one, ITT, included all data available from all subjects.

For the calculation of anti-PRP GMCs, antibody levels below the assay cut-off were given an arbitrary value of one half of the cut-off value. The GMCs for anti-PRP antibodies were compared between groups using the one-way ANOVA test (with Tukey test, for multiple comparisons, performed if the one-way ANOVA test showed a statistically significant difference between the groups).

In the study report submitted to the BLA, the analysis of reactogenicity was limited to tabulation of serious adverse events.

There were no pre-specified non-inferiority criteria or acceptance criteria for any of the study endpoints.

7.2.2.10 Results

7.2.2.10.1 Populations Enrolled/Analyzed

The study period was November 9, 1995 through July 2, 1996.

Five hundred and forty-nine infants aged 11 to 16 weeks were enrolled in the study and randomly allocated to one of the four study groups. Table 46 provides information on subject enrollment and eligibility for analysis.

Table 46. Study DTPa-HBV-IPV-012 Subject enrollment and eligibility for analysis

	Group				
	1	2	3	4	All
Number of subjects enrolled	219	110	110	110	549
Number of subjects included in the analysis of reactogenicity	219	110	110	110	549
Elimination due to:					
Demographics protocol violation	1				1
Medication forbidden by protocol			1		1
Non-compliance with vaccination schedule	5	5	2	2	14
Non-compliance with blood sampling schedule	11	3	7	3	24
Number of subjects included in the analysis of immunogenicity	202	102	100	105	509 (92.7%)

Group 1: Pediarix (DTaP-HBV-IPV, GSK) + Hiberix
Group 2: Pediarix + ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur
Group 3: Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Group 4: Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.
Demographics protocol violation was in a subject who was 11 weeks of age
Medication forbidden by protocol: subject taking hydrocortisone
14 subjects did not comply with vaccination schedule (missed visits)
24 subjects non-compliance with blood sampling schedule: not adhering to an interval of 7 days between pre-vaccination blood sample and dose 1, or to an interval of 21-42 days between dose 3 and the final blood sample.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-012-report-body.pdf, page 17

Table 47 presents reasons for drop outs.

Table 47. Study DTPa-HBV-IPV-012 Reasons for drop out

	Number of Subjects				Reason For Drop Out*			
	Planned	Entered	Completed	Dropped	Serious Adverse Event	Protocol Violation	Consent Withdrawal	Lost to Follow-Up
Overall	550	549	541	8	1	1	5	1
Group 1	220	219	217	2			1	1
Group 2	110	110	106	4	1		3	
Group 3	110	110	109	1			1	
Group 4	110	110	109	1		1		

Group 1: Pediarix (DTaP-HBV-IPV, GSK) + Hiberix
Group 2: Pediarix + ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur
Group 3: Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Group 4: Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.
Source: m 5.3.5.4.3 dtpa-hbv-ipv-012-report-body.pdf, page 18

There was one withdrawal due to a serious adverse event in a subject in group 2 (Pediarix + ActHIB). The subject was hospitalized for fever three days after dose 2.

7.2.2.10.2 Subject Demographics

Among the 549 subjects enrolled in the study, the mean age at the first dose was 13.2 weeks (range 11-16 weeks). The ITT cohort was comprised of 47.7% females and 52.3% males. There were no statistically significant differences between groups with regard to age and gender. All subjects were Caucasian.

7.2.2.10.3 Immunogenicity Outcomes

Results of anti-PRP immunogenicity analyses are presented in Table 48.

Table 48. Study DTPa-HBV-IPV-012 Anti-PRP seroprotection rates and GMCs, ATP analysis

			≥0.15 mcg/ml		≥1.0 mcg/ml		GMC		
							mcg/ml	95% CI	
Group	Timing	N	n (%)	95% CI	n (%)	95% CI			
1	Pre	202	65 (32.2)	(25.5, 38.9)	8 (4.0)	(1.9, 7.9)	0.132	0.116	0.150
	PIII	202	202 (100)	(97.7, 100)	194 (96.0)	(92.1, 98.1)	7.198	6.236	8.307
2	Pre	102	25 (24.5)	(16.8, 34.2)	6 (5.9)	(2.4, 12.9)	0.115	0.097	0.135
	PIII	101	100 (99.0)	(93.8, 99.9)	95 (94.1)	(87.0, 97.6)	6.661	5.437	8.161
3	Pre	100	35 (35.0)	(25.2, 44.8)	9 (9.0)	(4.5, 16.8)	0.144	0.117	0.176
	PIII	100	100 (100)	(95.4, 100)	88 (88.0)	(79.6, 93.4)	5.770	4.422	7.529
4	Pre	105	32 (30.5)	(21.2, 39.8)	5 (4.8)	(1.8, 11.3)	0.124	0.105	0.146
	PIII	105	105 (100)	(95.6, 100)	95 (90.5)	(82.8, 95.1)	4.953	4.015	6.110

Group 1: Pediarix (DTaP-HBV-IPV, GSK) + Hiberix
Group 2: Pediarix + ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur
Group 3: Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Group 4: Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.
PedvaxHIB was administered at 3 and 6 months of age. All other study vaccines were administered at 3, 4.5, and 6 months of age.
Pre = pre-vaccination; PIII = approximately one month after the third dose of Hiberix, ActHIB or HibTITER; approximately one month after the second dose of PedvaxHIB.
N = total number of subjects tested; n = number of subjects with anti-PRP level ≥0.15 mcg/ml or 1.0 mcg/ml
Source: m 5.3.5.4.3 dtpa-hbv-ipv-012-report-body.pdf, page 21

There was no statistically significant difference between the four groups in post-vaccination anti-PRP levels ≥0.15 mcg/ml (p = 0.396, Fisher's exact test). There was a statistically significant difference between the four groups in post-vaccination anti-PRP levels ≥ 1.0 mcg/ml (p = 0.045, Fisher's exact test). Pair-wise comparisons showed no statistically significant difference between the groups. There was a statistically significant difference between the four groups in post-vaccination anti-PRP GMCs (p=0.0343, one-way ANOVA). Tukey test, for multiple comparisons, showed the statistically significant difference was between groups 1 and 4.

7.2.2.10.4 Serious Adverse Events

There were no deaths reported during the study. Twenty-six subjects reported at least one non-fatal serious adverse event (11 in group 1, 2 in group 2, 4 in group 3 and 9 in group 4). All serious adverse events except one were considered by the investigator to be unrelated to vaccination. The serious adverse event considered by the investigator to be related to vaccination was a case of fever three days after the second dose of study vaccines in a subject in Study Group 2.

Table 49 presents the incidence of specific serious adverse events, according to vaccine group for the period 0-30 days post-vaccination.

Table 49. Study DTPa-HBV-IPV-012 Percentage of subjects reporting the occurrence of serious adverse events within the 31 day (Days 0-30) post-vaccination period following any vaccine dose, Total Vaccinated Cohort

		Group 1 N = 219				Group N = 110				Group 3 N = 110				Group 4 N = 110			
				95% CI				95% CI				95% CI			95% CI		
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		9	4.1	1.9	7.7	2	1.8	0.2	6.4	3	2.7	0.6	7.8	8	7.3	3.2	13.8
Blood and lymphatic system disorders	Anaemia	2	0.9	0.1	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0	0	0.0	0.0	3.3
	Hypochromic anaemia	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
Gastrointestinal disorders	Enteritis	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Enterocolitis	0	0.0	0.0	1.7	1	0.9	0.0	5.0	0	0.0	0.0	3.3	0	0.0	0.0	3.3
General disorders and administration site conditions	Pyrexia	0	0.0	0.0	1.7	1	0.9	0.0	5.0	0	0.0	0.0	3.3	0	0.0	0.0	3.3
Infections and infestations	Bacterial infection	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Bronchitis	1	0.5	0.0	2.5	1	0.9	0.0	5.0	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Bronchopneumonia	3	1.4	0.3	4.0	0	0.0	0.0	3.3	2	1.8	0.2	6.4	0	0.0	0.0	3.3
	Furuncle	0	0.0	0.0	1.7	0	0.0	0.0	3.3	1	0.9	0.0	5.0	0	0.0	0.0	3.3
	Gastroenteritis	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Laryngitis	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Otitis media	1	0.5	0.0	2.5	0	0.0	0.0	3.3	1	0.9	0.0	5.0	0	0.0	0.0	3.3
	Pharyngitis	4	1.8	0.5	4.6	0	0.0	0.0	3.3	1	0.9	0.0	5.0	3	2.7	0.6	7.8
	Pneumonia	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Upper respiratory tract infection	0	0.0	0.0	1.7	1	0.9	0.0	5.0	0	0.0	0.0	3.3	0	0.0	0.0	3.3
	Viral infection	3	1.4	0.3	4.0	2	1.8	0.2	6.4	1	0.9	0.0	5.0	3	2.7	0.6	7.8
Injury, poisoning and procedural complications	Injury	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
Metabolism and nutrition disorders	Dehydration	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3
	Vitamin D deficiency	1	0.5	0.0	2.5	1	0.9	0.0	5.0	0	0.0	0.0	3.3	3	2.7	0.6	7.8
Nervous system disorders	Convulsion	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Epilepsy	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
	Neurotoxicity	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3
	Syncope	0	0.0	0.0	1.7	0	0.0	0.0	3.3	0	0.0	0.0	3.3	1	0.9	0.0	5.0
Reproductive system and breast disorders	Oedema genital	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3

Table continued on next page

		Group 1 N = 219				Group N = 110				Group 3 N = 110				Group 4 N = 110			
				95% CI				95% CI				95% CI			95% CI		
Primary System Organ Class	Preferred Term	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
Respiratory, thoracic and mediastinal disorders	Dyspnoea	3	1.4	0.3	4.0	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3
	Respiratory failure	2	0.9	0.1	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3
Skin and subcutaneous tissue disorders	Dermatitis allergic	1	0.5	0.0	2.5	0	0.0	0.0	3.3	0	0.0	0.0	3.3	0	0.0	0.0	3.3

Group 1: Pediarix (DTaP-HBV-IPV, GSK) + Hiberix
Group 2: Pediarix + ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)], Sanofi Pasteur
Group 3: Pediarix + HibTITER [Haemophilus b Conjugate Vaccine (Diphtheria CRM_{197} Protein Conjugate)] (no longer licensed in the U.S.), Wyeth Pharmaceuticals, Inc.
Group 4: Pediarix + PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)], Merck & Co., Inc.
PedvaxHIB was administered at 3 and 6 months of age. All other study vaccines were administered at 3, 4.5, and 6 months of age.
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting at least once the symptom
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Source: m 5.3.5.4.3 DTPa-HBV-IPV-012 Additional Statistical Report.pdf, pages 5-7

Further clarification is provided for the serious adverse events of neurotoxicity and respiratory failure reported in the group that received Pediarix and Hiberix (Table 49). The case coded as neurotoxicity was in a child who developed fever, irritability, vomiting, diarrhea, and dehydration, with onset of symptoms 17 days after the third dose of study vaccines. He was hospitalized, treated with intravenous fluids and antibiotics, and recovered. One case coded as respiratory failure was in a subject hospitalized for bronchopneumonia and "grade 1 respiratory insufficiency" with onset of symptoms 28 days after the second dose of Pediarix and Hiberix. She recovered and was discharged from the hospital after 10 days. The second case coded as respiratory failure was in a subject hospitalized for "acute bilateral bronchopneumonia II" 15 days after the first dose of Pediarix and Hiberix. She recovered and was discharged from the hospital after 10 days.

7.2.2.11 Comments and Conclusions

The immunogenicity results of this study provide suggestive evidence that a primary series of Hiberix administered concomitantly with Pediarix at 3, 4.5, and 6 months of age is as immunogenic as a primary series of ActHIB administered on the same schedule or PedvaxHIB given at 3 and 6 months of age. These data are viewed as supportive in the evaluation of the effectiveness of a booster dose of Hiberix. However, in view of some limitations of the study (e.g., non-U.S. schedule, some currently recommended vaccines not concomitantly administered with the Haemophilus b Conjugate Vaccines), ----------b(4)----------. The data on serious adverse events from this study did not raise any particular safety concerns for Hiberix, but the study was not of sufficient size to adequately evaluate relatively infrequently occurring events.

8 Overview of Immunogenicity (Effectiveness) Across Trials

8.1 Study Design and Methods

All six booster studies that evaluated the immunogenicity of Hiberix were conducted in healthy children who were previously primed with Haemophilus b Conjugate Vaccine as part of their participation in primary vaccination studies. All were open studies except for study DTPa-HBV-IPV-035 which was conducted in a double-blind manner for two Hiberix formulations, only one of which is relevant to this review. All subjects received one booster dose of Hiberix concomitantly at a separate site with a DTaP combination vaccine as an intramuscular injection. In two of the studies (Studies DTPa-IPV-013p and DTPa-HBV-IPV-010), Hiberix was to be administered in the deltoid muscle. In four of the studies (Studies DTPa-HBV-032, DTPa-HBV-020, DTPa-IPV-026 and DTPa-HBV-IPV-035), Hiberix was to be administered in the anterolateral thigh. All DTaP combination vaccines administered concomitantly with Hiberix contained the same DTaP, IPV and/or Hepatitis B vaccine components as Pediarix. Although some of the vaccines used are licensed in the U.S. (Infanrix, Kinrix, and Pediarix), only Infanrix was used according to the schedule approved in the U.S. (Study DTPa-IPV-026). Neither Kinrix nor Pediarix is licensed in the U.S. for use as the fourth dose of DTaP. Vaccines and schedules used for priming were presented in Table 2 (Section 5.2). Haemophilus b Conjugate Vaccines used for priming included Hiberix, two currently licensed vaccines (ActHIB and PedvaxHIB) and HibTITER, which is no longer licensed in the U.S. None of the booster immunization studies included a comparator group that received a booster dose with a U.S.-licensed Haemophilus b Conjugate Vaccine.

Pre-vaccination blood samples were collected just prior to booster vaccination at visit 1. In Study DTPa-HBV-IPV-010, pre-vaccination blood samples also may have been collected up to 7 days prior to booster vaccination. Approximately one month after booster vaccination with Hiberix, a second blood sample was taken. The interval between pre- and post-vaccination blood samples,

as described in the protocols, was 30 to 35 days. This range served as a target range in all booster studies rather than an absolute criterion for inclusion or exclusion of subjects from the ATP analysis. This range was expanded to 21 to 42 days to maximize inclusion into the analysis of immunogenicity. This expansion was performed prior to analysis while the statistician was still blinded to the study database.

In four of the booster studies (DTPa-IPV-013p, DTPa-HBV-020, DTPa-IPV-026, and DTPa-HBV-IPV-010), anti-PRP antibodies were measured by -b(4)- performed by GSK. In Study DTPa-HBV-032, anti-PRP antibodies were measured by -b(4)- performed by GSK. In Study DTPa-HBV-IPV-035, anti-PRP antibodies were measured by -b(4)- in the laboratory of --b(4)- ---------- In E-mail correspondence June 30, 2009, CBER's assay reviewer for the Hiberix BLA indicated that the anti-PRP assays used in the clinical studies of Hiberix were acceptable.

In one supportive primary immunization study, Study DTPa-HBV-IPV-012, infants were randomized to receive Hiberix, ActHIB, HibTITER, or PedvaxHIB at 3, 4.5, and 6 months of age, concomitantly with Pediarix. Anti-PRP antibodies were measured by -b(4)- performed by GSK on the day of the first vaccination and approximately one month following the third dose.

For all of the Hiberix immunogenicity data presented in this review, the composition of Hiberix was the same as that intended for licensure in the U.S., as described in Section 1.2.3

8.2 Immunogenicity Endpoints

In the six booster immunization studies that evaluated the immune response to Hiberix, pre- and post-vaccination anti-PRP GMCs and the proportions of subjects with anti-PRP $\geq$0.15 mcg/ml and $\geq$1.0 mcg/ml were evaluated. As discussed in section 6, an anti-PRP level of 0.15 mcg/ml has been accepted as a minimum protective level[3,4] and an anti-PRP level of 1.0 mcg/ml has been accepted as predicting long-term (at least one year) protection[5,6] against invasive disease due to *H. influenzae* type b. Since many subjects are expected to have an anti-PRP level $\geq$0.15 mcg/ml prior to booster vaccination as a result of persistent immunity following primary immunization, the most informative parameters for evaluation of booster vaccination with Hiberix are GMCs and anti-PRP levels $\geq$1.0 mcg/ml. None of the booster immunization studies compared Hiberix to a U.S. licensed vaccine. Acceptance criteria for the immune response to a booster dose of Hiberix were not pre-specified in any of the booster immunization studies.

In Study DTPa-HBV-IPV-012, anti-PRP immune responses following primary immunization with Hiberix, ActHIB, PedvaxHIB or HibTITER were compared using statistical significance testing. Non-inferiority analyses were not performed.

8.3 Immunogenicity Findings

The ATP cohort for immunogenicity in the six booster immunization studies included a total of 415 subjects who received Hiberix (range per study: 42 to 108). Across these six studies, the mean age at the booster dose of Hiberix for the ATP immunogenicity cohorts ranged from 15.4 months to 18.6 months. Although in two of the studies, some children received the booster dose of Hiberix as young as 11 or 12 months of age, across the six studies, there were only 30 subjects 11 to 14 months of age in the ATP cohort for immunogenicity. Considering the ATP cohorts for immunogenicity across studies, approximately 76% of subjects were 15 to 18 months of age and approximately 17% were 19 to 25 months of age. Approximately half of subjects were male. Studies were conducted in Europe (Germany and Lithuania), Latin America (Argentina and Brazil) and Canada. Most subjects in all studies were of White/Caucasian origin. Approximately 75% of the ATP cohort for immunogenicity across the six booster studies had been primed with

Hiberix. Across the studies, there were 98 subjects in the ATP immunogenicity analyses who had been primed with a U.S. licensed Haemophilus b Conjugate Vaccine: 42 subjects from Study DTPa-HBV-IPV-010 primed with ActHIB; 27 subjects from Study DTPa-HBV-IPV-035 primed with ActHIB; 20 subjects from Study DTPa-IPV-026 primed with ActHIB; and 9 subjects from Study DTPa-HBV-IPV-035 primed with PedvaxHIB.

Across the six studies, the proportion of subjects with a pre-booster vaccination anti-PRP level $\geq$0.15 mcg/ml ranged from 71.4% to 97.6%. All 414 subjects had an anti-PRP level $\geq$0.15 mcg/ml following a booster dose of Hiberix. The proportion of subjects with a pre-booster vaccination anti-PRP level $\geq$1.0 mcg/ml ranged from 12.7% to 65.9%, depending on the study. All but three of the 414 subjects had an anti-PRP level $\geq$1.0 mcg/ml following a booster dose of Hiberix. Across the six studies, pre-booster vaccination anti-PRP GMCs ranged from 0.25 mcg/ml to 1.9 mcg/ml and post-booster vaccination anti-PRP GMCs ranged from 47.8 mcg/ml to 137 mcg/ml, corresponding to increases ranging from 45- to 188-fold.

In Study DTPa-HBV-IPV-012, following primary immunization with Hiberix, all 202 subjects had an anti-PRP level $\geq$0.15 mcg/ml and 96% had an anti-PRP level $\geq$1.0 mcg/ml; the post-vaccination anti-PRP GMC in the Hiberix group was 7.2 mcg/ml. There was no statistically significant difference between the four groups (Hiberix, ActHIB, HibTITER, PedvaxHIB) in the proportion of subjects with a post-primary vaccination anti-PRP level $\geq$0.15 mcg/ml. There was a statistically significant difference between the four groups in post-primary vaccination anti-PRP $\geq$1.0 mcg/ml (Hiberix 96.0%; ActHIB 94.1%; HibTITER 88%; PedvaxHIB 90.5%) and in post-primary vaccination anti-PRP GMCs (Hiberix 7.2; ActHIB 6.7; HibTITER 5.8; PedvaxHIB 4.9), with Hiberix comparing favorably to the other vaccines.

8.4 Immunogenicity Conclusions

The available data demonstrate a robust immune response against PRP elicited by a booster dose of Hiberix in children who were predominantly 15 to 18 months of age. Too few children 12 to 14 months of age were evaluated to draw conclusions about the immune response to a booster dose of Hiberix in this age group. The overall robust immune response against PRP appeared to be consistent, regardless of priming vaccine (Hiberix, ActHIB, PedvaxHIB or HibTITER). However, most of the available data were in children who had been primed with Hiberix. Across the studies, 98 subjects previously primed with a U.S. licensed vaccine were included in the ATP immunogenicity analyses: 89 subjects primed with ActHIB and nine subjects primed with PedvaxHIB. In the booster immunization studies, Hiberix was administered concomitantly with various DTaP combination vaccines that contained components of Pediarix.

The immunogenicity results from primary immunization study, Study DTPa-HBV-IPV-012, are considered supportive for the evaluation of the immunogenicity of a booster dose of Hiberix. Although formal non-inferiority analyses were not presented, under the conditions of this study (e.g., 3, 4.5, 6 month vaccination schedule and concomitant administration with only Pediarix), three doses of Hiberix elicited anti-PRP seroprotection rates and GMCs that appeared to be as good as those elicited by a primary series of three doses of ActHIB or a primary series of two doses of PedvaxHIB. Based on these data, it seems reasonable to expect that the immune response to PRP following booster vaccination with Hiberix likely would be as good as that following booster vaccination with a U.S. licensed vaccine.

The available immunogenicity data on Hiberix were obtained from studies of generally healthy children who were almost exclusively Caucasian. There are no data on the effectiveness of Hiberix in children who may be at increased risk for invasive disease due to *H. influenzae* type b, including American Indian/Alaska Native children and children with certain immunosuppressive

conditions (e.g., human immunodeficiency virus infection, asplenia, immunoglobulin deficiency, sickle cell disease, bone marrow transplant recipients, children receiving chemotherapy for malignant neoplasms). Some immunosuppressive conditions may be associated with impaired anti-PRP antibody responses to conjugate vaccines.

9 Overview of Safety Across Trials

9.1 Overall Safety Database

Across the seven booster immunization studies (Table 2), a total of 1,008 subjects received Hiberix as a booster dose and were monitored for safety. None of the booster immunization studies included a comparator group that received a booster dose with a U.S.-licensed Haemophilus b Conjugate Vaccine. Across the seven studies, the mean age at receipt of Hiberix ranged from 15.9 to 18.7 months. Approximately half of subjects were male and most subjects were of White/Caucasian origin.

The majority of the safety data on use of Hiberix as a booster dose was obtained from subjects who received a primary series with Hiberix. The safety database on use of Hiberix as a booster dose includes 234 subjects primed with ActHIB, 217 subjects primed with HibTITER (no longer licensed in the U.S.), and 27 subjects primed with PedvaxHIB.

In two supportive primary immunization studies, a total of 1,396 subjects received primary vaccination with Hiberix and a total of 4,625 subjects received primary vaccination with another Haemophilus b Conjugate Vaccine (ActHIB, PedvaxHIB, or HibTITER).

9.2 Safety Assessment Methods

In the seven booster immunization studies, reactogenicity following vaccination was actively monitored. Occurrence of specific local and general adverse events on the day of vaccination and on the subsequent 3 days was solicited from parents/guardians using diary cards. Pain, redness and swelling at the injection site were solicited in all studies. Solicited general adverse events included fever, vomiting, diarrhea, loss of appetite, restlessness, unusual crying, irritability/fussiness, and sleeping more than usual. Pre-specified symptom intensity scales were applied in each study.

The parents/guardians were instructed to immediately inform the investigator of the occurrence of any severe sign or symptom manifested by vaccinees at any time throughout the study periods. In all studies, unsolicited adverse events, including serious adverse events, were monitored during the 31-day (Day 0 to Day 30) post-vaccination period after each dose. For all studies except DTPa-HBV-032, a serious adverse event was defined as any experience which occurred during the study that, in the investigator's opinion, suggested a significant hazard to the subject’s health. This included:

- life-threatening events,
- hospitalization or prolongation of hospitalization,
- severe or permanent disability,
- death,
- congenital abnormality (in offspring),
- early onset reactions within one hour after vaccination such as anaphylaxis, vasovagal reaction, hyperventilation,
- development of new cancer,
- laboratory tests suggesting significant system dysfunction,
- any experience that the investigator regards as serious or that would suggest any significant hazard that may be associated with the use of the vaccine.

In study DTPa-HBV-032, the serious adverse event definition included only the first five criteria above and any important medical event that might jeopardize the subject or might require intervention to prevent one of the outcomes of the first five criteria.

All analyses of safety (solicited and unsolicited adverse events) included in the BLA were descriptive. For the two supportive primary immunization studies, only data on serious adverse events were included in the BLA.

9.3 Significant/Potentially Significant Events

9.3.1 Deaths

In the seven booster immunization studies, among a total of 1,008 subjects who received Hiberix as a booster dose concomitantly with a DTaP combination vaccine, there were no deaths reported.

There were no deaths reported in one of the supportive primary immunization studies, Study DTPa-HBV-IPV-012 (219 subjects in the Pediarix + Hiberix group). Four deaths were reported in Study DTPa-HBV-IPV-011, the larger of the two primary immunization studies. None of the deaths were thought by the investigator to be related to vaccination. Of the four deaths, two occurred in subjects who received Pediarix + Hiberix (N = 1177). One subject died due to SIDS 18 days following the second dose of Hiberix. One subject died 36 days following the first dose of Hiberix, presumably due to a convulsive disorder of undetermined etiology that had initially manifested four days after the first dose of Hiberix.

9.3.2 Serious Adverse Events

Review of the safety data on serious adverse events from the seven booster immunization studies and the two supportive primary immunization studies raised no important safety concerns.

Across the seven booster immunization studies, among a total of 1,008 subjects who received Hiberix as a booster dose concomitantly with a DTaP combination vaccine, two subjects reported a serious adverse event occurring within 31 days post-vaccination. One subject was hospitalized for impaired consciousness due to accidental drug ingestion 18 days post-vaccination. One subject was hospitalized with pneumonia 12 days post-vaccination. Neither of these events is considered attributable to receipt of Hiberix.

In the largest of the two supportive primary immunization studies, in which subjects received Pediarix administered concomitantly with either Hiberix (N=1177), ActHIB (N=1173), HibTITER (N=1174), or PedvaxHIB (N=1171); or Infanrix and OPV administered concomitantly with ActHIB (N=776), serious adverse events were monitored during the period Days 0-30 following each vaccine dose (2 doses of PedvaxHIB; 3 doses of Hiberix, ActHIB, or HibTITER). The percentage of subjects reporting at least one serious adverse event was 1.9% following Pediarix + Hiberix, 1.5% following Pediarix + ActHIB, 1.2% following Pediarix + HibTITER, 1.4% following Pediarix + PedvaxHIB, and 1.8% following Infanrix + ActHIB + OPV. None of the serious adverse events reported following Hiberix were considered by the investigator as attributable to receipt of Hiberix.

9.3.3 Dropouts

Information on study completion for the Hiberix groups for the seven booster immunization studies is provided in Table 50. For Study DTPa-HBV-032, subjects were enrolled as infants to participate in both a primary and booster phase. For this study, the data in Table 50 reflect all subjects included in the primary and booster phases. Across the seven booster immunization studies, there were no drop outs due to an adverse event.

Table 50. Study completion: reasons for drop-out in the seven booster studies, Hiberix groups

Study	Number of subjects enrolled	Number of subjects completed	Reasons for drop out						
			Serious adverse event	Non-serious adverse event	Protocol violation	Consent withdrawal (not due to an adverse event)	Migration from study area	Lost to follow-up	Other
DTPa-HBV-032*	199	141	0	0	4	10	0	37	7
DTPa-IPV-013p	64	64	0	0	0	0	0	0	0
DTPa-HBV-020	138	138	0	0	0	0	0	0	0
DTPa-IPV-026	92	90	0	0	0	1	0	1	0
DTPa-HBV-IPV-010	43	42	0	0	0	1	0	0	0
DTPa-HBV-IPV-035	150	149	0	0	0	0	0	1	0
DTPa-HBV-IPV-028	375	368	0	0	0	0	0	7	0

*The numbers reflect all subjects included in the primary and booster phase of Study DTPa-HBV-032. Of the 199 subjects enrolled, 146 received a booster dose of Hiberix.
Source: module 2.7.4, summary-clin-safety.pdf, page 31

9.4 Other Safety Findings

9.4.1 Solicited Local Reactions and General Adverse Events

In the seven booster immunization studies, Hiberix was administered concomitantly with a DTaP combination vaccine: either Infanrix; DTPa-HBV (not licensed in the U.S.); Kinrix; or Pediarix. In these studies, Kinrix and Pediarix were both used in schedules that are not approved in the U.S. In the U.S., it is expected that Hiberix would be routinely administered with a DTaP vaccine not combined with other antigens. Safety data on commonly occurring adverse events following a booster dose of Hiberix administered concomitantly with DTaP are limited to 65 subjects from Study DTPa-IPV-026. These subjects also received concomitant OPV (no longer licensed in the U.S.). Study DTPa-HBV-IPV-028 provides the largest number of subjects (N = 371) monitored for commonly occurring adverse events following booster immunization with Hiberix (see Table 41 in Section 7.1.7.9.5.1). In this study, subjects received Pediarix concomitantly with Hiberix. Data from other studies, not included in the Hiberix BLA, have shown that primary vaccination with Pediarix is associated with increased rates of fever compared to separately administered Infanrix, IPV, and Hepatitis B vaccine.[9] Thus, rates of fever observed in Study DTPa-HBV-IPV-028 may be higher than rates that would be observed when Hiberix is administered concomitantly with Infanrix or another DTaP vaccine.

9.4.2 Post-Marketing Experience

A review of the post-marketing experience with Hiberix, covering a 12-year period in which approximately -b(4)- million doses of Hiberix were distributed in other countries, was provided in Section 5.1.2. Based on three post-marketing cases, GSK has been closely monitoring leukocytoclastic vasculitis. Based on one report, GSK has also identified type III hypersensitivity reactions as a potential risk and has committed to closely monitor such events.

9.5 Safety Conclusions

The safety data from the seven studies in which Hiberix was administered as a booster dose and the two supportive primary immunization studies raise no particular concerns about the safety of booster vaccination with Hiberix. These studies, combined with the post-marketing experience with Hiberix in other countries, support the safety of Hiberix for booster vaccination in children 15 months through 4 years of age. See Section 10.2 for a discussion of use of Hiberix for catch-up booster vaccination in children 19 months through 4 years of age.

Under this BLA, licensure of Hiberix is being considered only for booster immunization. Most of the available safety data on booster immunization with Hiberix were in children previously primed with Hiberix. Although safety data on booster immunization with Hiberix in children previously primed with a U.S.-licensed Haemophilus b Conjugate Vaccine is limited (234 subjects primed with ActHIB and 27 subjects primed with PedvaxHIB), it is expected that the safety profile of Hiberix following priming with either Hiberix or another manufacturer's Haemophilus b Conjugate Vaccine would not substantially differ.

10 Additional Clinical Issues

10.1 Directions For Use

In clinical studies of Hiberix, the lyophilized vaccine and the saline diluent were supplied in separate vials. Using a syringe with a needle, the saline was added to the vial of lyophilized vaccine. The lyophilized vaccine was reconstituted with shaking. The needle was changed prior to withdrawing the reconstituted vaccine. Not all of the clinical protocols specified the allowed time between reconstitution and use of Hiberix. Some of the protocols specified that the

lyophilized vaccine was to be reconstituted immediately prior to use. Some of the protocols further specified that the Hiberix should be used promptly after reconstitution. One of the protocols specified that Hiberix should be used within 30 minutes after reconstitution.

In all of the clinical studies, Hiberix was administered intramuscularly. In five of the booster immunization studies, the protocol specified the anterolateral thigh as the site for Hiberix administration. In two of the booster immunization studies, the protocol specified the deltoid as the site for Hiberix administration.

Hiberix intended for use in the U.S. will be supplied as a vial of lyophilized vaccine, accompanied by a prefilled syringe containing saline diluent. The proposed directions for use are as follows:

1) Cleanse vial stopper of lyophilized vaccine. Attach appropriate needle to the prefilled syringe of saline diluent and insert into vial.
2) Transfer entire contents of the syringe of saline diluent into vial of lyophilized vaccine.
3) With the needle still inserted, vigorously shake the vial of lyophilized vaccine.
4) After reconstitution, withdraw 0.5 mL of reconstituted vaccine into syringe. Administer by intramuscular injection. Recommended injection sites are the anterolateral thigh or deltoid.

The proposed storage and handling instructions specify that:

- lyophilized vaccine vials should be stored refrigerated between 2^{o} and 8°C (36° and 46°F), protected from light.
- diluent should be store refrigerated between 2° and 8°C (36° and 46°F) or at a controlled room temperature between 20° and 25°C (68° and 77°F).
- after reconstitution, Hiberix should be administered promptly or within 24 hours.
- after reconstitution, Hiberix should be stored between ------b(4)- ---------- and discarded if not used within 24 hours.

The BLA includes stability data on Hiberix final container vaccine reconstituted with saline diluent. Stability was assessed after reconstitution with saline diluent and storage for 24 hours at -----b(4)----------. Please refer to the CBER product review of the Hiberix BLA for CBER's assessment of stability data and the acceptability of the proposed directions for storage and handling of Hiberix.

10.2 Dose Regimen

GSK has proposed the following dose regimens for Hiberix:

- a single 0.5 ml booster dose in children 15 months through 4 years of age who have received a primary series of any other licensed Haemophilus b Conjugate Vaccine;
- a single 0.5 ml dose in children 15 months of age and older previously unvaccinated against invasive disease due to *H. influenzae* type b.

As reviewed in Sections 8.4 and 9.5, the available data support booster vaccination with Hiberix in children previously primed with a licensed Haemophilus b Conjugate Vaccine.

The booster immunization studies of Hiberix were conducted in children who were predominantly 15 to 18 months of age. GSK has requested approval for use of Hiberix for booster immunization in children 15 months through 4 years of age. While routine booster vaccination with Hiberix is intended for children 15 to 18 months of age, there is an anticipated need for catch-up booster vaccination in children 19 months through 4 years of age whose booster dose

was delayed. The safety and effectiveness of a booster dose of Hiberix in children 19 months through 4 years of age is supported by the clinical data on booster vaccination in children 15 to 18 months of age. It is anticipated that the safety profile of Hiberix, when used as a booster dose in children 19 months through 4 years of age, would not meaningfully differ from that observed in children 15 to 18 months of age. It is also expected that previously primed children 19 months through 4 years of age would have an acceptable immune response to booster vaccination with Hiberix. Previous experience with unconjugated Haemophilus b Polysaccharide Vaccines which elicit robust anti-PRP immune responses in children 4 to 5 years of age[7] provides support for this view.

GSK has proposed that a single dose of Hiberix be used for catch-up immunization in unvaccinated children 15 months of age and older. However, there are no data to evaluate the effectiveness of a single dose of Hiberix in previously unvaccinated children.

10.3 Special Populations: Pediatrics

Table 51 summarizes GSK's proposals to address the requirements of the Pediatric Research Equity Act (PREA). CBER concurs with GSK's proposals. CBER's justifications for granting a partial waiver and deferral of studies in the specified age groups are presented in Sections 10.3.1, 10.3.2, and 10.3.3. The proposed approach to meeting the requirements of PREA for Hiberix were discussed with FDA's Pediatric Review Committee on June 24, 2009. The Committee concurred with the approach.

Table 51. Summary of GSK's proposed approach to PREA requirements for Hiberix

Pediatric age group	**How PREA requirements are addressed**
0 to < 6 weeks	Waiver requested
6 weeks to 14 months	Deferral requested
15 months to 4 years (prior to 5th birthday)	Studied in age group 15 to 18 months; extrapolation of safety and effectiveness from age group 15 to 18 months to age group 19 months to 4 years
5 years to 17 years (prior to 18th birthday)	Waiver requested

10.3.1 Infants 0 to <6 Weeks of Age: Request for Waiver of Studies

GSK has requested a waiver of pediatric studies in infants 0 to <6 weeks of age based on Section 505B(a)(4)(B)(iii) of PREA: the drug or biological product – (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients in that age group.

With the exception of Hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g., weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life. Available data on two other Haemophilus b Conjugate Vaccines, HibTITER and ActHIB, suggest that neonatal immunization does not provide evidence of substantially earlier or enhanced protection compared with vaccination beginning at 2 months of age.[10,11] Moreover, there is the concern that vaccination of neonates potentially may be associated with suppression of antibody responses to subsequently administered vaccines. A reduced immune response to some vaccine

antigens has been observed in infants and young children previously vaccinated in the neonatal period with PedvaxHIB[10,12], DT (Diphtheria and Tetanus Toxoids Adsorbed)[10], Daptacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed)[13] and an acellular pertussis vaccine[14].

In 1991, the Advisory Committee on Immunization Practices (ACIP) of the U.S. Department of Health and Human Services recommended that all U.S. infants starting at age 2 months receive Haemophilus b Conjugate Vaccines[15]. By 1996, the incidence of reported invasive disease caused by *H. influenzae* type b among children <5 years of age, 0.3 per 100,000, had declined by >99% compared to the pre-vaccine era when the incidence was estimated at 100 per 100,000.[16] During the years 2002-2006, the average annual incidence of reported invasive disease due to *H. influenzae* type b in children <5 years of age was 0.1 per 100,000.[17] Some cases of disease occur in infants <6 months of age who may be too young to have completed the primary vaccination series. However, it is thought that attaining and maintaining high vaccination coverage at the community level, according to the vaccination schedule recommended by the ACIP, should further reduce oropharyngeal colonization with *H. influenzae* type b in young children, and thereby, interrupt transmission and decrease exposure of susceptible infants.[16, 18]

In view of the epidemiology of invasive disease due to *H. influenzae* type b, the success of the current vaccination schedule, and limitations of immune responses in neonates, use of Hiberix in infants 0 to <6 weeks of age in the U.S. is not thought to represent a meaningful therapeutic benefit over vaccination beginning at 6 weeks of age, and Hiberix is not likely to be used in a substantial number of infants 0 to <6 weeks of age.

10.3.2 Children 5 to 17 Years of Age: Request for Waiver of Studies

GSK has requested a waiver of pediatric studies in children 5 to 17 years of age based on the following sections of PREA:

Section 505B(a)(4)(B)(iii): the drug or biological product – (I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and (II) is not likely to be used in a substantial number of pediatric patients in that age group

and

Section 505.B. (a)(4)(B)(i): necessary studies are impossible or highly impracticable

A booster dose administered in the second year of life completes the ACIP recommended immunization series for Haemophilus b Conjugate Vaccine.[19] Because of the negligible risk of developing invasive disease due to *H. influenzae* type b, the ACIP does not generally recommend vaccination with Haemophilus b Conjugate Vaccine for children 5 years of age and older,[19] and Hiberix would not represent a meaningful benefit to healthy persons in this age range. In this age group, vaccination with Haemophilus b Conjugate Vaccine may be considered for those children who are unimmunized and who have underlying conditions (e.g., sickle cell disease, asplenia, human immunodeficiency virus infection, certain other immunodeficiency syndromes, and malignant neoplasms) that may predispose them to invasive disease due to *H. influenzae* type b. Given the reported high coverage rates for vaccination with Haemophilus b Conjugate Vaccine by 35 months of age, the number of unimmunized children 5 years of age and older in the U.S. is expected to be limited. The additional requirement for specific underlying medical conditions would further limit the number of children in this age group who would be considered for receipt of Hiberix. In addition, it is expected that these children would be geographically dispersed, making studies of Hiberix highly impracticable.

10.3.3 Children 6 Weeks to 14 Months of Age: Request for Deferral of Studies

GSK has requested a deferral of pediatric studies in children 6 weeks to 14 months of age based on the following grounds. The BLA requesting approval of Hiberix for booster vaccination in children 15 months through 4 years of age was filed under the accelerated approval regulations (21 CFR Part 601, Subpart E) in the context of a shortage of Haemophilus b Conjugate Vaccines. The vaccine shortage led to a national recommendation by the CDC to defer the Haemophilus b Conjugate Vaccine booster dose, routinely administered in the second year of life, for children who are not at high risk of infection with *H. influenzae* type b, during the period December 18, 2007 through June 25, 2009. The booster immunization studies included in the Hiberix BLA were completed in the mid- to late-1990s. Waiting for results of a study of Hiberix in children 6 weeks to 14 months of age would delay the licensure of Hiberix for booster immunization and, therefore, delay delivery of vaccine supply that is expected to help accomplish catch-up vaccination in children whose booster dose was deferred as a result of the vaccine shortage.

GSK plans to conduct a clinical trial, Study Hib-097, to fulfill the PREA requirement for pediatric studies for the age group 6 weeks to 14 months of age and to support approval of Hiberix for a 3-dose primary series. The trial is also intended to verify the clinical benefit of booster vaccination with Hiberix, in accordance with the accelerated approval regulations. GSK expects to initiate this study by September 2009 and to submit the final study report by January 2013. Key elements of the planned trial are provided in Section 12.2.1 of this review.

11 Conclusions—Overall

Under the accelerated approval regulations, the available safety and immunogenicity data from clinical studies, combined with the post-marketing safety experience with Hiberix in other countries, support the approval of booster immunization with Hiberix for the prevention of invasive disease due to *H. influenzae* type b. The available data support use of Hiberix in children 15 months through 4 years of age who were previously primed with another manufacturer's Haemophilus b Conjugate Vaccine. The application of the accelerated approval regulations in the context of the Haemophilus B Conjugate Vaccine shortage and the requirement for a post-marketing study to verify clinical benefit of booster immunization with Hiberix was discussed previously in Section 4.3.2 of this review. Plans for a post-marketing study to confirm the clinical benefit of booster immunization with Hiberix and to satisfy requirements of PREA are outlined in Section 12.2.1 of this review.

12 Recommendations

12.1 Approval Recommendation

I recommend approval of Hiberix, under the accelerated approval regulations, for active booster immunization for the prevention of invasive disease due to *H. influenzae* type b in children 15 months through 4 years of age (prior to fifth birthday) who have received a primary series with any other licensed Haemophilus b Conjugate Vaccine.

12.2 Recommendations on Postmarketing Actions

12.2.1 Clinical Trial Postmarketing Requirement

GSK has committed to conduct a randomized clinical trial to evaluate the safety and immunogenicity of Hiberix compared to a U.S. licensed vaccine when administered to healthy infants and children at 2, 4, 6, and 15-18 months of age, concomitantly with other recommended vaccines. This study is intended to: fulfill the requirement of PREA for pediatric studies for the age group 6 weeks to 14 months of age; provide the pivotal clinical data to support licensure of

Hiberix for primary immunization; and as required by CBER for accelerated approval, to verify and further describe the clinical benefit of booster immunization with Hiberix. Recommendations for any additional post-marketing safety studies of Hiberix will be contingent upon CBER's review of the data from the planned clinical trial.

GSK expects to submit a protocol for the planned trial in July 2009, to initiate the study by September 2009, and to submit the final study report by January 2013. In the Hiberix BLA, GSK submitted a concept protocol for the planned trial. In Information Request letters issued April 23, 2009 and June 1, 2009, CBER conveyed recommendations for revisions to be incorporated in the clinical trial protocol. As per these recommendations and GSK's responses, key elements of the planned trial have been agreed upon between CBER and GSK, as follows:

- The study will be conducted in the U.S. in a population that is representative of U.S. infants and children in terms of race/ethnicity.
- The primary vaccination phase will include close safety monitoring in 3,000 subjects who receive Hiberix and 1,000 subjects who receive a U.S. licensed Haemophilus B Conjugate Vaccine.
- Priming and booster doses of Hiberix and Control vaccine will be administered concomitantly with U.S. licensed vaccines recommended for use on the same or overlapping schedule.
- Immunogenicity evaluations will be performed in a subset of subjects following primary vaccination, prior to booster vaccination, and following booster vaccination.
- Primary endpoints include:
    - lot consistency evaluation of Hiberix in terms of post-dose 3 anti-PRP GMCs
    - non-inferiority of Hiberix vs. control vaccine(s) in terms of the percentage of subjects with anti-PRP $\geq$0.15 mcg/ml and anti-PRP $\geq$1.0 mcg/ml following primary vaccination
    - non-inferiority of Hiberix vs. control vaccine(s) in terms of the percentage of subjects with anti-PRP $\geq$1.0 mcg/ml following booster vaccination
    - non-inferiority of immune responses to concomitantly administered vaccines given with Hiberix vs. given with control vaccine(s) in terms of diphtheria and tetanus seroprotection rates, pertussis antibody GMTs, pertussis antibody seroresponse rates, seroprotection rates for polioviruses, and anti-pneumococcal seroresponse rates.

12.2.2 Pharmacovigilance Plan

Please refer to the CBER epidemiology review for the Hiberix BLA for CBER's assessment and recommendations regarding GSK's pharmacovigilance plan for Hiberix.

12.3 Recommendations Regarding PREA

As requested by GSK and outlined in Section 10.3, I recommend waiver of studies of Hiberix in pediatric populations 0-<6 weeks of age and 5 to 17 years of age, and deferral of a study in the age group 6 weeks to 14 months of age. The post-marketing requirement and plans to conduct the deferred study were discussed in Section 12.2.1. The requirement for pediatric studies in the age group 15 months through 4 years of age is fulfilled with this approval.

13 Labeling

The package insert submitted by the applicant was in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. No major labeling issues have been identified.

Specific comments on the labeling proposed by GSK were itemized in a separate review memo dated June 26, 2009.

14 References

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