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

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Subject: Clinical Review of Biologics License Application for GlaxoSmithKline Biologicals' Meningococcal C and Y and Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (proposed proprietary name: MenHibrix)

To: BLA STN# 125363

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA #: 125363

1.1.2 Related Master File and INDs

- IND 11706: GSK's Haemophilus b and *Neisseria meningitidis* Serogroups C and Y – Conjugate (Tetanus Toxoid Conjugate) Vaccine
- IND 13278: GSK's *Neisseria meningitidis* Serogroups A, C, W-135, and Y – Conjugate (Tetanus Toxoid Conjugate) Vaccine

1.1.3 Reviewer Name, Division, and Mail Code

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1.1.4 Submission Received by FDA

August 12, 2009; Complete Responses received April 15, 2011 and December 1, 2011

1.2 Product

1.2.1 Proper Name

Meningococcal Groups C and Y and Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) [referred to as Hib-MenCY-TT]

1.2.2 Proposed Proprietary Name

MenHibrix

1.2.3 Product Formulation

Each 0.5 mL contains 2.5 mcg polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b, 5 mcg *Neisseria meningitidis* serogroup C capsular polysaccharide (PSC), and 5 mcg *Neisseria meningitidis* serogroup Y capsular polysaccharide (PSY), each covalently bound to tetanus toxoid (total --b(4)--).

1.3 Applicant

GlaxoSmithKline (GSK) Biologicals

1.4 Pharmacologic Class

Vaccine

1.5 Proposed Indication

Active immunization for the prevention of invasive disease caused by *H. influenzae* type b and *N. meningitidis* serogroups C and Y. The proposed age range for use is 6 weeks through 15 months of age. Given that children up to 18 months of age received the final formulation of Hib-MenCY-TT in early clinical studies, we recommend approval of Hib-MenCY-TT for immunization in children 6 weeks through 18 months of age. Thus, children who have received the first 3 doses in the Hib-MenCY-TT series but have their 4th dose slightly later than 15 months of age, could receive the 4th dose of Hib-MenCY-TT through 18 months of age.

1.6 Dosage Forms and Route of Administration

Hib-MenCY-TT is a solution for intramuscular injection (0.5 ml dose) supplied as vials of lyophilized vaccine to be reconstituted with the accompanying vial of saline diluent.

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3 Executive Summary

Background

With this BLA, GSK seeks approval of their Haemophilus b + *Neisseria meningitidis* serogroups C and Y Conjugate Vaccine (Tetanus Toxoid Conjugate) (proposed proprietary name, MenHibrix) for active immunization as a four dose series for the prevention of invasive disease caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y. The proposed age range for use of Hib-MenCY-TT is 6 weeks to 15 months of age. Given that children up to 18 months of age received the final formulation of Hib-MenCY-TT in early clinical studies, we recommend approval of Hib-MenCY-TT for immunization in children 6 weeks through 18 months of age. Thus, children who have received the first 3 doses in the Hib-MenCY-TT series but have their 12 or 15 month pediatric visit slightly later could receive the 4th dose of Hib-MenCY-TT through 18 months of age.

Currently, there are no other manufacturers of this particular combination of vaccine components. Other manufacturers of licensed Haemophilus b Conjugate Vaccines in the U.S. include Merck & Co., Inc., which 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]. GSK produces Hiberix [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)]. 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 and Hiberix, which are approved for booster immunization only. Sanofi-Pasteur produces Menactra [meningococcal serogroups A, C, W-135, and Y Conjugate Vaccine (Diptheria Toxoid Conjugate)], which is licensed for use in children as young as 9 months of age. However, currently, no meningococcal conjugate vaccine is licensed for use in infants as young as 2 months of age in the U.S.

Clinical trials demonstrating prevention of disease caused by *Hemophilus influenzae* type b and meningococcal disease caused by serogroups C and Y were not performed as part of the clinical development program. Assessment of the product's effectiveness is inferred from serologic assays. For meningococcal antigens, a serum bactericidal assay using human complement was used. The CBER serology review noted concerns with the serum bactericidal assay used in the evaluation of meningococcal Y immunogenicity (hSBA-MenY). Specifically, a decrease in bactericidal assay titers was observed over time. In communications with GSK during the review process, CBER requested an explanation and supporting data that their assays were working reliably and consistently. These requests were communicated to GSK in two Complete Response (CR) letters. Based on GSK's responses to the second CR letter received December 1, 2011, CBER assay reviewers determined that the hSBA-MenC, and hSBA-MenY assays used in these clinical trials were acceptable to support an evaluation of the effectiveness of the meningococcal antigens in Hib-MenCY-TT.

General Description of Clinical Studies

This BLA for Hib-MenCY-TT contains reports of six completed vaccination studies of doses 1 – 3, five of which also evaluated a fourth dose. Two additional studies evaluated immune memory and antibody persistence after a 3rd dose or antibody persistence after a 4th dose. The studies included a comparator group that received a U.S. licensed *Haemophilus* b (Hib) Conjugate Vaccine for doses 1 - 3. The six clinical studies of doses 1- 3 provide safety data on a total of

7521 children who received Hib-MenCY-TT. In the five clinical studies of dose 4, 7023 subjects received Hib-MenCY-TT; 6686 children received four consecutive doses of Hib-MenCY-TT. An additional 1290 subjects in a separate clinical development program received at least one dose of Hib-MenCY-TT in study MenACWY-TT-057, but only a blinded dataset on Serious Adverse Events (SAEs) in that study was submitted. Clinical studies were conducted in Germany and Belgium, Australia, Mexico, and the United States.

Clinical Studies Effectiveness Data

The evaluation of effectiveness of Hib-MenCY-TT in prevention of Hib 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[1] and data from passive antibody studies[2],[3] 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.

Evaluation of the effectiveness of the meningococcal C and Y components in MenHibrix was based on serogroup-specific bactericidal antibody responses using hSBA. Data from Goldschneider[4] demonstrated that an intrinsic human complement-based Serum Bactericidal Activity (hSBA) assay titer of $\geq$ 1:4 was associated with protection from meningococcal serogroup C. Clinical studies in adults of polysaccharide vaccines demonstrated protection from invasive meningococcal disease caused by serogroups A and C. A determination of effectiveness of polysaccharide vaccines containing serogroups Y and W-135 was based on SBA titers for serogroups Y and W-135 that were similar to SBA titers directed against serogroup C, for which clinical efficacy had been demonstrated. Licensure of meningococcal conjugate vaccine for use in individuals older than 2 years of age was based on SBA titers that are non-inferior to responses observed for other previously licensed meningococcal vaccines (either polysaccharide or conjugate vaccines). For children under age 2 years, use of bactericidal antibody as measured by hSBA was discussed at a meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in 2011, and CBER was advised that hSBA would be acceptable to infer effectiveness in this population[5]. Due to the characteristics of the applicant's hSBA assays, a threshold titer of $\geq$ 1:8 was utilized as the criterion for demonstration of effectiveness following administration of MenHibrix.

Across six studies that evaluated the immunogenicity of doses 1 – 3 of Hib-MenCY-TT, the According to Protocol (ATP) cohorts for immunogenicity included a total of 1467 U.S. subjects (range per study: 70 to 522 subjects) who received Hib-MenCY-TT. All subjects were 5 to 16 weeks of age at first vaccination. Across the five studies evaluating the immunogenicity of dose 4 of Hib-MenCY-TT, the ATP cohorts for immunogenicity included a total of 1458 U.S. subjects (range per study: 42 – 554). All subjects were 11 – 18 months of age at fourth vaccination. Anti-PRP antibodies were measured by Enzyme Linked Immunosorbent Assay (ELISA) using CBER reference serum lot (b)(4), while meningococcal responses were measured as titers based on the hSBA assay in the studies whose results would support licensure. The anti-PRP assays and hSBA-MenC and hSBA-MenY assays used in the clinical studies have been reviewed and found adequate by CBER assay reviewers (internal communications 12/18/2009; review memo 3/27/2012).

Across the three later stage development studies of doses 1 - 3, the proportion of Hib-MenCY-TT subjects with a post-dose 3 vaccination anti-PRP level $\geq$1.0 mcg/mL ranged from 93.5% to 96.3%. For the Hib comparator recipients, these proportions ranged from 84.4% to 91.2%. Across these same 3 studies, the proportion of Hib-MenCY-TT recipients with post-dose 3 hSBA-MenC titers $\geq$ 1:8 ranged from 95.9% to 100%. For one of these studies, the proportion of

subjects with such hSBA assay titers were compared in a post-hoc analysis to the corresponding proportion in the *Menomune* comparator group (ages 3 – 5 years), which was 30.2%. For the other 2 studies, the comparator Hib group had proportions with post-dose 3 hSBA-MenC titers $\geq$ 1:8 ranging from 0.0% to 6.7%. For hSBA-MenY, proportions of Hib-MenCY-TT participants with titers $\geq$ 1:8 ranged from 89.4% to 100% post-dose 3. Corresponding proportions for the *Menomune* and Hib comparator groups were 47.5% and 0.0 – 1.9%, respectively.

Across the 3 later stage development studies evaluating dose 4, all participants had an anti-PRP level $\geq$0.15 mcg/mL. The proportion of Hib-MenCY-TT and Hib subjects with a pre-fourth vaccination anti-PRP level $\geq$1.0 mcg/mL ranged from 56.2% to 66.6% and from 41.1% to 46.4%, respectively. Following the fourth dose, the proportion of Hib-MenCY-TT subjects with an anti-PRP level $\geq$1.0 mcg/mL ranged from 98.9% to 99.6%. For Hib vaccine recipients, this proportion ranged from 98.4% to 99.2%. Across these studies, pre-fourth vaccination anti-PRP Geometric Mean Concentrations (GMCs) ranged from 1.073 to 1.617 mcg/mL in Hib-MenCY-TT recipients and from 0.734 to 0.810 mcg/mL in Hib subjects. Following dose four, anti-PRP GMCs ranged from 28.6 mcg/mL to 34.9 mcg/mL in Hib-MenCY-TT participants and from 19.0 mcg/mL to 21.0 mcg/mL in Hib vaccine control subjects.

Across the three later stage development studies evaluating dose 4, the proportion of Hib-MenCY-TT subjects with post-dose 4 hSBA-MenC and hSBA-MenY titers $\geq$ 1:8 ranged from 96.9% to 99.2% and from 95.4% to 98.8%, respectively. For Hib recipients, these proportions ranged from 0.0% to 21.8% and from 2.7% to 72.5%, respectively. Based on low levels of anti-capsular antibody against polysaccharides for MenC and MenY, as measured by ELISA, it appears that these hSBA titers may be related to the meningococcal serogroup B outer membrane protein conjugate in the Hib vaccine used as the control for the 4th dose. For Hib-MenCY-TT subjects, pre-dose 4 GMTs ranged from 68.1 to 180.3, while post-dose 4 GMTs ranged from 657.1 to 2039.8 for hSBA-MenC; for hSBA-MenY, pre-dose 4 GMTs ranged from 11.3 to 119.1, while post-dose 4 GMTs ranged from 246.6 to 1389.5. Based on the submitted data, Hib-MenCY-TT appears immunogenic for meningococcal serogroups C and Y, as well as for *H. influenzae* type b.

Clinical Studies Safety Data

In the Hib-MenCY-TT studies included in the BLA, specific solicited adverse events were monitored for at least 4 days post-vaccination in five studies of doses 1 – 3 and in four studies of dose 4. Serious and non-serious unsolicited adverse events were monitored during Days 0-30 post-vaccination in five studies of doses 1 – 3 and in four doses of dose 4, as well. In the later phase studies, specific adverse events of interest (SAEs, new onset chronic disease, rash, AEs resulting in an emergency room visit) were followed for 6 months following the last immunization. Across the six studies of doses 1 - 3, there were 26 drop outs due to an adverse event or serious adverse event among 7522 subjects (0.3%) who received Hib-MenCY-TT. Across the studies of dose 4, there was one subject who dropped out due to a serious adverse event among 6767 Hib-MenCY-TT subjects.

In the six studies of doses 1 - 3, among a total of 7521 subjects who received Hib-MenCY-TT, there were 11 deaths reported, while there were 7 deaths reported among the 2779 Hib recipients. Death was reported in an additional subject who had received a non-licensure formulation of Hib-MenCY-TT. In the five studies of dose 4, among the 6687 Hib-MenCY-TT recipients, there were 2 reported deaths, while there were no deaths reported among the 2267 Hib recipients. None of the deaths after any dose were thought by the investigator to be related to vaccination. Based on a throrough review of all death reports, the CBER clinical reviewer concurs that none of the deaths observed during the study were related to any of the vaccines received.

Across studies of doses 1 – 3 administered on the U.S. schedule (Hib-MenCY-TT-001, -005, -007, -009, and -011), at least one SAE occurring within the 31-day post-vaccination period was reported by 1.8% of subjects in the Hib-MenCY-TT group and 2.1% of subjects in the Hib group. Across studies Hib-MenCY-TT-005, -007, -009, and -011, at least one SAE occurring from Day 0 after dose 1 through the day preceding administration of dose 4 was reported by 4.8% of Hib-MenCY-TT participants and 5.0% of Hib recipients. Across studies of dose 4 on a U.S. schedule (Hib-MenCY-TT-006, -008, -010, and -012), at least one SAE occurring within the 31-day post-vaccination period after dose 4 was reported by 0.5% of subjects in each treatment group. From day 0 after dose 4 through the end of the Extended Safety Follow-up ESFU period, at least one SAE was reported in 2.5% of Hib-MenCY-TT subjects and in 2.0% of the Hib participants. All SAEs reported in study MenACWY-TT-057 and submitted to this BLA were blinded as to treatment group, except for those four SAEs which resulted in death. One 4 month old Hib-MenCY-TT recipient developed Hemolytic Uremic Syndrome (H.U.S.) of unknown etiology 43 days after dose 1 and died of H.U.S. and septic shock. Two children died of Sudden Infant Death Syndrome (SIDS), and one died of leukemia. All children had received concomitant vaccinations. In all but one case, the investigator determined the deaths to be unrelated to vaccination. The investigator determined that one case of SIDS was related to vaccination. However, as the SIDS occurred 89 days after vaccination, as well as the fact that other vaccines were administered concomitantly, the clinical reviewer's opinion is that the death cannot be determined to be related to MenHibrix. No deaths were reported in the fourth dose phase of study MenACWY-TT-057.

Across studies, Hib-MenCY-TT was generally no more reactogenic than the Hib vaccine control on the basis of the incidence overall per subject of solicited local and general AEs reported within a 4-day post-vaccination period. Pain was the most frequently reported local AE after doses 1 – 3, occurring in 73.8% of Hib-MenCY-TT recipients and 73.5% of Hib vaccine control recipients across studies Hib-MenCY-TT-001, -005, -007, and -009. Redness was the most frequently reported local AE after dose 4, reported in 47.8% and 54.9% of Hib-MenCY-TT and Hib vaccine recipients, respectively, in studies Hib-MenCY-TT-006, -008, and -010. Irritability was the most frequently reported solicited general AE after doses 1 – 3, reported in 88.7% and 90.0% of Hib-MenCY-TT and Hib subjects, respectively across studies Hib-MenCY-TT-001, -005, -007, and -009. Irritability was also the most frequently reported general AE after dose 4, reported in 57.9% and 61.9% of Hib-MenCY-TT and Hib participants, respectively, across studies Hib-MenCY-TT-006, -008, and -010.

Across studies Hib-MenCY-TT-001, -005, -007, and -009, unsolicited AEs were reported in 61.9% and 62.5% of Hib-MenCY-TT and Hib subjects, respectively. One Hib-MenCY-TT subject reported pyelonephritis as an unsolicited AE (0.0%). Sixteen Hib-MenCY-TT participants (0.4%) and 7 Hib recipients (0.7%) reported urinary tract infections as unsolicited AEs. An additional 2 Hib-MenCY-TT subjects reported *Escherichia* urinary tract infections. Erythema multiforme was reported in 1 Hib-MenCY-TT recipient. Petechiae were reported in 2 Hib-MenCY-TT subjects (0.0%) and 2 Hib subjects (0.1%). Purpura was reported in 1 Hib-MenCY-TT participant. Urticaria was reported in 9 Hib-MenCY-TT participants (0.2%) and 3 Hib subjects (0.2%). Papular urticaria was reported in 2 Hib-MenCY-TT subjects and 1 Hib subject. Following dose 4, across studies Hib-MenCY-TT-006, -008, and -010, unsolicited AEs were reported in 42.5% and 41.4% of Hib-MenCY-TT and Hib vaccine subjects, respectively. Idiopathic Thrombocytopenic Purpura (ITP) was reported in 1 Hib-MenCY-TT recipient. Urinary tract infections were reported as unsolicited AEs in 6 Hib-MenCY-TT and 4 Hib subjects. Petechiae were reported in 2 Hib-MenCY-TT participants. Urticaria was reported in 10 Hib-MenCY-TT subjects (0.3%) and 6 Hib subjects (0.5%). Eczema was reported in 40 (1.1%)

Hib-MenCY-TT subjects and 4 (0.3%) Hib vaccine control subjects. The submitted safety data did not raise concerns regarding the safety of Hib-MenCY-TT.

Post-Marketing Safety Experience
There is no post-marketing safety experience, as Hib-MenCY-TT is not licensed anywhere at this time.

Pediatric Research Equity Act (PREA)
Based on clinical studies of immunization with Hib-MenCY-TT in children 6 weeks through 18 months of age, an indication for use in children 6 weeks through 18 months of age was presented to the Pediatric Review Committee (PeRC), and the PeRC concurred. Thus, children who have received the first 3 doses in the Hib-MenCY-TT series but have their 12 or 15 month pediatric visit slightly later could receive the 4^{th} dose of Hib-MenCY-TT through 18 months of age.

A waiver to conduct studies of MenHibrix in children 0 to <6 weeks of age is justified because the product fails to represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is unlikely to be used in a substantial number of children 0 – <6 weeks of age. A waiver to conduct studies of MenHibrix in children 19 months to less than 17 years of age is justified because in these age groups, use of Hib-MenCY-TT is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules, and Hib-MenCY-TT is not likely to be used in a substantial number of patients.

Conclusions and Approval Recommendation
The available immunogenicity data, obtained in generally healthy children, demonstrate a robust immune response against PRP and meningococcal serogroups C and Y elicited by 4 doses of Hib-MenCY-TT administered concomitantly with DTaP-HBV-IPV and Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (PCV7) at doses 1, 2, and 3 and with MMRII, V, and PCV7 at dose 4. Data are not available on the effectiveness of Hib-MenCY-TT 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 Hib-MenCY-TT raised no significant concerns about the safety of Hib-MenCY-TT. There was an apparent case imbalance in the number of subjects reporting urinary tract infections/pyelonephritis in a pivotal safety study, with a higher occurrence among Hib-MenCY-TT subjects. However, across all studies, this was not the case. Additionally, at this time, there is no apparent biological plausibility that Hib-MenCY-TT would cause urinary tract infections or pyelonephritis.

The available clinical data are considered adequate to support use of Hib-MenCY-TT as a 4 dose immunization series in children 6 weeks through 18 months of age.

Recommendations for Post-Marketing Actions
As recommended by CBER, GSK has committed to conduct a Phase IV trial in the U.S. In the proposed trial, Hib-MenCY-TT will be administered concomitantly with other vaccines that are recommended for U.S. children, specifically Havrix and Rotarix. The planned trial is intended to provide confirmatory evidence of the safety of immunization with Hib-MenCY-TT. GSK expects to initiate the study by October 31, 2013 and to submit the final study report by December 15, 2016.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls (CMC)

Please see CBER CMC and CMC assay reviews. Issues related to the stability and precision of the hSBA assay were included in CBER's Complete Response letters to the applicant. In her March 27, 2012 hSBA serology review of the applicant's responses, as well as additional CBER analyses, the CBER assay reviewer found that the hSBA-MenC, and hSBA-MenY assays appeared adequate to support an evaluation of the effectiveness of Hib-MenCY-TT. The hSBA data for MenC and MenY are presented using the 1:8 cutoff.

4.2 Animal Pharmacology/Toxicology

Pre-clinical toxicity studies were conducted in order to identify and evaluate toxicity findings following intramuscular (IM) administration of the GSK Biologicals' Hib-MenCY-TT vaccine. The toxicological profile of the Hib-MenCY-TT vaccine was studied in GLP-compliant studies. Please see CBER toxicology review for full details.

5 Clinical and Regulatory Background

5.1 Meningococcal and Hib Disease

Meningitis and sepsis are the principle manifestations of invasive disease due to *Neisseria meningitidis* (*N. meningitidis*) and *Haemophilus influenzae* type b (Hib). Other important clinical presentations of meningococcal disease include pneumonia and bacteremia. Even with appropriate medical treatment, the case-fatality ratio is 10 – 14%, and 11 – 19 % of survivors of meningococcal disease experience long-term sequelae, such as neurosensory hearing loss, skin necrosis, seizures, and amputation[6]. The mortality rate due to invasive Hib disease overall is 3 – 6%, and 20 - 30% of survivors experience long-term sequelae, including permanent hearing loss[7].

5.2 Epidemiology of Invasive Meningococcal and Hib Disease in Infants and Toddlers

The highest incidence of meningococcal disease occurs in children <2 years of age. Based on data from the Active Bacterial Core Surveillance (ABCs) for *N. meningitidis*[8], the incidence of invasive meningococcal C disease in the United States among children ages < 1 year and 1 – 2 years, respectively, was 0.19/100,000 and 0.0/100,000 in 2009. For invasive meningococcoal Y disease, these rates were 0.58/100,000 for children ages < 1 year and 0.00/100,000 for children ages 1 -2 years. During 1999-2008, the combined annual incidence of meningococcal serogroups C and Y per 100,000 was 2.3 for children 0 – 2 months, 2.5 for children from 3 – 5 months, 2.0 for children 6 – 8 months, 0.7 for children 9 – 11 months, and 0.4 for children 1 year old[9].

Routine Hib immunization in the US has reduced the incidence of invasive Hib disease by more than 99% in children younger than five years[10]. Based on data from the Active Bacterial Core Surveillance (ABCs) for *H. influenzae* type b[11], in 2008, the incidence of invasive Hib disease in the United States was 0.08/100,000[5] among children younger than five years; in infants younger than one year, the 2009 incidence was 0.0/100,000, while the incidence was 0.20/100,000 in children 1 – 2 years, and 0.07/100,000 in children 2 – 4 years.

5.3 Basis of Clinical Evaluation for Licensure

The licensure of Hib-MenCY-TT is based on the demonstration of meningococcal and Hib effectiveness inferred from serological markers of protection, demonstration of safety, and lot consistency in clinical studies.

5.3.1 Regulatory History

During the first cycle review process, the CMC serology reviewer described concerns with the serum bactericidal assay using human complement that was the basis for evaluation of meningococcal Y immunogenicity (hSBA-MenY), specifically, a decrease in bactericidal assay titers over time. The greatest drop in GMTs was observed in study Hib-MenCY-TT-005, although drops in GMTs were also noted in studies Hib-MenCY-TT-009/-010. The applicant submitted its full response on December 1, 2011 to address CBER's concerns regarding stability of the hSBA MenY assay used in the analysis of the pivotal clinical samples. CBER recommended that, if interpolated and normalized data were used, an evaluation of the clinical endpoints should be performed using 1:16 and 1:32 cutoffs. The CBER statistical reviewer, outlined the results of the analyses based on the 1:16 and 1:32 cutoffs, and results were sufficiently similar to those obtained with the 1:8 cutoff that the 1:8 cutoff was utilized. CBER assay reviewers determined that the hSBA-MenC, and hSBA-MenY assays appeared adequate to support an evaluation of the effectiveness of Hib-MenCY-TT. Therefore, the hSBA data for MenC and MenY are presented using the 1:8 cutoff.

5.3.2 Meningococcal and Hib Serological Markers of Protection

In April 2011, use of an immunologic surrogate of protection was discussed at a FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting. The committee concurred that human bactericidal activity with human complement (hSBA), could be used to infer effectiveness of meningococcal conjugate vaccines in children age <2 years.

Based on an efficacy study with Haemophilus b Polysaccharide Vaccine[12] and data from passive antibody studies[13], an anti-PRP antibody concentration of 0.15 mcg/mL was established as a minimum antibody level of short-term protection. In September 1999, use of an immunologic correlate of protection to infer effectiveness of Hib conjugate vaccines was discussed at a FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting.[24] The committee concurred with this licensure approach.

5.3.3 Rationale for Selected Formulation

See section 8.3.

5.3.4 Previous Human Experience

MenC and PRP antigens in Hib-MenCY-TT are components included in a combination MenC-Hib vaccine (Mentorix) manufactured by GSK, that is not licensed in the US; PRP is available as a monovalent Hib vaccine (Hiberix). In 2009, Hiberix was licensed in the US for use as a booster (4^{th} dose) in children 15 months through 4 years of age. Both Mentorix and Hiberix are available in other countries.

5.4 Postmarketing Experience

There are no postmarketing data available for Hib-MenCY-TT.

6 Clinical Studies

6.1 BLA Sections Reviewed

Amendment 0 (August 12, 2009)
m 1.3.4 Financial Disclosure
m 1.9 Pediatric Administrative Information
m 1.14.1.2 Annotated Draft Labeling Text
m 1.14.1.3 Draft Labeling Text

m 2.5 Clinical Overview
m 2.7.4 Safety Information – Summary of Clinical Safety
m 2.7.3 Efficacy Information – Summary of Clinical Efficacy
m 5.2 Tabular Listing of all Clinical Studies
m 5.3.5.1 Clinical Study Reports
m 5.3.6 Reports of Postmarketing Experience

Amendment 1 (August 26, 2009):
m 1.11.2 Safety Information Amendment (response to CBER request of June 19, 2009)
m 1.6.3 GSK minutes of pre-BLA telecom
m 5.3.5.1 Summary of SAEs, NOCDs, rash over 4 doses for studies Hib-MenCY-TT-005/-006, -007/-008, -009/-010, and -011/-012

Amendment 2 (January 8, 2010):
m 1.6.3 GSK minutes of December 10, 2009 telecon
m 1.11.3 Response to CBER request

Amendment 12 (April 15, 2011):
m 1.11.3 Clinical Items (Items 13 – 20)

Amendment 24 (January 30, 2012):
m 1.14.1 Package Insert (PI) revisions

Amendment 28 (April 13, 2012):
m 1.14.1.2 PI revisions

Amendment 36 (June 12, 2012):
m 1.11.2

Amendment 37 (June 13, 2012):
m 1.11.3 Demography data table
m 1.14.1.2, 1.14.1.3 PI revisions

6.2 Summary of Clinical Studies

Six clinical studies of doses 1 – 3, five of which evaluated dose 4, and two antibody persistence studies were included in the BLA. Studies with objectives to evaluate the safety and immunogenicity of a 4-dose series of Hib-MenCY-TT were designated with one set of study numbers for doses 1-3 [Hib-MenCY-TT -009, -007, -005 and -011], and separate study numbers for the evaluation of a 4th Hib-MenCY-TT dose [Hib-MenCY-TT -010, -008,-006, and -012, respectively]. Across the clinical studies, the age range of subjects enrolled was 2 – 6 months for doses 1 – 3, 12 – 18 months for dose 4, and 11 – 36 months for antibody persistence. For ease of reference, each study number is presented in a distinct row in Table 1 (Overview of Clinical Studies).

Table 1: Overview of Clinical Studies

Study [No.] Country	Description as revelant to US licensure	Study Start/ End	Vaccination schedule	Immunizations in Hib-MenCY-TT group	Number of subjects
					Total Cohort receiving license formulation
Hib-MenCY-TT-009 [103813] United States Australia Mexico	Phase 3 lot-to-lot consistency, immunogenicity, and safety (doses 1-3) Concomitant vaccine: diphtheria (D), tetanus (T), poliovirus (IPV), pertussis (PT, FHA, PRN),hepatitis B (HBV)	February 2006/August 2007	2, 4, 6 months	Hib-MenCY-TT + DTaP-HBV-IPV + PCV7 Permitted:Influenza,Rotavirus	3136
Hib-MenCY-TT-010 [105067] United States Australia Mexico	Phase 3 immunogenicity and safety (4th dose) Concomitant vaccine: MMR,V	December 2006/February 2008 (active), August 2008 (ESFU)	12 – 15 months	Hib-MenCY-TT + MMR + V + PCV7 Permitted: Influenza, hepatitis A	2769
Hib-MenCY-TT-007 [102370] Australia	Phase 2 immunogenicity and safety (doses 1-3)	April 2005/July 2006	2, 4, 6 months	DTaP-HBV-IPV + PCV7 + Hib-MenCY-TT	661
Hib-MenCY-TT-008 [102371] Australia	Phase 2 immunogenicity and safety (4th dose) Concomitant vaccine: MMR,V	March 2006/February 2007 (active), July 2007 (ESFU)	12 – 15 months	Hib-MenCY-TT + MMR + V + PCV7	625 *who received Hib-MenCY-TT + DTaP-HBV-IPV + Prevnar for doses 1 – 3* 204 *who received ActHIB + DTaP-HBV-IPV + Prevnar in study -007*

Hib-MenCY-TT-005 [101858] United States	Phase 2 immunogenicity and safety (doses 1-3) Concomitant vaccine: pertussis (PT, FHA, PRN), PCV7, D,T,IPV,HBV	August 2004/March 2006	2, 4, 6 months	Hib-MenCY-TT + DTaP-HBV-IPV + PCV7	287
Hib-MenCY-TT-006 [102015] United States	Phase 2 immunogenicity and safety (4th dose) Concomitant vaccine: PCV7 (post-dose 4)	July 2005/May 2006	12 – 15 months	Hib-MenCY-TT + PCV7	236* *who received Hib-MenCY-TT + Prevnar + DTaP-HBV-IPV doses 1 – 3* 132 *who received ActHIB + Prevnar + DTaP-HBV-IPV for doses 1 - 3*
Hib-MenCY-TT-011 [105987] United States, Mexico	Phase 3 safety (doses 1-3)	September 2006/October 2007 (active), March 2008 (ESFU)	2, 4, 6 months	Hib-MenCY-TT + DTaP-HBV-IPV + PCV7 Permitted: Influenza vaccine, RV	3278
Hib-MenCY-TT-012 [105988] United States, Mexico	Phase 3 safety (4th dose)	July 2007/November 2008	12 – 15 months	Hib-MenCY-TT + PCV7, MMR, and V Permitted: Influenza, Hepatitis A	3010
Hib-MenCY-TT-013 [107824] United States	Phase 2 one year antibody persistence	September 2006/November 2007	Not applicable	Not applicable	138 *who received Hib-MenCY-TT doses 1 – 3* 62 *who received ActHIB doses 1 - 3*
MenACWY-TT-057** United States	Phase 3 safety and immunogenicity	Not given	2, 4, 6 months	Hib-MenCY-TT + DTaP-HBV-IPV Co-admin of PCV7 strongly encouraged Permitted: Influenza, RV	1290

Hib-MenCY-TT-001 [792014/001] Australia	Phase 2 dose ranging	March 2003 /February 2004	2, 4, 6 months	DTaP-HBV-IPV + PCV7 + Hib-MenCY-TT	82
Hib-MenCY-TT-003 [792014/003] Belgium Germany	Phase 2 dose ranging	March 2003/ December 2003	2, 3, 4 months	Hib-MenCY-TT + Infanrix hexa	78
Hib-MenCY-TT-004 [100381/004] Germany	Phase 2 dose ranging study and evaluation of fourth dose	January 2004/October 2004	12 – 18 months	Hib-MenCY-TT + Infanrix hexa	47

Total cohort = all vaccinated subjects
The symbol "+"indicates that two vaccines are administered concomitantly in two separate injections.
Infanrix penta = Diphtheria and Tetanus Toxoids and Acellular Pertussis, Hepatitis B, Inactivated Poliovirus Vaccine Combined (GSK Biologicals)
Infanrix hexa = Diphtheria and Tetanus Toxoids and Acellular Pertussis, Hepatitis B, Inactivated Poliovirus Vaccine and Hemophilus influenzae type b Vaccine Combined (GSK Biologicals)
DTaP-HBV-IPV: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, (GSK Biologicals)
ActHIB (PRP-T):Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) (Sanofi Pasteur Inc)
PedvaxHIB (PRP-OMP): Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (Merck & Co, Inc)
PCV7: Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals Inc.).
V: Varicella Virus Vaccine Live (manufactured by Merck & Co., Inc.
MMR: Measles, Mumps, and Rubella Virus Vaccine Live (MMR, manufactured by Merck & Co., Inc.
*In study Hib-MenCY-TT-006, the 236 subjects in the total vaccinated cohort of the Hib-MenCY-TT group includes 235 subjects from the Hib-MenCY-TT group who received a fourth dose of Hib-MenCY-TT vaccine at approximately 12 to 15 months of age after 3 doses of Hib-MenCY-TT vaccine at 2, 4, and 6 months and one subject who was assigned incorrectly to the Hib-MenCY-TT group in the fourth dose phase after having received 3 doses of ActHIB in study Hib-MenCY-TT-005
** MenACWY-TT: Safety and immunogenicity trial that included participants who received Hib-MenCY-TT at age 2,4,6 months (all subjects), followed by vaccinations at age 12-15 months: MenACWY-TT + PRP-T (study group 1), Hib-MenCY-TT (study group 2), PRP-T (study group 2)
Source: m 2.7.3 sum-clin-eff-prev-hibmency.pdf, m 2.7.4 summary-clin-safety.pdf, m 5.3.5.1 clinical study reports

6.3 Review Strategy

Data from all clinical studies contributed to the safety of MenHibrix. Study Hib-MenCY-TT -009/010 was the pivotal immunogenicity trial to evaluate a 4-dose series of Hib-MenCY-TT in infants/toddlers. Lot-to-lot consistency was evaluated in Hib-MenCY-TT -009. The safety and immunogenicity of childhood vaccines co-administered with Hib-MenCY-TT were studied in Hib-MenCY-TT -005/006, -008, and -009/010.

6.4 Good Clinical Practices and Data Integrity

A form 483 was issued by CBER's Bioresearch Monitoring (BiMO) inspections at site –b(4)- due to protocol violations, record discrepancies, and inadequacies in investigational drug disposition records. The BiMO reviewer's evaluation did not reveal problems that impact the data submitted in the application (May 13, 2010 memo).

The applicant identified protocol violations of Good Clinical Practice at one of the study sites, which enrolled subjects in studies Hib-MenCY-TT-009/010, and -011/012. Subjects from this site were excluded from the According to Protocol analyses.

Based on financial data returned to the applicant, significant payments of other sorts from the sponsor of the covered study ($25,000 threshold), as specified in 21CFR 54.2, was exceeded for one of the covered studies, study Hib-MenCY-TT-013. This study was an antibody persistence study, in which no vaccination occurred, and no study- or procedure-related serious adverse events were reported by these investigators or any other investigators. Antibody titers of the serum samples drawn in this study were measured using assays performed by blinded laboratory personnel at GSK. Therefore, no sensitivity analysis was performed to assess for the potential impact on the collected data. The applicant reported no investigators as having proprietary interest in the tested product, or as having significant equity interest in the sponsor of the covered study product.

7 Clinical Pharmacology (Immunogenicity)

See section 5.3.2.

8 Clinical Studies

8.1 Pivotal Clinical Studies

8.1.1 Study 103813: Hib-MenCY-TT-009 (Primary vaccination)/ Study 105067: Hib-MenCY-TT-010 (Fourth dose vaccination)

A phase III, randomized, multinational study, double-blinded for the immunogenicity and consistency evaluation of 3 Hib-MenCY-TT vaccine lots and single-blinded and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) compared to monovalent Hib vaccine in healthy infants at 2, 4, 6, and 12 to 15 months of age.

The primary vaccination study period was the timeframe that includes data collected from the day of 1st vaccination (Day 0) to 6 months after the third dose. The fourth dose vaccination study period was the timeframe that pertains to data collected just prior to the 4th Hib-MenCY-TT dose to 6 months after the 4th dose.

Objectives

The study protocol identified 3 different study cohorts based on their investigative site location:

- Cohort 1: U.S. Safety and Immunogenicity Cohort; to include 1080 subjects in Hib-MenCY-TT-009 in the U.S. on which all immunogenicity analyses were based. These subjects also contributed to the safety analyses.
- Cohort 2: Safety Only Cohort; to include 1920 subjects in Hib-MenCY-TT-009 at U.S. sites and at least 1200 additional subjects from the other countries to reach a total of 3120 subjects. Only safety objectives were assessed in this cohort.
- Cohort 3: Non-U.S. Safety and Immunogenicity Cohort; to include the first 200 subjects enrolled at the single center in Mexico. Only descriptive immunogenicity results were reported for this cohort. These subjects also contributed to the safety analyses.

Primary objectives:

Primary vaccination – Cohort 1 in Hib-MenCY-TT-009:

- To demonstrate lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT co-administered with *Pediarix*® (DTaP-HBV-IPV) following 3 primary doses in terms of immunogenicity for PRP, MenC, and MenY.

Fourth dose vaccination -- Cohort 1 in Hib-MenCY-TT-010:

- To demonstrate non-inferiority of the anti-PRP immune response in the group that received 4 doses of Hib-MenCY-TT compared with the group that received 4 doses of licensed monovalent Hib vaccines, with 4th doses administered concomitantly with *MMR*®$_{II}$ (MMR) and *Varivax*® (V)
- To evaluate the MenC and MenY immune responses as measured by serum bactericidal activity assay sourced with human complement (hSBA) to 4 doses of Hib-MenCY-TT (3 pooled lots) co-administered with DTaP-HBV-IPV at 2, 4, and 6 months of age and with MMR and V at 12 to 15 months of age
- To evaluate the specific effect of a 4th dose of Hib-MenCY-TT co-administered with MMR and V at 12 to 15 months of age in terms of a 4th dose vaccine response measured by hSBA-MenC and hSBA-MenY

Primary vaccination – Cohort 1 in Hib-MenCY-TT-009:

- To demonstrate non-inferiority of the anti-PRP immune response of Hib-MenCY-TT vaccine compared to *ActHIB*® (Hib), each co-administered with DTaP-HBV-IPV, following 3 primary doses

Fourth dose vaccination -- Cohort 1 in Hib-MenCY-TT-010 and subjects in the Hib-MenCY-TT and Hib groups in study Hib-MenCY-TT-008:

- To demonstrate non-inferiority of MMR when co-administered with a 4th dose of Hib-MenCY-TT compared to MMR co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with V.
- To demonstrate non-inferiority of immune response to V, measured by ----------(b)(4)----------, co-administered with a 4th dose of Hib-MenCY-TT compared to V co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with MMR

Secondary objectives: (*powered secondary objectives)

Primary vaccination – Cohort 1 in Hib-MenCY-TT-009:

- *To evaluate the MenC immune response as measured by hSBA to 3 doses of Hib-MenCY-TT (3 pooled lots), co-administered with DTaP-HBV-IPV
- *To evaluate the MenY immune response as measured by hSBA to 3 doses of Hib-MenCY-TT (3 pooled lots), co-administered with DTaP-HBV-IPV
- *To demonstrate non-inferiority of immune responses to 3 doses of DTaP-HBV-IPV when co-administered with Hib-MenCY-TT compared to when co-administered with Hib

- To evaluate lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT in terms of percentage of subjects with anti-PRP concentrations ≥0.15 mcg/mL and ≥1.0 mcg/mL one month after 3rd dose
- To evaluate lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT in terms of percentage of subjects with MenC and MenY hSBA titers ≥ 1:4 and ≥ 1:8
- To evaluate immunogenicity following 3-dose primary series of Hib-MenCY-TT compared to that of Hib, each co-administered with DTaP-HBV-IPV, in terms of percentage of subjects with anti-PRP concentrations ≥0.15 mcg/mL and in terms of Geometric Mean Concentrations (GMCs)
- To evaluate hSBA-MenC and hSBA-MenY Geometric Mean Titers (GMTs) following 3 doses of Hib-MenCY-TT and Hib and to evaluate percentage of subjects with hSBA-MenC and hSBA-MenY antibody titers ≥ 1:4 following 3-dose primary series of Hib-MenCY-TT and Hib
- To evaluate immunogenicity following 3-dose primary series of DTaP-HBV-IPV co-administered with Hib-MenCY-TT compared to that of DTaP-HBV-IPV co-administered with Hib with respect to diphtheria, tetanus, PT, FHA, PRN, hepatitis B, and poliovirus types 1, 2, and 3. Hepatitis B antibody titers were stratified by presence or absence of a birth dose of hepatitis B vaccine
- Exploratory analysis for the primary endpoints per vaccine group stratified according to whether or not subjects received co-administered influenza vaccine
- To summarize the percentage of subjects with anti-PSC and anti-PSY antibody concentrations ≥ 0.3 mcg/mL and ≥ 2.0 mcg/mL and the anti-polysaccharide C (PSC) and anti-polysaccharide Y (PSY) GMCs, as measured by ELISA, in the Hib-MenCY-TT (pooled lots) and the Hib treatment groups 1 month after primary vaccination

Primary vaccination – Cohort 3 in Hib-MenCY-TT-009:

- Exploratory evaluation of antibody response to PRP, MenC, and MenY following 3-dose primary series in a subset of subjects (N=200) from Mexico

Primary vaccination – Cohorts 1, 2, and 3 in Hib-MenCY-TT-009:

- *To demonstrate non-inferiority of Hib-MenCY-TT in terms of incidence of fever > 39.5°C/103.1°F within the 4-day follow-up period after any dose compared to Hib, each administered as a 3-dose primary series and each co-administered with DTaP-HBV-IPV
- To evaluate safety and reactogenicity of a 3-dose primary series of Hib-MenCY-TT compared to Hib, each co-administered with DTaP-HBV-IPV
- To summarize safety of a 3-dose primary vaccination course of Hib-MenCY-TT compared to Hib, stratified by receipt of PCV7, influenza, and rotavirus vaccines

Persistence – Cohort 1 in Hib-MenCY-TT-010:

- To demonstrate the persistence of antibodies to MenC induced by 3 primary doses of Hib-MenCY-TT vaccine immediately prior to the 4th dose at 12 to 15 months of age.
- To determine, prior to 4th dose of Hib-MenCY-TT or monovalent Hib vaccine at 12-15 months old, persistence of PRP and *N. meningitidis* serogroups C and Y antibodies induced by 3 primary doses of Hib-MenCY-TT vaccine or Hib, each co-administered with DTaP-HBV-IPV, in terms of anti-PRP GMCs and antibody concentrations ≥0.15 mcg/mL and ≥1.0mcg/mL, hSBA-MenC and hSBA-MenY GMTs, antibody titers ≥ 1:4
- Exploratory evaluation of persistence of hSBA-MenY antibody titers ≥ 1:8
- To summarize the percentage of subjects with anti-PSC and anti-PSY antibody concentrations ≥ 0.3 mcg/mL and ≥ 2.0 mcg/mL and anti-PSC and anti-PSY GMCs, as measured by ELISA, in the Hib-MenCY-TT (pooled lots) and the Hib treatment groups immediately prior to the 4th dose vaccination

Persistence – Cohort 3 in Hib-MenCY-TT-010:

- Exploratory evaluation of persistence of antibodies to PRP, MenC, and MenY in a subset of subjects (N=200) from Mexico

Fourth dose vaccination – Cohort 1 in Hib-MenCY-TT-010:

- To evaluate the immunogenicity of a 4th dose of Hib-MenCY-TT compared to a 4th dose of monovalent Hib vaccine, each co-administered with MMR and V, in terms of subjects with anti-PRP antibody concentrations ≥ 0.15 mcg/mL and GMCs
- To evaluate the immunogenicity of a 4th dose of Hib-MenCY-TT or monovalent Hib vaccine, each co-administered with MMR and V, to *N. meningitidis* serogroups C and Y in terms of hSBA-MenC/Y antibody titers ≥ 1:4
- To summarize the percentage of subjects with anti-PSC and anti-PSY antibody concentrations ≥ 0.3 mcg/mL and ≥ 2.0 mcg/mL and the anti-PSC and anti-PSY GMCs, as measured by ELISA, in the Hib-MenCY-TT (pooled lots) and the *PedvaxHIB*® (Hib) treatment groups 1 month after a 4th dose vaccination

Fourth dose vaccination – Cohort 3 in Hib-MenCY-TT-010:

- Exploratory evaluation of the antibody responses to PRP, MenC, and MenY after the 4th dose in a subset of subjects (N=200) from Mexico

Fourth dose vaccination –Cohort 1 in Hib-MenCY-TT-010 and subjects in the Hib-MenCY-TT and Hib groups in Hib-MenCY-TT-008:

- To demonstrate non-inferiority of MMR when co-administered with a 4th dose of Hib-MenCY-TT compared to MMR co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with V
- To demonstrate the non-inferiority of V co-administered with a 4th dose of Hib-MenCY-TT compared to V co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with MMR in terms of immunogenicity to varicella, measured by –b(4)--
- To evaluate the immunogenicity in terms of anti-measles GMCs, anti-mumps GMTs, anti-rubella GMCs, and anti-varicella GMTs of MMR and V when co-administered with a 4th dose of Hib-MenCY-TT compared with immunogenicity of MMR and V when co-administered with a 4th dose of monovalent Hib vaccine

Fourth dose vaccination – Cohort 1 in Hib-MenCY-TT-010; U.S. subjects only:

- Exploratory evaluation of the percent of subjects with anti-H1N1, anti-H3N2, and anti-B antibody titers ≥ 1:40, as measured by hemagglutination inhibition assay (HIA), in subjects who received 2 doses of influenza vaccine within the same influenza season of which one dose is concomitant with the study vaccine (defined as within 28 days before to 7 days after administration of study vaccines)

Fourth dose vaccination – Cohort 1 in Hib-MenCY-TT-010 and subjects in the Hib-MenCY-TT and Hib groups in Hib-MenCY-TT-008:

- Exploratory evaluation of the percent of subjects with mumps seroresponse ≥ $51ED_{50}$ in initially seronegative subjects (< $24ED_{50}$)

Fourth dose vaccination – Cohorts 1, 2, and 3 in Hib-MenCY-TT-010:

- To demonstrate the non-inferiority of Hib-MenCY-TT vaccine in terms of incidence of fever > 39.5°C/103.1°F, compared to Hib, within the 4-day follow-up period after the 4th dose.
- To evaluate safety and reactogenicity of a 4th dose of Hib-MenCY-TT vaccine compared to Hib
- To summarize the safety of a 4th dose of Hib-MenCY-TT compared to that of Hib, stratified by receipt of PCV7, influenza vaccine, hepatitis A vaccine, and MMR and V

Study Design: This study was a randomized, controlled, multi-national Phase 3 trial. Randomization was 1:1:1:1 to each of the 3 manufacturing lots of Hib-MenCY-TT or monovalent Hib vaccine, each co-administered with DTaP-HBV-IPV at doses 1 -3 and with MMR and V vaccines at dose 4. PCV7 was not routinely provided, but co-administration with each of the 4 doses was strongly encouraged. In study Hib-MenCY-TT-009, 99.0% of the Primary Total

Vaccinated cohort received co-administered DTaP-HBV-IPV and PCV7 with each dose of Hib-MenCY-TT or monovalent Hib at 2, 4, and 6 months of age. In study Hib-MenCY-TT-010, 89.9% of subjects were fully co-vaccinated with Hib-MenCY-TT or Hib, PCV7, MMR and V. Co-administration of influenza vaccine, rotavirus vaccine, and humanized monoclonal antibody for protection against respiratory syncytial virus was permitted. In study Hib-MenCY-TT-009, the majority of subjects in the Primary Total Vaccinated cohort did not receive a rotavirus (87.5%) or influenza vaccine (75.0%). In study Hib-MenCY-TT-010, 98.8% of the Fourth dose Total Vaccinated cohort did not receive concomitant influenza vaccination. The study was double-blind for the 3 Hib-MenCY-TT vaccine lots and single-blind for Hib-MenCY-TT versus monovalent Hib vaccine. Extended safety follow-up after the 4th vaccination was unblinded. Study personnel administering the vaccines were not blinded to the treatment assignment due to differences in vaccine packaging and appearance. For the evaluation of serious adverse events (SAEs), new onset chronic diseases (NOCDs), rashes, and adverse events (AEs) resulting in emergency room (ER) visits, the database from the primary phase were pooled with study Hib-MenCY-TT-011, and the database from the 4th dose phase were pooled with study Hib-MenCY-TT-012. Evaluation of measles, mumps, rubella, and varicella endpoints was to be based on pooled data from studies Hib-MenCY-TT-010 and Hib-MenCY-TT-008.

Study Period: February 22, 2006 - August 27, 2007 (Hib-MenCY-TT-009)

December 29, 2006 – August 5, 2008 (Hib-MenCY-TT-010)

Population

Study Hib-MenCY-TT-009 was conducted at 86 centers in the U.S.*, 1 center in Mexico, and 4 centers in Australia. Study Hib-MenCY-TT-010 was conducted at 85 centers in the U.S.*, 1 center in Mexico, and 4 centers in Australia.

*The applicant eliminated data from one U.S. center with 261 subjects in evaluation of doses 1 - 3 and 189 subjects in evaluation of dose 4 from the analyses due to GCP violations and protocol non-compliance. Post-hoc sensitivity analyses performed regarding the incidence of fever > 39.5°C, SAEs, NOCD, rash, and AEs prompting an ER or physician office visit as well as evaluation of the between group difference for proportions of subjects with anti-PRP concentration $\geq$ 1.0 mcg/mL and proportions of subjects with hSBA-MenC and hSBA-MenY $\geq$ 1:8 post-4th vaccination suggested that elimination of data from this center did not impact the clinical outcomes. For these sensitivity analyses, safety data were categorized by treatment assignment as follows: where vaccine accountability could be reconciled and the treatment received could be confirmed, treatment assignment was reconciled with the treatment assignment given by the investigator in the clinical database; if vaccine accountability could not be reconciled and treatment assignment could not be confirmed, the assignment given by the investigator was used.

Inclusion criteria

- Subjects for whom the investigator believed that parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary card, return for follow-up visits).
- A male or female between and including 6 and 12 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study**.**

- Born after 36 weeks gestation.
- Infants who had not received a previous dose of hepatitis B vaccine or those who had received only 1 dose of hepatitis B vaccine administered at least 30 days prior to enrollment.
- Infants could have received a birth dose of BCG vaccine.

Exclusion criteria

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (For corticosteroids, this was prednisone at $\geq$ 0.5 mg/kg/day, or the equivalent. Inhaled and topical steroids were allowed).
- Planned administration/administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of study vaccine(s). *Palivizumab*®, PCV7, rotavirus vaccine, and influenza vaccine were allowed.
- Previous vaccination against *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, and/or poliovirus; more than one previous dose of hepatitis B vaccine.
- History of *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, hepatitis B, and/or poliovirus disease.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccines, including dry natural latex rubber.
- Major congenital defects or serious chronic illness.
- History of any neurologic disorders or seizures.
- Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever. All vaccines could have been administered to persons with a minor illness such as diarrhea and mild upper respiratory infection with or without low-grade febrile illness, i.e. rectal temperature <38.0°C, axillary/oral temperature <37.5°C, tympanic temperature on oral setting <37.5°C, or tympanic temperature on rectal setting <38.0°C.
- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
- Concurrent participation in another clinical study, at any time during the study period, in which the subject had been or was exposed to an investigational or a non-investigational product (pharmaceutical product or device).

Subjects were not to receive MMR and V if any of the following criteria applied:

- History of measles, mumps, rubella, or varicella
- Previous vaccination against measles, mumps, rubella, or varicella
- Hypersensitivity to any component of the vaccines, including gelatin or neomycin

- Patients receiving immunosuppressive therapy
- Individuals with blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting bone marrow or lymphatic systems
- Individuals with primary and acquired immunodeficiency states
- Individuals with a family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient was demonstrated
- Individuals with active tuberculosis
- Acute disease at time of fourth dose vaccination. (Acute disease was defined as the presence of moderate or severe illness with or without fever)

Reasons for deferring vaccination:

- Acute disease, defined as moderate or severe illness with or without fever.
- Fever (defined as rectal temperature ≥38.0°C (≥100.4°F), axillary/oral temperature ≥37.5°C (≥99.5°F), tympanic temperature on oral setting ≥37.5°C (≥99.5°F), or tympanic temperature on rectal setting ≥38.0°C (≥100.4°F).

Vaccine composition and administration

Hib-MenCY-TT: *Haemophilus influenzae* type b polysaccharide (2.5 mcg) conjugated to tetanus toxoid (5 to 7 mcg); *Neisseria meningitidis* serogroup C capsular polysaccharide (5 mcg) conjugated to tetanus toxoid (5 to 5.5 mcg); *Neisseria meningitidis* serogroup Y capsular polysaccharide (5 mcg) conjugated to tetanus toxoid (5 to 7 mcg); Tetanus toxoid ~ 18 mcg total; Tris-HCL pH 6.8 1.6 mM; NaCl 150 mM; sucrose 12.6 mg. Lyophilized, monodose vials, reconstituted with saline diluent. Administered intramuscularly (IM).

ActHIB (Hib or PRP-T): *Haemophilus influenzae* type b polysaccharide (10 mcg) conjugated to tetanus toxoid (24 mcg); sucrose 8.5%. Administered IM.

Liquid PedvaxHIB (Hib or PRP-OMP): PRP 7.5 mcg; *N. meningitidis* serogroup B outer membrane protein complex 125 mcg; aluminum 225 mcg; sodium chloride 0.9%. Administered IM.

Pediarix/Infanrix penta (DTaP-HBV-IPV) [same formulation; referred to as Pediarix or DTaP-HBV-IPV]: Diphtheria toxoid ≥ 30 IU (25 Lf); tetanus toxoid ≥ 40 IU (10 Lf); pertussis toxin (PT) 25 mcg; filamentous hemagglutinin (FHA) 25 mcg; pertactin (PRN) 8 mcg; recombinant hepatitis B surface antigen (HBs) 10 mcg; poliovirus type 1 (Mahoney) 40 D antigen units; poliovirus type 2 (MEF-1) 8 D antigen units; poliovirus type 3 (Saukett) 32 D antigen units; aluminum adjuvant not more than 0.85 mg by assay; 2-phenoxyethanol 2.5 mg; residual formaldehyde ≤ 100 mcg; thimerosal < 12.5 ng mercury/dose; polysorbate 80 ≤ 100 mcg; sodium chloride 4.5 mg; neomycin ≤ 0.05 ng per dose; polymixin B per dose ≤ 0.01 ng. Administered IM.

Prevnar/Prevenar (PCV7) [same formulation; referred to as Prevnar or PCV7]: 2 mcg each of saccharide of serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 mcg of serotype 6B (16 mcg total saccharide), 20 mcg of CRM197 carrier protein, aluminum as aluminum phosphate adjuvant 0.125 mg. Administered IM.

MMRII (MMR): measles virus ≥ 1000 $TCID_{50}$ (tissue culture infectious doses), mumps virus 20000 $TCID_{50}$, rubella virus 1000 $TCID_{50}$ Administered subcutaneously (SQ).

Varivax (V): varicella virus > 1350 pfu, sucrose approximately 25 mg, hydrolyzed gelatin 12.5 mg, sodium chloride 3.2 mg, modosodium L-glutamate 0.5 mg, sodium phosphate dibasic 0.45

mg, potassium phosphate monobasic 0.08 mg, potassium chloride 0.08 mg, MRC-5 cells, including DNA and protein – residual components, sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum – trace quantities. Administered SQ.

Due to difficulties in obtaining PCV7 for the Hib-MenCY-TT clinical program, infant doses of PCV7 for U.S. subjects were: supplied by the investigator, sourced without charge from the Australian government, and provided as a study vaccine to Mexican participants.

MMR, V, and the 4th dose of PCV7 were provided as study vaccines to subjects in the the U.S. safety and immunogenicity cohort (cohort 1). MMR and V vaccines were not mandated as concomitant vaccines for the safety only cohort (cohort 2) and the Mexico safety and immunogenicity cohort (cohort 3), but were permitted to be administered during the study according to U.S. prescribing practices and labeled indications. For all participants, PCV7 vaccine was not mandated as a concomitant vaccine, but was permitted to be administered during the study according to U.S. prescribing practices and labeled indications. Approximately 90% of subjects across groups were vaccinated with MMR, V, PCV7, and the 4th dose of either Hib-MenCY-TT or Hib on the same day. Influenza, rotavirus, hepatitis A vaccines were permitted to be administered according to local recommendations. The vast majority (> 97%) of subjects did not receive influenza or hepatitis A vaccines concomitantly with the 4th dose of either Hib-MenCY-TT or Hib.

Endpoints

Primary endpoints:

Cohort 1 in Hib-MenCY-TT-009:

1. Lot-to-lot consistency: anti-PRP GMCs, hSBA-MenC GMTs, hSBA-MenY GMTs

Cohort 1 in Hib-MenCY-TT-010:

2. Immunogenicity with respect to anti-PRP concentration $\geq$1.0 mcg/mL (42 days post-4th vaccination)
3. Immunogenicity with respect to hSBA Men C and Men Y titers $\geq$ 1:8 (42 days post-4th vaccination)
4. Immunogenicity with respect to hSBA-MenC post/pre titer and hSBA-MenY post/pre titer after 4th dose of Hib-MenCY-TT (42 days post-4th vaccination)

Cohort 1 in Hib-MenCY-TT-009:

5. Immunogenicity with respect to anti-PRP concentration $\geq$ 1.0 mcg/mL (1 month post-3rd dose)

Cohort 1 in Hib-MenCY-TT-010 and subjects in the Hib-MenCY-TT and Hib groups in Hib-MenCY-TT-008 (42 days post-4th vaccination):

6. Co-administration with MMR (42 days post-4th dose): Anti-measles concentration $\geq$ 150 mIU/mL in initially seronegative subjects (< 150 mIU/mL), anti-mumps titer $\geq$ 28 ED_{50} in subjects with initial anti-mumps antibody < 28 ED_{50}, anti-rubella concentrations $\geq$ 10 IU/mL in initially seronegative subjects (< 4 IU/mL)
7. Co-administration with V (42 days post-4th dose): Anti-varicella titer $\geq$ 1:5 dilution in initially seronegative subjects (< 1:5)

Secondary endpoints:

Primary vaccination: Cohort 1 in Hib-MenCY-TT-009 – 1 month after 3rd dose:

- Anti-PRP GMCs and antibody concentrations $\geq$ 0.15 mcg/mL and $\geq$ 1.0 mcg/mL (except for the evaluations specified in the primary objectives)
- hSBA-MenC GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- hSBA-MenY GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- Anti-D antibody concentration $\geq$ 0.1 IU/mL and GMCs
- Anti-T antibody concentration $\geq$ 0.1 IU/mL and GMCs
- Anti-HBs GMCs and antibody concentrations $\geq$ 10.0 mIU/mL stratified by presence or absence of a birth dose of hepatitis B vaccine
- Anti-PT, anti-FHA, and anti-PRN antibody concentrations $\geq$ 5 EL.U/mL and GMCs
- Anti-poliovirus types 1, 2, and 3 antibody titers $\geq$ 8 ED_{50} and GMTs
- Anti-PSC and anti-PSY concentrations $\geq$ 0.3 mcg/mL and $\geq$ 2.0 mcg/mL and GMCs

Primary vaccination: Cohort 3 in Hib-MenCY-TT-009 – 1 month after 3rd dose:

- Anti-PRP GMCs and antibody concentrations $\geq$ 0.15 mcg/mL and $\geq$ 1.0 mcg/mL
- hSBA-MenC GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- hSBA-MenY GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- Anti-PSC and anti-PSY concentrations $\geq$ 0.3 mcg/mL and $\geq$ 2.0 mcg/mL and GMCs

Primary vaccination: Cohorts 1, 2, and 3 in Hib-MenCY-TT-009:

- Fever > 39.5°C/103.1°F in the 4-day follow-up period after any dose (pooled Hib-MenCY-TT vaccine lots vs. Hib)
- Incidence of solicited local (pain, redness, and swelling) and general (fever, irritability/fussiness, drowsiness, and loss of appetite) symptoms within 4 days following each vaccine dose
- Incidence of unsolicited symptoms within 31 days (day 0 – 30) following each dose of Hib-MenCY-TT vaccine and Hib
- From dose 1 through 6 months after the last primary dose or until administration of the 4th dose (whichever comes first), the following were evaluated: SAEs, NOCD, incidence of rash, incidence of ER visits or physicians' office visits unrelated to well-child care, vaccination, injury, or common acute illnesses such as upper respiratory tract infections, otitis media, pharyngitis, gastroenteritis

Persistence: Cohort 1 in Hib-MenCY-TT-010 – prior to the 4th dose vaccination:

- hSBA-MenC antibody titers $\geq$ 1:8 with LL of the 95% CI $\geq$ 70%

Persistence: Cohorts 1 and 3 in Hib-MenCY-TT-010 – prior to the 4th dose vaccination:

- Anti-PRP GMCs and concentrations $\geq$ 0.15 mcg/mL and $\geq$ 1.0 mcg/mL
- hSBA-MenC GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- hSBA-MenY GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- Anti-PSC and anti-PSY GMCs and antibody concentrations $\geq$ 0.3 mcg/mL and $\geq$ 2.0 mcg/mL

Fourth dose vaccination: Cohort 1 in Hib-MenCY-TT-010 – 42 days after 4th dose vaccination:

- Anti-PRP GMCs and concentrations $\geq$ 0.15 mcg/mL and $\geq$ 1.0 mcg/mL (except for endpoints noted under primary objectives)
- hSBA-MenC antibody titers $\geq$ 1:4
- hSBA-MenY antibody titers $\geq$ 1:4
- Anti-PSC and anti-PSY GMCs and antibody concentrations $\geq$ 0.3 mcg/mL and > 2.0 mcg/mL

Fourth dose vaccination: Cohort 3 in Hib-MenCY-TT-010 – 1 month after 4th dose vaccination:

- Anti-PRP GMCs and concentrations $\geq$ 0.15 mcg/mL and $\geq$ 1.0 mcg/mL
- hSBA-MenC GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8
- hSBA-MenY GMTs and antibody titers $\geq$ 1:4 and $\geq$ 1:8

- Anti-PSC and anti-PSY GMCs and antibody concentrations $\geq$ 0.3 mcg/mL and $\geq$ 2.0 mcg/mL

Fourth dose vaccination: Cohort 1 in Hib-MenCY-TT-010 and subjects in the Hib-MenCY and Hib groups in Hib-MenCY-TT-008 – 42 days after 4th dose vaccination:

- Anti-measles GMCs and concentration $\geq$ 200 mIU/mL in initially seronegative subjects (<150 mIU/mL)
- Anti-mumps GMTs and concentration $\geq$ 28 ED_{50} and $\geq$ 51 ED_{50} in initially seronegative subjects (< 24 ED_{50})
- Anti-rubella GMCs and concentration $\geq$ 4 IU/mL in initially seronegative subjects (< 4 IU/mL)
- Anti-varicella GMTs and titer $\geq$ 1:40 dilution in initially seronegative subjects (< 1:5)

Fourth dose vaccination: Cohort 1 in Hib-MenCY-TT:

- Percent of subjects with anti-H1N1, anti-H3N2, and anti-B antibody titers $\geq$ 1:40, as measured by HIA, in subjects who received 2 doses of influenza vaccine within the same influenza season of which at least one dose is concomitant with the study vaccine. For the purposes of this study, concomitant administration of influenza vaccine was defined as administration within 28 days before to 7 days after administration of study vaccines

Fourth dose vaccination: Cohorts 1, 2, and 3 in Hib-MenCY-TT-010:

- Fever > 39.5°C/103.1°F in the 4-day follow-up period after the 4th dose

Fourth dose vaccination: Cohorts 1, 2, and 3 in Hib-MenCY-TT-010:

- Incidence of solicited local symptoms (pain, redness, swelling at injection site, increase in limb circumference) within 4 days following 4th dose
- Incidence of increased circumferential swelling at the injected limb(s) within 4 days after 4th dose vaccination. Increased circumferential swelling was defined as either swelling with a diameter of > 50 mm or a > 50 mm increase in the circumference of the mid-limb when compared to baseline measurement, or any diffuse swelling that interferes with or prevents everyday activities
- Incidence of solicited general symptoms (fever, irritability/fussiness, drowsiness, loss of appetite) within 4 days following 4th dose

Fourth dose vaccination: Cohort 1 in Hib-MenCY-TT-010:

- Incidence of general symptoms specific to measles, mumps, rubella, and varicella vaccination (fever, rash/exanthema, parotid/salivary gland swelling, and any suspected signs of meningism including febrile convulsions) within 43 days after vaccination

Fourth dose vaccination: Cohorts 1, 2, and 3 in Hib-MenCY-TT-010:

- Incidence of unsolicited symptoms during the 31-day follow-up period following 4th dose
- From the 4th dose of Hib-MenCY-TT and Hib through the end of the 6-month safety follow-up, incidence of SAEs, NOCD, rash, and ER visits or physicians' office visits not related to well-child care, vaccination, injury, or common acute illnesses such as upper respiratory tract infections, otitis media, pharyngitis, gastroenteritis.

Randomization

Performed using a central randomization system on Internet (SBIR) using a minimization procedure accounting for center. Some sites performed home visits and, for logistical reasons, needed to randomize subjects prior to the first visit. In these cases, if a child's parents decided not to enroll their child in the study, the vial was reassigned in the randomization system.

Due to the volume of blood required to perform the immunogenicity analyses, 2 randomly selected subsets were used within the US (Cohort 1) and non-US subjects (Cohort 3) according to the following:

Primary Vaccination: All subjects were assayed for PRP, hSBA-MenC, hSBA-MenY, anti-PSC, and anti-PSY. Additionally, 70% of the subjects were assayed for D, T, PT, FHA, PRN, poliovirus types 1, 2 and 3, and HBsAg. Anti-PSC and anti-PSY were tested in those subjects in Cohorts 1 and 3 that had sera available.

Fourth dose Vaccination: All subjects were assayed for PRP, anti-PSC and anti-PSY. Additionally, 70% of all subjects were assayed for hSBA-MenC and hSBA-MenY, while the other 30% of all subjects were assayed for rSBA-MenC and rSBA-MenY. Further, U.S. subjects (i.e., Cohort 1) were assayed for measles, mumps, rubella, varicella, and (where applicable) influenza H1N1, H3N2, and B. Anti-PSC and ant-PSY were tested in those subjects in Cohorts 1 and 3 that had sera available.

Surveillance

Safety parameters:

The protocol, case reporting form, and safety reporting were reviewed with investigators and site personnel prior to study initiation.

Study participants were observed for 30 minutes post-vaccination and were monitored for local and systemic reactions for 4 days post-immunization, with reactions reported on daily diary cards by subjects' guardians. Solicited adverse events included localized symptoms, such as pain, redness, and swelling at the injection site in the primary vaccination phase and increase in mid-limb circumference in addition to these symptoms in the 4th dose phase. Solicited systemic adverse events were fever, irritability/fussiness, drowsiness, and loss of appetite. The protocol-specified mechanism for this diary card return was via mail. A telephone contact was schedule Day 1 – Day 3 to remind parents or guardians to complete the diary card and to inquire about the occurrence of any serious adverse events. The diary card compliance rate was approximately 95% for evaluation of doses 1 – 3 and > 90% for evaluation of dose 4.

Approximately 53% - 60% of subjects' temperatures were measured via the protocol-specified, rectal route for doses 1 – 3. Approximately 40% to 47% measured temperature via the axillary route. For dose 4, the axillary route was the protocol-specified route for measuring temperature.

Data on unsolicited adverse events were collected via daily recording on diary cards during the 30 days post-immunization; these diary cards were collected at the next visit for all subjects following doses 1 and 2, and at the visit for blood sampling for subjects in the immunogenicity cohorts. Unsolicited AE data was collected via scripted telephone call occurring 31 to 48 days after the 3rd and 4th vaccinations for subjects who did not have a blood sampling visit.

Data on medically attended visits, NOCD, and rash were collected throughout the study by asking subjects' guardians via telephone contact or visit days 182 - 194 if the subjects received medical attention defined as hospitalization, emergency room visit, or visit to or from medical personnel for any reason.

A 43-day follow-up of solicited general adverse events, such as fever, rash/exanthema, parotid/salivary gland swelling, and suspected signs of meningitis/febrile seizures was performed in subjects enrolled in Cohort 1 after administration of MMR and V.

Serious adverse events were collected throughout the study period via telephone contact days 1 – 3 and days 31 – 48 and telephone contact or visit days 182-194 (Cohort 1). For Cohort 2, telephone contact occurred days 31 - 37.

Immunogenicity (methods):
Serum samples were obtained from Cohorts 1 and 3 one month post-3rd vaccination, prior to 4th vaccination, and 1.5 months post-4th vaccination.

Assay methods and laboratories:
Table 2: Assay methods and laboratories

Marker	Assay method	Test kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory**
hSBA-MenC	hSBA	in-house	dilution	1:4	GSK Bio
hSBA-MenY	hSBA	in-house	dilution	1:4	GSK Bio
anti-PSC	ELISA	in-house	mcg/mL	0.3	GSK Bio
anti-PSY	ELISA	in-house	mcg/mL	0.3	GSK Bio
anti-D*	ELISA	in-house	IU/mL	0.1	GSK Bio
anti-T*	ELISA	in-house	IU/mL	0.1	GSK Bio
anti-PT*	ELISA	in-house	ELU/mL	5	GSK Bio
anti-FHA*	ELISA	in-house	ELU/mL	5	GSK Bio
anti-PRN*	ELISA	in-house	ELU/mL	5	GSK Bio
anti-HBs	ELISA	in-house	mIU/mL	10	GSK Bio
anti-polio 1	Neutralization	in-house	ED_{50}	1:8	GSK Bio
anti-polio 2	Neutralization	in-house	ED_{50}	1:8	GSK Bio
anti-polio 3	Neutralization	in-house	ED_{50}	1:8	GSK Bio
anti-PRP	ELISA	in-house	mcg/mL	0.15	GSK Bio
anti-measles	ELISA	------(b)(4)----------	mIU/mL	150	GSK Bio
anti-mumps	Neutralization	in-house	ED50	24	GSK Bio
anti-rubella	ELISA	------(b)(4)----------	IU/mL	4	GSK Bio
anti-varicella	(b)(4)	in-house	dil. -1	5	--(b)(4)----------
anti-H1N1	Hemagglutination inhibition	in-house	dil. -1	10	GSK Bio
anti-H3N2	Hemagglutination inhibition	in-house	dil. -1	10	GSK Bio
anti-B	Hemagglutination inhibition	in-house	dil. -1	10	GSK Bio

Source: Table 6, Hib-MenCY-TT-009 clinical study report, page 109 and Table 8, Hib-MenCY-TT-010 clinical study report, page 141
***** ELISA or multiplex
****** All serological assays will be performed in the GSK Biologicals' central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures with adequate controls.
----------**(b)(4)**----------
§ ED_{50} = Endpoint dilution 50

Statistical plan

Sample size calculations

Sample size estimations were based on the following numbers of planned enrolled (evaluable) participants:

Study #	Hib-MenCY-TT	Hib	Total
Hib-MenCY-TT 009 (Cohort 1: US safety and immuno)	810	270	1080
Hib-MenCY-TT 009 (Cohort 2: Safety - US and non-US)	2340	780	3120
Hib-MenCY-TT 009 (Cohort 3: non-US safety and immuno)	150	50	200
Hib-MenCY-TT 010 (Cohort 1: US safety and immuno)	618	198	816
Hib-MenCY-TT 010 (Cohort 2: Safety - US and non-US)	2015	678	2693
Hib-MenCY-TT 010 (Cohort 3: non-US safety and immuno)	136	47	183

The planned sample size of 1080 subjects in Cohort 1, 3120 subjects in Cohort 2, and 200 subjects in Cohort 3 enabled global power to reach all primary objectives 75 %. The power relative to the first primary objective of lot-to-lot consistency was $\geq$ 99.6%.

Primary Hypotheses

1. To establish **lot-to-lot consistency** by demonstrating that for each pair of lots and for immune response to each antigen (anti-PRP, hSBA-MenC, hSBA-MenY), the two-sided 95% CI on the GMCs/GMTs ratio between lots is within [0.5, 2.0] interval.
2. To establish **non-inferiority of immunogenicity with respect to anti-PRP concentration $\geq$1.0 mcg/mL after 4th vaccination** by demonstrating the lower limit of 95% CI for (pooled Hib-MenCY-TT – Hib) in percentage of subjects with anti-PRP concentrations $\geq$1.0 mcg/mL is $\geq$-10%.
3. To evaluate **immunogenicity 6 weeks after 4th vaccination with respect to hSBA Men C and Men Y titers $\geq$ 1:8** by determining the lower limits of the exact 95% CI for percentage of subjects with hSBA titers $\geq$1:8 is $\geq$90% for MenC and MenY.
4. To evaluate the **specific effect of a 4th dose of Hib-MenCY-TT** in terms of immune response measured by hSBA-MenC and hSBA-MenY with the following criteria for immunogenicity for MenC and MenY: lower limit of the asymptotic 95% CI for the geometric mean of the individual ratio of titers post-dose 4/pre-dose 4 $\geq$ 2.
5. To demonstrate non-inferiority of **immunogenicity post-3rd dose with respect to anti-PRP concentration $\geq$1.0 mcg/mL** following 3 doses of Hib-MenCY-TT compared to Hib by demonstrating the lower limit of the standardized asymptotic 95% CI for [pooled Hib-MenCY-TT – Hib] in percentage of subjects with anti-PRP concentrations $\geq$ 1.0 mcg/mL is $\geq$ -10%.
6. To demonstrate **non-inferiority of MMR with respect to immune response to antigen components** after co-administration with 4th vaccination of study vaccines by determining lower limit of 95% CI as $\geq$-5% for the difference (Hib-MenCY-TT – Hib) in percentage of subjects with anti-measles concentration $\geq$150 mIU/mL, anti-mumps titer $\geq$ 28 ED_{50}, anti-rubella concentration $\geq$10 mIU/mL 42 days post-4th dose.
7. To demonstrate **non-inferiority of V with respect to anti-varicella immune response** after co-administration with 4th vaccination of study vaccines by establishing lower limit of 95%CI of $\geq$-10% on difference (Hib-MenCY-TT – Hib) in percentage of subjects with anti-varicella titer $\geq$1:5

Secondary Hypotheses

- To evaluate the **MenC immune response after 3 doses of Hib-MenCY-TT** by determining that the lower limit of the exact 95% CI for the percentage of subjects with hSBA-MenC titers $\geq$ 1:8 is $\geq$ 90%.

- To evaluate the **MenY immune response after 3 doses of Hib-MenCY-TT** by determining that the lower limit of the exact 95% CI for the percentage of subjects with hSBA-MenC titers $\geq$ 1:8 is $\geq$ 85%.

- To demonstrate **non-inferiority of immune response to DTaP-HBV-IPV co-admininstered with Hib-MenCY-TT or Hib** one month after 3rd dose by showing lower limits of 95% CIs as **either**: $\geq$-10% on the difference (pooled Hib-MenCY-TT – Hib) in percentages of subjects with concentrations $\geq$0.1 IU/mL or titers $\geq$ 8 ED_{50} for Diphtheria and tetanus antigens or poliovirus antigens, respectively **OR** $\geq$0.67 on the GMC ratios ($GMC_{\text{pooled Hib-MenCY-TT}}/GMC_{\text{Hib}}$) for each pertussis antigen, PT, FHA, and PRN.

- To demonstrate the **non-inferiority of Hib-MenCY-TT in terms of incidence of fever > 39.5°C/103.1°F** within the 4-day follow-up period after any dose compared to *ActHIB*®, each administered as a 3-dose primary series and each co-administered with DTaP-HBV-IPV with the lower limit of the 95% CI of $\geq$ -2.4% on (Hib – pooled HibMenCY-TT) in percentage of subjects with fever > 39.5°C/103.1°F

- To demonstrate **persistence of antibodies to MenC induced by 3 primary doses of Hib-MenCY-TT** vaccine immediately prior to 4th dose at 12 to 15 months of age by showing a lower limit of 95% CI of $\geq$ 70% for the percentage of subjects with hSBA-MenC titers $\geq$ 1:8

- To demonstrate **non-inferiority of MMR with respect to immune response to antigen components** after co-administration with 4th vaccination of study vaccines by determining lower limit of 95% CI as $\geq$-5% for the difference (Hib-MenCY-TT – Hib) in perecentage of subjects with anti-measles concentration $\geq$200 mIU/mL, anti-mumps titer $\geq$ 28 ED_{50} (in initially seronegative subjects with anti-measles < 150 mIU/mL and anti-mumps < 24 ED_{50}) 42 days post-4th dose.

- To demonstrate **non-inferiority of V with respect to anti-varicella immune response** after co-administration with 4th vaccination of study vaccines by establishing lower limit of 95% CI of $\geq$-10% on difference (Hib-MenCY-TT – Hib) in percentage of subjects with anti-varicella titer $\geq$1:40

- To demonstrate the **non-inferiority of Hib-MenCY-TT in terms of incidence of fever > 39.5°C/103.1°F** within the 4-day follow-up period after any dose compared to Hib within 4 days of 4th vaccination with the lower limit of the 95% CI of $\geq$ -1.6% on (Hib – pooled HibMenCY-TT) in percentage of subjects with fever > 39.5°C/103.1°F

Criteria for meeting other secondary endpoints were not defined in the protocol.

Populations analyzed

Total vaccinated cohort:

The total vaccinated cohort for the primary vaccination study period included all participants who received at least one of the initial 3 doses in the 4 dose series, and the total vaccinated cohort for

the 4th dose vaccination study period included all participants who received a 4th dose of study vaccine, excluding subjects from the dropped U.S. site. Analyses were performed according to the vaccine received.

Safety analyses for the first 3 doses were performed on the primary total vaccinated cohort, and safety analyses for the fourth dose were based on the Fourth dose total vaccinated cohort.

According-to-Protocol (ATP) cohort:
The ATP safety cohort for the primary vaccination study period included all subjects eligible for inclusion in the Primary total vaccinated cohort, who met all inclusion and no exclusion criteria, received at least 1 dose of vaccine according to the treatment assigned during the primary vaccination study period, for whom the location of the injection site was known, and who had not received a vaccine not specified in the protocol during the primary vaccination study period.

The Fourth dose ATP cohort for safety included all eligible subjects who met all inclusion criteria and no exclusion criteria for the study, who had received 3 vaccine doses in Hib-MenCY-TT-009, who received the fourth dose, and who had not received a vaccine not specified or forbidden in the protocol, and who were not excluded from the primary ATP cohort for immunogenicity, unless the reason for exclusion was non-compliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at the post-dose 3 timepoint.

Analysis of immunogenicity post-dose 3 was based on the primary ATP cohort for immunogenicity (Primary ATP cohort with available assay results for antibodies against at least one study vaccine antigen for the blood sample taken 1 month after the third dose). If the percentage of enrolled subjects with serological results excluded from this ATP cohort was >5%, a second analysis based on the total vaccinated cohort was to be performed. There were 296/991 (29.9%) subjects in the Primary Total Vaccinated Cohort 1 not eligible for inclusion in the Primary ATP Cohort for Immunogenicity.

The primary analysis of antibody persistence was performed on all eligible subjects from the Fourth dose ATP cohort for safety who had immunogenicity results at the pre-fourth dose timepoint for at least one antigen in Cohort 1. The primary analysis of immune response to the fourth dose was based on the Fourth dose ATP Cohort for immunogenicity in Cohort 1.

Pre- and post-fourth dose immunogenicity analyses were performed separately on data from Cohort 1 and Cohort 3. The non-inferiority of co-administration with MMR and V was to be performed on data pooled from the post-4th dose timepoint in this study and a non-U.S. study conducted in Australia under IND.

Safety Analyses
Safety analyses included number and percentage of participants with occurrence of adverse events that were defined according to MedDRA terms, and categorized by study group. Descriptive summaries were to be presented across countries and by country, by receipt of hepatitis A vaccination (dose 4) and overall, by receipt of rotavirus vaccination (first 3 doses) and overall, by receipt of co-administered vaccines and overall.

Immunogenicity Analyses

Immunogenicity analyses included number and percentage of participants with immune responses to antigens in study vaccines and to antigens in co-administered vaccines, within group analysis for seroresponse, and between group analyses among study vaccines for non-inferiority. Within group analyses were to be presented across countries and by country, by receipt of hepatitis A

vaccination (dose 4) and overall, by receipt of rotavirus vaccination (first 3 doses) and overall, by receipt of co-administered vaccines and overall.

Protocol Amendments (Amendments to IND):
Amendment 1: 2 February 2006. Guidelines added regarding pre-informed consent procedure for studies that performed home visits. Procedure included to offer the Hib control group enrolled in Australia a licensed meningococcal serogroup C vaccine after completion of the safety follow-up.

Amendment 2: 7 March 2006. Protocol amended to allow sites to co-administer rotavirus vaccine with study vaccines or according to local recommendations.

Amendment 3: 5 October 2006. Anti-HBs antibody were measured by an in-house ELISA. Demonstration of immunogenicity was based on U.S. subjects (Cohort 1), and sample size calculations were revised accordingly. Protocol primary immunogenicity objectives and secondary objectives were revised to include an evaluation of hSBA-MenC and hSBA-MenY. Procedures were clarified to specify that no conversion factor would be applied to the axillary/tympanic temperatures to obtain a rectal temperature equivalent. PCV7, MMR and V were provided as study vaccines to subjects for administration with the 4th dose of Hib-MenCY-TT or Hib. Analyses were provided based on country and co-administered vaccines.

Amendment 4: 19 March 2009. Evaluation of the immunogenicity of the vaccine as a 4 dose series was included as a primary endpoint. Assessment of hSBA-MenC and hSBA-MenY following the 3rd vaccination were included as secondary objectives. Secondary analyses were provided for fever analysis and DTaP-HBV-IPV concomitant vaccine evaluation. GMT ratios (post-/pre- fourth dose) for hSBA-MenC and hSBA-MenY were included as a primary endpoint, analyses of MMR, V antibody responses at alternative levels/titers were provided, the interval for blood sampling for inclusion in the Fourth dose ATP Cohort for Immunogenicity for Cohort 1 was defined as 35 – 56 days post-fourth dose. In a response to a CBER information request, immunogenicity data was provided to support the defined interval. Additional analyses were provided based on subjects with blood sampling interval of 35 – 77 days.

Other important changes:
Sensitivity analyses were included to address CBER concerns regarding potential differences between the populations used for analyses of the primary vaccination phase and the fourth dose population.

Results:

Population

A total of 4441 subjects were enrolled in study Hib-MenCY-TT-009, but 261 subjects from one site were excluded, leaving 4180 (Hib-MenCY-TT n=3136, Hib n=1044) subjects in the Primary Total Vaccinated Cohort. The number of withdrawals in study Hib-MenCY-TT-009 was 331 (Hib-MenCY-TT 248 withdrawals, Hib 83 withdrawals); 3849 individuals completed the 3-dose vaccination course study Hib-MenCY-TT-009 through 1 month post-dose 3 (2888 Hib-MenCY-TT participants and 961 Hib subjects), and 3853 subjects completed through the ESFU post-dose 3 (2898 Hib-MenCY-TT participants and 955 Hib subjects). The most common reason for withdrawal was consent withdrawal (133 subjects total), with 74 subjects lost to follow-up, 33 withdrawn for protocol violations, 7 for SAEs (all HibMenCY-TT recipients), and 4 for AEs (3

HibMenCY-TT and 1 Hib participant). There were 4 deaths, 3 among Hib-MenCY-TT recipients, and 1 in a Hib recipient.

A total of 3883 toddlers were enrolled in study Hib-MenCY-TT-010, 189 participated at the dropped site, and 3581 subjects completed the study (Hib-MenCY-TT n=2682, Hib n= 899). A total of 111 subjects were withdrawn. One subject in the Hib-MenCY-TT group withdrew due to an SAE and died 29 days post-4th vaccination due to trauma from a motor vehicle accident. Eleven subjects (10 Hib-MenCY-TT recipients and 1 Hib participant) withdrew consent. Two subjects, one in each treatment group, moved from the study area. Sixty-five subjects with complete vaccination were lost to follow-up, 53 in the Hib-MenCY-TT group and 12 in the Hib group. Thirty-two subjects (22 in the Hib-MenCY-TT group and 10 in the Hib group) were classified as other. The number of subjects who completed the ESFU post-dose 4 was 3531 (2640 in the Hib-MenCY-TT group and 891 in the Hib group). All enrolled subjects except subjects who withdrew consent during the active phase of the study were contacted to complete the ESFU.

Safety population:
The Primary Total Vaccinated cohort population for safety included 4180 participants (Hib-MenCY-TT n=3136, Hib n=1044). For the Primary Total Vaccinated Cohort 1, there were 991 subjects (Hib-MenCY-TT n=744, Hib=247). The Primary ATP safety cohort included 4096 subjects (Hib-MenCY-TT n=3074, Hib n=1022). The Primary ATP safety Cohort 1 included 971 subjects (Hib-MenCY-TT n=731, Hib n=240). A secondary analysis based on the Primary ATP safety cohort was not performed, as < 5.0% of enrolled subjects were not eligible for inclusion in the Primary ATP safety cohort safety analysis. The 4th dose Total Vaccinated Cohort 1 included 816 subjects (Hib-MenCY-TT n=618, Hib n=198). A secondary analysis based on the Fourth dose ATP Cohort for Safety was performed since > 5% of subjects were excluded from the Fourth dose Total Vaccinated Cohort; there were 690 subjects from Cohort 1 in this cohort (Hib-MenCY-TT n= 513, Hib n= 177). The overall Fourth dose Total Vaccinated Cohort was the basis for safety analyses following the 4th dose and included 3692 subjects (Hib-MenCY-TT n= 2769, Hib n= 923), while the overall Fourth dose ATP Safety Cohort included 3293 subjects (Hib-MenCY-TT n=2466, Hib n= 827). The denominators used in the safety analyses were as follows: solicited local AEs – all doses with solicited local symptoms documented as either present or absent; solicited general AEs – all doses with a solicited general AE documented as either present or absent; unsolicited AE from day 0 to day 30 – all doses administered; concomitant medication (which would include antipyretics) – all doses administered.

Immunogenicity population:
The Primary ATP Immunogenicity Cohort 1 included 695 subjects (Hib-MenCY-TT n=522, Hib n=173). The most common reasons for why approximately 29.9% of subjects in the Primary Total Vaccinated cohort, Cohort 1 were excluded from the Primary ATP immunogenicity cohort were: essential serological data missing, non-compliance with blood sampling schedule, and non-compliance with vaccination schedule. **Primary immunogenicity analyses were based on the Primary ATP cohort for immunogenicity, Cohort 1.** Protocol pre-specified, supplemental immunogenicity analyses were performed on the Primary Total Vaccinated cohort, Cohort 1, since more than 5% of enrolled subjects with serological results available in any vaccine group were not eligible for inclusion in the Primary ATP cohort for immunogenicity. These supplemental analyses suggested similar results to the primary immunogenicity analyses, with the exception that criteria for lot-to-lot consistency were met. **Analysis of antibody persistence** was based on the 4th dose ATP safety Cohort 1, which included 690 subjects (Hib-MenCY-TT n= 513, Hib n= 177). **Analysis of 4th dose immunogenicity** was based on the 4th dose ATP immunogenicity cohort 1, which included 521 participants (Hib-MenCY-TT n=389, Hib n=132),

which was approximately 63.8% of the subjects in the Fourth dose Total Vaccinated Cohort, Cohort 1. The most common reason for exclusion from the 4th dose ATP immunogenicity cohort was essential serological data missing. Since more than 5% of the enrolled subjects with serological results were excluded from the Fourth dose ATP cohort for safety for the persistence analysis and the Fourth dose ATP Cohort for immunogenicity, additional analyses were performed on the Fourth dose Total Vaccinated Cohort. Results were fairly similar.

Safety:

Overall safety profile:

Over the first 3 doses, the overall incidence [95% CI] of any reaction (solicited and unsolicited) in each of the 3 HibMenCY-TT lots was: Lot A 95.6% [94.1, 96.7], Lot B 97.3% [96.2, 98.2], 96.2% [94.8, 97.3]. The overall incidence of any adverse event (solicited and unsolicited) was 96.4% [3022/3136] in the Hib-MenCY-TT group (all lots pooled) and 95.2% [994/1044] in the Hib group. The confidence intervals (CI) overlapped. The incidence of grade 3 adverse events overall/subject was 27.3% [856/3136] in the pooled Hib-MenCY-TT group and 34.4% [359/1044] in the Hib group. The confidence intervals did not overlap.

Following the fourth dose, the overall incidence of adverse events during the 4-day post-vaccination period was 79.5% [2201/2769] in the Hib-MenCY-TT group and 83.0% [766/923] in Hib recipients.

Very few subjects outside the US received influenza or hepatitis A vaccination. Even among US subjects, no conclusions may be reached regarding concomitant administration of Hib-MenCY-TT with influenza or hepatitis A vaccines due to the relatively small number of subjects in each group (N= 29 for HibMenCY-TT and N=16 for Hib) who received a concomitant influenza vaccination or hepatitis A vaccination (N=80 for HibMenCY-TT and N= 26 for Hib).

Immediate reactions:

None

Local reactions:

Over doses 1 - 3, the overall occurrence per subject of any (solicited and unsolicited) grade 3 local reactions was reported as 18.4% [576/3136] and 25.7% [268/1044] of pooled Hib-MenCY-TT and Hib recipients, respectively. The 95% confidence intervals (CIs) did not overlap. Local reactions of any severity were reported in 87.8% [2752/3136] and 87.0% [908/1044] of pooled Hib-MenCY-TT and Hib participants, respectively. The respective 95% CIs were (86.6, 88.9) and (84.8, 89.0). The incidence [95% CI] of any systemic reaction (solicited and unsolicited) in each of the 3 HibMenCY-TT lots was: Lot A 87.4% [85.2, 89.4], Lot B 88.5% [86.4, 90.4], 87.3% [85.2, 89.3].

The most frequently reported solicited local reaction in all groups, pain, was reported in 78.3% of pooled Hib-MenCY-TT participants and 80.6% of Hib subjects. The incidence of grade 3 pain was 15.1% in the pooled HibMenCY-TT group and 22.8% in the Hib group. In the Hib-MenCY-TT and Hib groups, injection site pain tended to decrease slightly with subsequent doses, while redness and swelling tended to increase. Similar trends were observed for all 3 HibMenCY-TT lots individually.

Table 3. Hib-MenCY-TT-009. Solicited local reactions (Days 0 – 3), Primary Total Vaccinated Cohort, Hib-MenCY-TT or Hib injection site

Reaction	Severity	HibMenCY Lot A		HibMenCY Lot B		HibMenCY Lot C		HibMenCY pooled Lots A, B, C			*HIB*		
		N =908 - 1013		N = 916 - 1025		N = 914 - 1018		N = 2738 - 3056			N=904 - 1008		
		n	%	n	%	n	%	n	%	95% CI	n	%	95% CI
Dose 1													
Redness	Any	227	22.4	223	21.8	223	21.9	673	22.0	20.6, 23.5	294	29.2	26.4, 32.1
	Grade 3	1	0.1	2	0.2	1	0.1	4	0.1	0.0, 0.3	15	1.5	0.8, 2.4
Swelling	Any	136	13.4	147	14.3	146	14.3	429	14.0	12.8, 15.3	196	19.4	17.0, 22.0
	Grade 3	5	0.5	2	0.2	3	0.3	10	0.3	0.2, 0.6	11	1.1	0.5, 1.9
Pain	Any	491	48.5	503	49.1	501	49.2	1495	48.9	47.1, 50.7	614	60.9	57.8, 63.9
	Grade 3	75	7.4	69	6.7	67	6.6	211	6.9	6.0, 7.9	133	13.2	11.2, 15.4
Dose 2													
Redness	Any	296	30.9	311	32.1	296	30.5	903	31.1	29.4, 32.8	320	33.6	30.6, 36.7
	Grade 3	3	0.3	1	0.1	2	0.2	6	0.2	0.1, 0.4	3	0.3	0.1, 0.9
Swelling	Any	192	20.0	186	19.2	179	18.4	557	19.2	17.8, 20.7	190	19.9	17.4, 22.6
	Grade 3	4	0.4	2	0.2	2	0.2	8	0.3	0.1, 0.5	2	0.2	0.0, 0.8
Pain	Any	438	45.7	445	45.9	465	47.8	1348	46.5	44.6, 48.3	514	53.9	50.7, 57.1
	Grade 3	56	5.8	44	4.5	59	6.1	159	5.5	4.7, 6.4	76	8.0	6.3, 9.9
Dose 3													
Redness	Any	342	37.7	327	35.7	301	32.9	970	35.4	33.6, 37.3	363	40.2	36.9, 43.4
	Grade 3	1	0.1	0	0.0	1	0.1	2	0.1	0.0, 0.3	4	0.4	0.1, 1.1
Swelling	Any	212	23.3	190	20.7	202	22.1	604	22.1	20.5, 23.7	231	25.6	22.7, 28.5
	Grade 3	4	0.4	1	0.1	1	0.1	6	0.2	0.1, 0.5	2	0.2	0.0, 0.8
Pain	Any	382	42.1	377	41.2	399	43.7	1158	42.3	40.4, 44.2	463	51.2	47.9, 54.5
	Grade 3	37	4.1	37	4.0	38	4.2	112	4.1	3.4, 4.9	46	5.1	3.7, 6.7

Source: modified from applicant-provided Tables and Supplements 129, 130, 131, 138, 139, 140, of the Hib-MenCY-TT-009 CSRs

N = number of subjects with the documented dose. According to pre-specified analysis plan, since < 5% of subjects in the Primary Total Vaccinated Cohort were excluded from the Primary Safety Cohort, analyses of rates of solicited reactions were not performed on the Primary Safety Cohort; thus, they are presented based on the Primary Total Vaccinated Cohort

n/%: number/percentage of subjects reporting the symptom at least once

Grade 3 redness defined as > 30.0 mm diameter

Grade 3 swelling defined as > 30.0 mm diameter

Grade 3 pain defined as “cried when limb was moved/spontaneously painful”

After any of the first three vaccinations, redness at the Hib-MenCY-TT or Hib site overall was more frequently reported in Mexican (50.8% and 58.3%) subjects compared with Australian subjects (47.9% and 49.0%) and U.S. subjects (46.6% and 53.2% for redness). Pain and swelling at the Hib-MenCY-TT or Hib injection site overall was least commonly reported in Australian subjects (44.6% and 45.0% for pain; 26.3% and 23.8% for swelling) compared to U.S. (66.6% and 75.7% for pain; 34.9% and 39.9% for swelling) or Mexican (88.9% and 93.5% for pain; 33.7% and 40.7% for swelling) subjects. For all injection sites, injection site pain was most commonly reported in Mexican subjects, as well. The 95% confidence intervals for the reported rates of injection site pain at any injection site after any of the first 3 doses were non-overlapping between countries, but did overlap for HibMenCY-TT and Hib group comparisons within each country.

Table 4: Local adverse reactions at the Hib-MenCY-TT (3 pooled lots) or Hib injection site (Days 0 – 3) after each of the first 3 doses, by country, Primary Total Vaccinated Cohort

Reaction	Severity	Australia				Mexico				United States			
		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib	
		N = 436 - 451		N = 140 - 150		N = 577 - 596		N = 195 - 199		N = 1725 - 2009		N = 569 - 659	
		n	%	n	%	n	%	n	%	n	%	n	%
Dose 1													
Redness	Any	93	20.6	35	23.3	167	28.0	75	37.7	413	20.6	184	27.9
	Grade 3	1	0.2	3	2.0	0	0.0	0	0.0	3	0.1	12	1.8
Swelling	Any	36	8.0	15	10.0	98	16.4	46	23.1	295	14.7	135	20.5
	Grade 3	0	0.0	1	0.7	0	0.0	0	0.0	10	0.5	10	1.5
Pain	Any	128	28.4	50	33.3	439	73.7	158	79.4	928	46.2	406	61.6
	Grade 3	5	1.1	3	2.0	131	22.0	55	27.6	75	3.7	75	11.4
Dose 2													
Redness	Any	134	30.0	41	28.1	188	32.4	73	37.4	581	31.0	206	33.7
	Grade 3	1	0.2	0	0.0	0	0.0	1	0.5	5	0.3	2	0.3
Swelling	Any	58	13.0	16	11.0	116	20.0	47	24.1	383	20.4	127	20.8
	Grade 3	0	0.0	1	0.7	2	0.3	0	0.0	6	0.3	1	0.2
Pain	Any	114	25.5	36	24.7	399	68.8	155	79.5	835	44.6	323	52.8
	Grade 3	3	0.7	1	0.7	95	16.4	44	22.6	61	3.3	31	5.1
Dose 3													
Redness	Any	156	35.8	51	36.4	201	34.8	72	36.9	613	35.5	240	42.2
	Grade 3	0	0.0	1	0.7	0	0.0	1	0.5	2	0.1	2	0.4
Swelling	Any	67	15.4	14	10.0	126	21.8	54	27.7	411	23.8	163	28.6
	Grade 3	0	0.0	0	0.0	0	0.0	0	0.0	6	0.3	2	0.4
Pain	Any	76	17.4	29	20.7	368	63.8	150	76.9	714	41.4	284	49.9
	Grade 3	2	0.5	0	0.0	71	12.3	29	14.9	39	2.3	17	3.0

Source: Modified from Supplements 217 – 225, Hib-MenCY-TT-009 CSR

After the 4th vaccination, local reactions were reported in 62.4% [1729/2769] of HibMenCY-TT participants and 68.7% [634/923] of Hib recipients. The most frequently reported solicited local reactions were pain and increase in arm circumference, which were reported in 52.2% and 53.8% of Hib-MenCY-TT subjects and 59.4% and 54.5% of Hib participants. There were a total of 22 large injection site reactions reported in 14 subjects (9 HibMenCY-TT recipients and 5 Hib subjects). For 12 of these reactions, no measurement was provided by the parent/guardian. Reported measurement values ranged from 50 – 70 mm in the HibMenCY-TT group and from 3 – 90 mm in the Hib group. None of these reactions was examined or confirmed by the investigator.

Table 5: Local adverse reactions at the Hib-MenCY-TT or Hib injection site (Days 0 – 3) following the 4th dose, Fourth dose Total Vaccinated Cohort

Reaction	Severity	Days	HibMenCY (pooled lots)			Hib		
			N=2522 - 2769			N=829 - 933		
			n	%	95% CI	n	%	95% CI
Pain	Any	0 - 3	1040	41.2	39.3, 43.2	439	53.0	49.5, 56.4
	Grade 3	0 - 3	43	1.7	1.2, 2.3	46	5.5	4.1, 7.3
Redness	Any	0 - 3	892	35.4	33.5, 37.3	397	47.9	44.4, 51.4
	Grade 3	0 - 3	15	0.6	0.3, 1.0	10	1.2	0.6, 2.2
Swelling	Any	0 - 3	635	25.2	23.5, 26.9	267	32.2	29.0, 35.5
	Grade 3	0 - 3	19	0.8	0.5, 1.2	9	1.1	0.5, 2.1
Increased arm circumference*	Any	0 – 3	793	28.6	27.0, 30.4	269	29.1	26.2, 32.2
	> 40.0 mm	0 – 3	13	0.5	0.3, 0.8	1	0.1	0.0, 0.6

Source: modified from applicant's Table 58 of the Hib-MenCY-TT-010 CSR
N = number of subjects with administered dose
n/%: number/percentage of subjects reporting the symptom at least once
Grade 3 redness: > 30 mm
Grade 3 swelling: > 30 mm
Grade 3 pain: cried when the limb was moved/spontaneously painful
Grade 3 increased arm circumference: > 40 mm

After the 4th vaccination, reported rates of any adverse event within 4-days post-vaccination were lowest in the U.S. (77.1% in the HibMenCY-TT group and 78.1% in the Hib group), compared with Australia (87.2% in the HibMenCY-TT group and 93.8% in the Hib group) and Mexico (80.8% in the HibMenCY-TT group and 89.6% in the Hib group). Some 95% CIs around the percentages of subjects reporting any AE were overlapping between countries. Except for Mexico, the 95% CIs around the point estimates for percentages of subjects reporting any adverse event overlapped between treatment groups within each country.

Table 6: Local adverse reactions at the Hib-MenCY-TT or Hib injection site (Days 0 – 3) following the 4th dose, Fourth dose Total Vaccinated Cohort, by country

Reaction	Severity	Australia				Mexico				United States			
		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib	
		N = 424		N = 144		N = 565		N = 193		N = 1533		N = 492	
		n	%	n	%	n	%	n	%	n	%	n	%
Pain	Any	97	22.9	55	38.2	298	52.7	136	70.5	645	42.1	248	50.4
	Grade 3	1	0.2	1	0.7	18	3.2	19	9.8	24	1.6	26	5.3
Redness	Any	147	34.7	86	59.7	215	38.1	81	42.0	530	34.6	230	46.7
	Grade 3	4	0.9	4	2.8	1	0.2	0	0.0	10	0.7	6	1.2
Swelling	Any	95	22.4	59	41.0	151	26.7	52	26.9	389	25.4	156	31.7
	Grade 3	10	2.4	5	3.5	0	0.0	0	0.0	9	0.6	4	0.8
Increased arm circumference	Any	132	29.6	44	30.1	250	44.1	93	48.2	624	35.5	205	35.1
	Grade 3	0	0.0	0	0.0	5	0.9	1	0.5	8	0.5	2	0.3

Source: Modified from applicant's Supplements 265 – 273 and 277 – 279, Hib-MenCY-TT-010 CSR
N = number of subjects with administered dose
n/%: number/percentage of subjects reporting the symptom at least once
Grade 3 redness: > 30 mm
Grade 3 swelling: > 30 mm
Grade 3 pain: cried when the limb was moved/spontaneously painful
Grade 3 increased arm circumference: > 40 mm

Systemic reactions:
Over doses 1 - 3, the incidence [95% CI] of any systemic reaction (solicited and unsolicited) in each of the 3 HibMenCY-TT lots was: Lot A 92.5% [90.7, 94.0], Lot B 95.4% [94.0, 96.6], Lot C 94.9% [93.4, 96.2]. The overall per subject occurrence of any systemic reaction (solicited and unsolicited) was 94.3% [2957/3136] for pooled Hib-MenCY-TT and 93.8% [979/1044] for Hib. The confidence intervals overlapped. The overall per subject occurrence of grade 3 systemic reactions (solicited and unsolicited) was 15.6% [489/3136] for pooled Hib-MenCY-TT and 19.2% [200/1044] for Hib. The confidence intervals did not overlap. Slightly more than half of subjects had temperatures measured by the protocol-specified rectal route for doses 1 – 3; slightly fewer than half of subjects had temperatures measured by the axilllary route for these doses.

There were clinically significant differences between countries in the rates of some systemic reactions, namely, fever. Lower observed rate of antipyretic use in Mexico may have contributed to the higher rates of fever there compared with the U.S. and Australia, but fever rates in the U.S. were noticeably higher compared with fever rates in Australia, despite similar observed rates of antipyretic use. Specifically, any antipyretic use was reported in 32.8% of Hib-MenCY-TT recipients and 32.0% of Hib recipients in Mexico, 73.7% of Hib-MenCY-TT recipients and 78.2% of Hib recipients in the U.S., and 69.1% of Hib-MenCY-TT recipients and 74.8% of Hib recipients in Australia. Prophylactic antipyretic use was highest in the U.S. (nearly one-third of subjects in both groups), while it was $\leq$ 5.5% in either treatment group in both Mexico and Australia.

Table 7: Solicited systemic adverse reactions, (Days 0 -3), Primary Total Vaccinated Cohort, after each of the first 3 doses

	Reaction	Severity	HibMenCY Lot A		HibMenCY Lot B		HibMenCY Lot C		HibMenCY pooled Lots A, B, C			HIB		
			N = 909 - 1013		N = 914 - 1025		N = 913 - 1018		N = 2738 - 3055			N=904 - 1008		
			n	%	n	%	n	%	n	%	95% CI	n	%	95% CI
Dose 1	Fever	Any	241	23.8	224	21.9	223	21.9	688	22.5	21.0, 24.0	228	22.6	20.1, 25.3
		Grade 3	1	0.1	0	0.0	0	0.0	1	0.0	0.0, 0.2	0	0.0	0.0, 0.4
	Irritability	Any	692	68.4	736	71.8	728	71.5	2156	70.6	68.9, 72.2	782	77.6	74.9, 80.1
		Grade 3	45	4.4	32	3.1	49	4.8	126	4.1	3.4, 4.9	78	7.7	6.2, 9.6
	Loss of appetite	Any	327	32.3	341	33.3	356	35.0	1024	33.5	31.8, 35.2	375	37.2	34.2
		Grade 3	5	0.5	4	0.4	6	0.6	15	0.5	0.3, 0.8	4	0.4	0.1, 1.0
	Drowsiness	Any	620	61.3	625	61.0	619	60.8	1864	61.0	59.3, 62.7	655	65.0	61.9, 67.9
		Grade 3	35	3.5	23	2.2	30	2.9	88	2.9	2.3, 3.5	32	3.2	2.2, 4.5
Dose 2	Fever	Any	260	27.1	281	29.0	262	27.0	803	27.7	26.1, 29.4	276	29.0	26.2, 32.0
		Grade 3	1	0.1	0	0.0	1	0.1	2	0.1	0.0, 0.2	1	0.1	0.0, 0.6
	Irritability	Any	664	69.2	717	74.0	693	71.3	2074	71.5	69.8, 73.2	708	74.4	71.5, 77.1
		Grade 3	49	5.1	51	5.3	52	5.3	152	5.2	4.5, 6.1	56	5.9	4.5, 7.6
	Loss of appetite	Any	300	31.3	324	33.4	297	30.6	921	31.8	30.1, 33.5	317	33.3	30.3, 36.4
		Grade 3	6	0.6	6	0.6	6	0.6	18	0.6	0.4, 1.0	8	0.8	0.4, 1.6
	Drowsiness	Any	515	53.7	545	56.2	528	54.3	1588	54.8	52.9, 56.6	552	58.0	54.8, 61.1
		Grade 3	22	2.3	31	3.2	32	3.3	85	2.9	2.3, 3.6	29	3.0	2.0, 4.3
Dose 3	Fever	Any	196	21.6	226	24.7	187	20.5	609	22.3	20.7, 23.9	206	22.8	20.1, 25.6
		Grade 3	0	0.0	1	0.1	5	0.5	6	0.2	0.1, 0.5	2	0.2	0.0, 0.8
	Irritability	Any	590	64.9	589	64.4	592	64.8	1771	64.7	62.9, 66.5	600	66.3	63.1, 69.4
		Grade 3	33	3.6	37	4.0	28	3.1	98	3.6	2.9, 4.3	42	4.6	3.4, 6.2
	Loss of appetite	Any	295	32.5	266	29.1	267	29.2	828	30.3	28.5, 32.0	285	31.5	28.5, 34.6
		Grade 3	4	0.4	4	0.4	6	0.7	14	0.5	0.3, 0.9	8	0.9	0.4, 1.7
	Drowsiness	Any	414	45.5	431	47.2	415	45.5	1260	46.1	44.2, 47.9	444	49.1	45.8, 52.4
		Grade 3	17	1.9	15	1.6	19	2.1	51	1.9	1.4, 2.4	15	1.7	10.2, 14.6

Source: Modified from applicant tables in Supplements 159 - 162, 170 – 173 Hib-MenCY-TT-009 CSR
N: number of subjects with at least one documented dose; n/%: number/percentage of subjects reporting the symptom at least once
Grade 3 drowsiness: drowsiness that prevented normal activity; Grade 3 fever: > 40.0C
Grade 3 loss of appetite: not eating at all; Grade 3 irritability: crying that could not be comforted/prevented normal activity

Table 8. Systemic adverse reactions, Hib-MenCY-TT (3 pooled lots) vs Hib (Days 0 – 3) after doses 1 - 3, by country, Primary Total Vaccinated Cohort

	Reaction	Severity	Australia				Mexico				United States			
			Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib	
			N = 435 - 451		N = 141 - 150		N = 578 - 596		N = 195 - 199		N = 1723 - 2008		N = 569 - 659	
			n	%	n	%	n	%	n	%	n	%	n	%
Dose 1	Drowsiness	Any	262	58.1	97	64.7	340	57.0	117	58.8	1262	62.8	441	66.9
		Grade 3	3	0.7	3	2.0	30	5.0	11	5.5	55	2.7	18	2.7
	Fever	Any	47	10.4	16	10.7	262	44.0	71	35.7	379	18.9	141	21.4
		Grade 3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0
	Irritability	Any	354	78.5	117	78.0	447	75.0	158	79.4	1355	67.5	507	76.9
		Grade 3	18	4.0	9	6.0	34	5.7	20	10.1	74	3.7	49	7.4
	Loss of appetite	Any	154	34.1	45	30.0	192	32.2	82	41.2	678	33.8	248	37.6
		Grade 3	1	0.2	0	0.0	3	0.5	2	1.0	11	0.5	2	0.3
Dose 2	Drowsiness	Any	228	50.9	69	47.3	281	48.4	106	54.1	1079	57.7	377	61.8
		Grade 3	4	0.9	3	2.1	21	3.6	10	5.1	60	3.2	16	2.6
	Fever	Any	64	14.3	21	14.4	255	43.9	83	42.3	484	25.9	172	28.2
		Grade 3	0	0.0	0	0.0	0	0.0	1	0.5	2	0.1	0	0.0
	Irritability	Any	344	76.8	105	71.9	405	69.7	145	74.0	1325	70.8	458	75.1
		Grade 3	23	5.1	5	3.4	40	6.9	17	8.7	89	4.8	34	5.6
	Loss of appetite	Any	152	33.9	45	30.8	169	29.1	67	34.2	600	32.1	205	33.6
		Grade 3	0	0.0	0	0.0	5	0.9	4	2.0	13	0.7	4	0.7
Dose 3	Drowsiness	Any	183	42.1	56	39.7	224	38.8	90	46.2	853	49.5	298	52.4
		Grade 3	3	0.7	1	0.7	18	3.1	6	3.1	30	1.7	8	1.4
	Fever	Any	42	9.7	13	9.2	170	29.4	58	29.7	397	23.0	135	23.7
		Grade 3	0	0.0	0	0.0	1	0.2	0	0.0	5	0.3	2	0.4
	Irritability	Any	303	69.7	99	70.2	335	58.0	129	66.2	1133	65.8	372	65.4
		Grade 3	16	3.7	5	3.5	25	4.3	13	6.7	57	3.3	24	4.2
	Loss of appetite	Any	143	32.9	43	30.5	166	28.7	70	35.9	519	30.1	172	30.2
		Grade 3	2	0.5	0	0.0	3	0.5	2	1.0	9	0.5	6	1.1

Source: Modified from Supplements 226 – 237, Hib-MenCY-TT-009 CSR
N: number of subjects with at least one documented dose; n/%: number/percentage of subjects reporting the symptom at least once
Grade 3 drowsiness: drowsiness that prevented normal activity; Grade 3 fever: > 40.0C
Grade 3 loss of appetite: not eating at all; Grade 3 irritability: crying that could not be comforted/prevented normal activity

Following the 4th dose, systemic AEs were reported in 67.8% [1878/2769] of HibMenCY-TT subjects and 72.6% [670/923] of Hib participants. The most frequently reported solicited general symptom was irritability, occurring in 58.7% of Hib-MenCY-TT subjects and 64.3% of Hib subjects. Grade 3 solicited general symptoms were reported in $\leq$ 3.7% of subjects. Fever was reported in 13.5% and 16.1% of Hib-MenCY-TT and Hib recipients, respectively. Grade 3 fever (> 40°C) was reported in < 1% of subjects in both groups. The majority of reported fevers were based on axillary temperature measurements (approximately 90% in both groups), while approximately 8 – 9% per group had rectal temperatures. Most fevers occurred on Days 0 and 1, and most fevers were < 39.0°C.

Table 9: Systemic adverse reactions after the 4th dose, Fourth dose Total Vaccinated cohort

Reaction	Severity	HibMenCY					Hib				
					95% CI					95% CI	
		N	n	%	LL	UL	N	n	%	LL	UL
Drowsiness	Any	2526	1088	43.1	41.1	45.0	830	381	45.9	42.5	49.4
	Grade 3	2526	42	1.7	1.2	2.2	830	13	1.6	0.8	2.7
Fever (axillary)	Any	2527	341	13.5	12.2	14.9	831	134	16.1	13.7	18.8
	> 40.0°C	2527	4	0.2	0.0	0.4	831	1	0.1	0.0	0.7
Irritability	Any	2526	1482	58.7	56.7	60.6	830	534	64.3	61.0	67.6
	Grade 3	2526	78	3.1	2.4	3.8	830	31	3.7	2.6	5.3
Loss of appetite	Any	2526	825	32.7	30.6	34.5	830	287	34.6	31.3	37.9
	Grade 3	2526	36	1.4	1.0	2.0	830	15	1.8	1.0	3.0

Source: applicant's Table 59, Hib-MenCY-TT-010 CSR
Hib-MenCY-TT = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses of Hib-MenCY-TT + DTaP-HBV-IPV + PCV7 in study Hib-MenCY-TT-009
Hib = PedvaxHIB + MMR + V + PCV7 in subjects who received 3 doses of ActHIB + DTaP-HBV-IPV + PCV7 in study Hib-MenCY-TT-009
N= number of subjects with the documented dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Grade 3 = drowsiness that prevented normal activity; temperature > 40.0°C; crying that could not be comforted/prevented normal activity; not eating at all

Too few subjects were co-vaccinated with influenza or hepatitis A vaccine to make any conclusions about systemic adverse events in this group or compare the occurrence of systemic adverse events in this group with the occurrence in subjects who were not co-vaccinated with these antigens.

Reported rates of systemic AEs after the 4th dose were more similar between the 3 countries as compared to after doses 1 – 3. Irritability was also the most frequently reported solicited general adverse event in all 3 countries, with a range of 43.7% - 66.2% among Hib-MenCY-TT subjects and

55.4% - 70.1% in Hib subjects. Mexico reported the lowest incidence of irritability in both treatment groups. Fever rates were slightly higher in Mexico as compared with Australia and the U.S. This may be related to the higher observed rate of antipyretic use in Australia (43.0% of Hib-MenCY-TT recipients and 54.1% of Hib recipients) and the U.S. (32.3% of Hib-MenCY-TT recipients and 37.0% of Hib recipients), compared with Mexico (21.5% of Hib-MenCY-TT recipients and 22.8% of Hib recipients).

Table 10: Systemic adverse reactions after the 4th dose, Fourth dose Total Vaccinated cohort, by country

Reaction	Severity	Australia				Mexico				United States			
		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib		Hib-MenCY-TT		Hib	
		N = 426		N = 144		N = 565		N = 193		N = 1535 - 1536		N = 493 - 494	
		n	%	n	%	n	%	n	%	n	%	n	%
Drowsiness	Any	150	35.2	63	43.8	191	33.8	79	40.9	747	48.7	239	48.5
	Grade 3	4	0.9	1	0.7	5	0.9	2	1.0	33	2.1	10	2.0
Fever	Any	59	13.8	23	16.0	113	20.0	49	25.4	169	11.0	62	12.6
	Grade 3	0	0.0	0	0.0	0	0.0	0	0.0	4	0.3	1	0.2
Irritability	Any	282	66.2	101	70.1	247	43.7	107	55.4	953	62.1	326	66.1
	Grade 3	23	5.4	7	4.9	16	2.8	3	1.6	39	2.5	21	4.3
Loss of appetite	Any	151	35.4	51	35.4	182	32.2	76	39.4	492	32.1	160	32.5
	Grade 3	4	0.9	0	0.0	15	2.7	4	2.1	17	1.1	11	2.2

Source: Modified from applicant's Supplements 302 – 316, Hib-MenCY-TT-010 CSR
N: number of subjects with at least one documented dose; n/%: number/percentage of subjects reporting the symptom at least once
Grade 3 drowsiness: drowsiness that prevented normal activity; Grade 3 fever: > 40.0C
Grade 3 loss of appetite: not eating at all; Grade 3 irritability: crying that could not be comforted/prevented normal activity

MMRV specific solicited symptoms during the 43-day (Days 0 – 42) follow-up period after the fourth dose vaccination (evaluated in the Fourth dose Total Vaccinated Cohort, on the U.S. Safety and Immunogenicity Cohort – Cohort 1):

Among 541 Hib-MenCY-TT subjects and 173 Hib subjects, there were no subjects who reported either meningismus or parotiditis. Proportions of subjects with rash or temperature of any intensity, grade 2 or 3, grade 3, and prompting medical attention were similar between treatment groups, with overlapping of the corresponding 95% CIs between the groups. Fever was reported in 38.7% [211/545] and 40.5% [70/173] of Hib-MenCY-TT and Hib recipients, respectively. The highest percentage of subjects experienced fever around days 8 to 10. Fever > 40°C was reported in 1.1% [6/545] Hib-MenCY-TT participants and 0.6% [1/173] Hib recipients. Rash was reported in 10.8% [59/544] and 10.9% [19/175] of Hib-MenCY-TT and Hib subjects, respectively.

Fever >39.5°C/103.1°F:

A co-secondary objective was to demonstrate the non-inferiority of Hib-MenCY-TT compared to Hib in terms of the incidence of fever > 39.5°C/103.1°F following co-vaccination with MMR and V. The between group difference in $p_{Hib} - p_{HibMenCY}$ was -0.11% [-0.66, 0.72], meeting the pre-specified criteria of the LL of the 95% CI $\geq$ -1.6%. For Hib-MenCY-TT Lot A, overall/subject, the between group difference in $p_{Hib} - p_{HibMenCYLot\ A}$ was -0.38% [-1.59, 0.80], while for Hib-MenCY-TT Lots B and C combined overall/subject, the between group difference in $p_{Hib} - p_{HibMenCYLots\ B\ and\ C}$ was 0.32% [-0.52, 1.37]

Unsolicited adverse events over one month post-vaccination:
Across doses 1 – 3, unsolicited systemic reactions were reported in 55.0% (Lot A group), 59.7% (Lot B group), 59.4% (Lot C group), and 58.0% and 57.7% of pooled Hib-MenCY-TT and Hib recipients, respectively. The most frequently reported unsolicited symptom in both groups was upper respiratory tract infection (16.7% and 16.6% in the Hib-MenCY-TT and Hib groups, respectively). Other unsolicited symptoms reported in more than 5% of the subjects in either the pooled HibMenCY-TT or Hib group were otitis media (10.7% of pooled Hib-MenCY-TT recipients and 10.0% of Hib participants), vomiting (6.3% and 6.2% of pooled HibMenCY-TT and Hib recipients, respectively), diarrhea (5.9% and 5.5% of pooled HibMenCY-TT and Hib subjects), teething (5.7% and 5.3% of pooled HibMenCY-TT and Hib participants, respectively), pyrexia (5.6% of pooled HibMenCY-TT subjects and 7.0% of Hib subjects), and cough (5.2% and 4.8% of pooled HibMenCY-TT and Hib recipients, respectively). At least one grade 3 unsolicited adverse event was reported in 8.6% of pooled HibMenCY-TT subjects and 9.0% of Hib subjects. Per HibMenCY-TT lot, this incidence was 9.1% for Lots A and C and 7.6% for Lot B. All grade 3 unsolicited adverse events were reported in < 1% of subjects except for otitis media (2.0% in pooled HibMenCY-TT subjects and 1.4% in Hib subjects) and upper respiratory tract infection (1.3% in both groups).

Following dose 4, the incidence of any unsolicited adverse event was similar between groups, occurring in 36.5% and 36.2% of Hib-MenCY-TT and Hib subjects, respectively. The most frequently reported unsolicited adverse event in both treatment groups was pyrexia, which was reported in 6.4% of Hib-MenCY-TT subjects and 6.9% of Hib subjects. Other unsolicited adverse events reported in ≥ 5% of subjects in either group were: upper respiratory tract infection (5.5% in Hib-MenCY-TT recipients and 5.4% in Hib participants), otitis media (4.9% in Hib-MenCY-TT subjects and 5.1% in Hib recipients), and teething (4.2% in Hib-MenCY-TT participants and 5.0% in Hib subjects). At least one grade 3 (severe) unsolicited adverse event was reported for 5.5% of Hib-MenCY-TT subjects and 6.4% of Hib subjects; all these events were reported in < 1% of participants in both groups except for pyrexia and otitis media. Grade 3 pyrexia was reported in 0.9% of Hib-MenCY-TT participants and 1.6% of Hib recipients, while grade 3 otitis media was reported in 0.9% of Hib-MenCY-TT subjects and 1.1% of Hib subjects.

An exploratory analysis was provided for unsolicited AEs of the four dose series. At least one unsolicited AE within 31 days of vaccination was reported in 64.8% of subjects in the Hib-MenCY-TT group and in 64.1% of subjects in the Hib group. All unsolicited AEs reported during this time period after any of the 4 doses occurred in < 10% of subjects in both groups except for the following AEs: upper respiratory tract infection (20.2% Hib-MenCY-TT participants and 20.0% Hib recipients), otitis media (13.8% of Hib-MenCY-TT subjects and 13.4% of Hib subjects), and pyrexia (10.4% and 11.9% of Hib-MenCY-TT and Hib subjects, respectively).

Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through the Extended Safety Follow Up (ESFU) period for Hib-MenCY-TT and Hib:

Over doses 1 - 3:
The reported rates of serious adverse events, new onset chronic disease, rash, and emergency rooms visits were similar across lots of Hib-MenCY-TT, as well as between either the individual lots of Hib-MenCY-TT and Hib or the pooled lots of Hib-MenCY-TT and Hib.

Table 11: Percentage of subjects with SAE, NOCD, rash, AE resulting in ER visit, ESFU, Primary Total Vaccinated Cohort, overall/subject after any of the first 3 doses, by individual and pooled lots of Hib-MenCY-TT vs Hib

	HibMenCY Lot A			HibMenCY Lot B			HibMenCY Lot C			HibMenCY pooled lots			*HIB*		
	N =1041			N = 1046			N = 1029			N = 3136			N=1044		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
At least one symptom (not including physician office visits)	247	23.7	21.2, 26.4	259	24.8	22.2, 27.5	249	23.7	21.2, 26.4	755	24.1	22.6, 25.6	255	24.4	21.8, 27.1
At least one symptoms (including physician office visits)	--	--	--	--	--	--	--	--	--	1552	49.5	47.7	51.3	515	49.3
Serious adverse event	40	3.8	2.8, 5.2	42	4.0	2.9, 5.4	44	4.2	3.1, 5.6	126	4.0	3.4, 4.8	50	4.8	3.6, 6.3
New onset chronic disease	60	5.8	4.4, 7.4	55	5.3	4.0, 6.8	48	4.6	3.4, 6.0	163	5.2	4.4, 6.0	52	5.0	3.7, 6.5
Rash	151	14.5	12.4, 16.8	171	16.3	14.2, 18.7	148	14.1	12.1, 16.4	470	15.0	13.8, 16.3	154	14.8	12.7, 17.0
Emergency room visit	75	7.2	5.7, 8.9	65	6.2	4.8, 7.9	77	7.3	5.8, 9.1	217	6.9	6.1, 7.9	72	6.9	5.4, 8.6
Physician Office Visits	--	--	--	--	--	--	--	--	--	1336	42.6	40.9	44.4	433	41.5

Source: Modified from applicant's Table 60 and Supplement 192, Hib-MenCY-TT-009 CSR
Hib-MenCY = 3 Hib-MenCY lot groups pooled: Hib-MenCY-TT Lot A, Lot B, or Lot C + DTaP-HBV-IPV (+ PCV7 if available)
Hib = ActHIB + DTaP-HBV-IPV (+ PCV7 if available)
At least one symptom = at least one symptoms experienced (regardless of the MedDRA Primary System Organ Class)
N = number of subjects with at least one administered dose

The reported rates of these events varied fairly substantially between Australia, Mexico, and the U.S., as presented in Table 12 below. Notably, new onset chronic diseases were reported in no Mexican subjects but in 11.9% of Austalian subjects and 5.2% of U.S. subjects. Further, rates of emergency room visits and physician office visits were markedly greater among Australian subjects (12.6% and 41.7%, respectively) and U.S. subjects (7.7% and 53.3%, respectively), compared with Mexican subjects (0% and 6.0%, respectively). The applicant notes the lower incidence of events identified for extended follow-up among Mexican subjects as compared with Australian and U.S. subjects but offers no explanation. It is possible that these differences are related to differences in availability of medical facilities and care-seeking behaviors.

Despite these differences, additional information regarding SAEs, NOCDs, rash, ER visits, and physician office visits is presented across countries in the text following this table in order to ensure capture of these events in all included subjects.

Table 12: Percentage of subjects with SAE, NOCD, Rash, AE resulting in ER visit, and AE resulting in MD visit through ESFU (Primary Total Vaccinated Cohort) after any of the first 3 doses, by country

	Australia						Mexico						United States					
	HibMenCY N = 453			Hib N = 151			HibMenCY N = 600			Hib N = 200			HibMenCY N = 2083			Hib N = 693		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
At least one symptom	267	58.9	54.3, 63.5	90	59.6	51.3, 67.5	55	9.2	7.0, 11.8	22	11.0	7.0, 16.2	1230	59.0	56.9, 61.2	403	58.2	54.4, 61.9
SAE	28	6.2	4.1, 8.8	8	5.3	2.3, 10.2	21	3.5	2.2, 5.3	11	5.5	2.8, 9.6	77	3.7	2.9, 4.6	31	4.5	3.1, 6.3
New onset chronic disease	54	11.9	9.1, 15.3	18	11.9	7.2, 18.2	0	0.0	0.0, 0.6	0	0.0	0.0, 1.8	109	5.2	4.3, 6.3	34	4.9	3.4, 6.8
Rash	120	26.5	22.5, 30.8	41	27.2	20.2, 35.0	1	0.2	0.0, 0.9	1	0.5	0.0, 2.8	349	16.8	15.2, 18.4	112	16.2	13.5, 19.1
ER visits	57	12.6	9.7, 16.0	14	9.3	5.2, 15.1	0	0.0	0.0, 0.6	1	0.5	0.0, 2.8	160	7.7	6.6, 8.9	57	8.2	6.3, 10.5
Physician office visits	189	41.7	37.1, 46.4	60	39.7	31.9, 48.0	36	6.0	4.2, 8.2	12	6.0	3.1, 10.2	1111	53.3	51.2, 55.5	361	52.1	48.3, 55.9

Source: modified from applicant's Tables 66, 67, 68, Hib-MenCY-TT-009 CS

Across all countries, there were 258 SAEs reported for 176 individuals [Hib-MenCY-TT n=126 subjects, 194 events; Hib n=50 subjects, 64 events]. Of the 126 pooled HibMenCY-TT subjects who experienced at least one SAE, the subjects were fairly evenly distributed across lots, with 40 in Lot A, 42 in Lot B, and 44 in Lot C. Acute infection (abscess, acarodermatitis, bronchiolitis, bronchitis, pneumonia, gastroenteritis, cellulitis, croup, HIV infection, urinary tract infection, sepsis, otitis media, pertussis, pyelonephritis, respiratory syncytial virus infection, upper respiratory tract infection, viral infection) accounted for 119/194 SAEs in Hib-MenCY-TT participants. Acute infection (abscess, bronchiolitis, pneumonia, cellulitis, croup, gastroenteritis, influenza, viral meningitis, nasopharyngitis, otitis media, pyelonephritis, respiratory syncytial virus infection, sinusitis, typhoid fever, urinary tract infection, viral infection, upper respiratory tract infection) accounted for 45/64 SAEs in Hib participants. Of the 257 non-fatal SAEs reported for 172 subjects, all were reported as recovered/resolved except the following: hemangioma of the left eye noted at birth with enlargement on Day 0/Dose 1 was surgically reduced on Day 21 post-dose 1 in a U.S. subject in HibMenCY-TT lot B group considered resolved with mild cosmetic sequelae; infantile spasm and tuberous sclerosis with onset Day 43 post-dose 3 in a U.S. subject in HibMenCY-TT Lot C group reported as not recovered/not resolved; HIV infection with onset Day 38 post-dose 1 in a U.S. subject in HibMenCY-TT Lot C group reported as not recovered/not resolved; complex febrile seizure with onset Day 143 post-dose 3 in a U.S. subject in the Hib group was reported as recovered/resolved with sequelae because a diagnostic electroencephalogram (EEG) was abnormal 3 days post-seizure.

Four deaths occurred during the ESFU prior to receipt of the 4th dose, 3 in the HibMenCY-TT group (2 in Lot B, 1 in Lot A), and 1 in the Hib group.

- An 8 month old male U.S. infant died of injuries related to child abuse 78 days after the 3rd Lot A HibMenCY-TT dose, DTaP-HBV-IPV, and PCV7. The baby had reportedly been thrown by his father 30 days after the 3rd vaccination.
- A 4 month old female U.S. infant died of Sudden Infant Death Syndrome (SIDS) on day 43 following the 1st Lot B HibMenCY-TT dose, DTaP-HBV-IPV, and PCV7.
- A 6 month old male Mexican infant died of "unknown" cause of death on day 30 after the 3rd Lot B HibMenCY-TT dose, DTaP-HBV-IPV, and PCV7 and day 11 post-vaccination with influenza vaccine. The child developed diarrhea, vomiting, and undocumented fever 1 day prior to death, was admitted to the hospital for treatment with oral hydration solutions and paracetamol and discharged the next day, afebrile, but with continued emesis. He was found pale and cold later on the day of discharge, and was dead on arrival in the physician's office.
- An 8 month old female Mexican infant died of bronchial aspiration on day 89 post-dose 3 of Hib, DTaP-HBV-IPV, and PCV7, and 1 day after her 2nd dose of influenza vaccine.

There were 207 occurrences of new onset of chronic diseases (NOCD) in 163 pooled Hib-MenCY-TT subjects and 59 occurrences in 52 Hib recipients (5.2% and 5.0% of pooled HibMenCY-TT and Hib subjects, respectively; 4.6% - 5.8% in each HibMenCY-TT lot group). The most frequently reported NOCD was eczema, occurring in 75/3136 pooled HibMenCY-TT participants and 21/1044 Hib subjects (2.4% in the pooled HibMenCY-TT group, 2.6% in Lot A, 2.4% in Lot B, 2.2% in Lot C, and 2.0% in the Hib group. All other NOCD events were reported in < 1% of subjects. Bronchial hyperreactivity was reported in 0.2% of pooled HibMenCY-TT subjects and 0.9% of Hib subjects, with a statistically significantly lower relative risk in the pooled HibMenCY-TT subjects. However, asthma, which is itself bronchial hyperreactivity, was reported in 0.6% of subjects in both groups, suggesting no difference in the relative risk for HibMenCY-TT or Hib subjects.

Rash was reported in 15.0% and 14.8%, respectively, of pooled Hib-MenCY-TT and Hib recipients. The most common rashes in both groups were "rash" (4.6% - 5.7% overall) and eczema (4.1% - 5.2% overall). Within the Hib-MenCY-TT group, there were no reported occurrences of petechiae, 1 of Henoch-Schonlein purpura (HSP), 5 of ecchymosis, 1 of purpura, 2 of erythema multiforme, 21 of urticaria, and 3 of papular urticaria. In the Hib group, the following occurrences were reported: 1 of petechiae, 0 HSP, 0 ecchymosis, 0 purpura, 0 erythema multiforme, 6 of urticaria, and 1 of papular urticaria. Five of the urticarial episodes in the pooled HibMenCY-TT group and 2 of the episodes in the Hib group occurred within 14 days of vaccination. Post-hoc analysis of the reports of purpura, petechiae, Henoch-Schonlein purpura, or ecchymosis indicated 7 occurrences of one of these events in the pooled HibMenCY-TT group (0.2%) and 1 occurrence in the Hib group (0.1%). Another post-hoc analysis of the reports of erythema multiforme or urticaria indicated 26 occurrences in the pooled HibMenCY-TT group (0.8%) and 7 occurrences in the Hib group (0.7%).

Emergency Room visits for at least one symptom occurred in 217 Hib-MenCY-TT and 72 Hib participants. The range was similar across groups (6.2% - 7.3% in the HibMenCY-TT groups and 6.9% in the Hib group). Acute infections (abscess, acarodermatitis, sinusitis, bronchiolitis, bronchitis, candidiasis, cellulitis, croup, otitis media, folliculitis, furuncle, gastroenteritis, influenza, pneumonia, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, roseola, tonsillitis, urinary tract infection, viral infection) comprised 176/343 ER diagnoses in the Hib-MenCY-TT group and 58/110 ER diagnoses in the Hib group. Pyrexia accounted for an additional 23 diagnoses in the pooled HibMenCY-TT group and 6 diagnoses in the Hib group. The most frequently reported events included otitis media in 32/3136 (1.0%) of pooled HibMenCY-TT subjects and 5/1044 (0.5%) Hib subjects, upper respiratory tract infection in 30/3136 (1.0%) pooled HibMenCY-TT and 9/1044 (0.9%) Hib subjects, and viral infection reported in 17/3136 (0.5%) pooled HibMenCY-TT and 8/1044 (0.8%) Hib vaccine recipients.

There were 1336 subjects visiting physicians' offices for 2811 symptoms in the pooled Hib-MenCY-TT group, and 433 subjects visiting physicians' offices for 902 symptoms in the Hib group. Proportions were closely aligned between groups (40.7% - 43.8% across HibMenCY-TT lots and 41.5% in the Hib group). Physician office visits were prompted most frequently by upper respiratory tract infection in both groups (13.8% in pooled Hib-MenCY-TT and 13.9% in Hib). Otitis media was another frequently reported AE resulting in a physician visit (11.1% and 10.6% in the Hib-MenCY-TT and Hib participants, respectively). Other symptoms occurring in at least 1% of subjects which prompted physician office visits included: conjunctivitis (2.7% in Hib-MenCY-TT subjects, 2.9% in Hib subjects); constipation (1.1% in HibMenCY-TT subjects, 0.9% in Hib subjects); diarrhea (1.3% in HibMenCY-TT recipients and 1.8% in Hib participants); gastroesophageal reflux disease (2.5% in HibMenCY-TT subjects and 1.4% in Hib subjects); vomiting (1.0% HibMenCY-TT subjects and 1.0% Hib subjects); pyrexia (1.9% HibMenCY-TT subjects and 2.3% Hib subjects); bronchiolitis (3.4% in Hib-MenCY-TT participants, 3.4% in Hib participants); candidiasis (1.5% HibMenCY-TT subjects and 1.5% Hib subjects); croup (0.9% HibMenCY-TT subjects and 1.4% Hib subjects); gastroenteritis (1.7% HibMenCY-TT subjects and 1.7% Hib subjects); pharyngitis (1.3% HibMenCY-TT subjects and 1.1% Hib subjects); sinusitis (1.3% HibMenCY-TT subjects and 1.4% Hib subjects); viral infection (2.0% HibMenCY-TT subjects and 1.6% Hib subjects); viral skin infection (1.0% HibMenCY-TT and 1.4% Hib subjects); viral upper respiratory tract infection (1.0% HibMenCY-TT subjects and 0.7% Hib subjects); bronchial hyperreactivity (0.6% HibMenCY-TT and 1.5% Hib subjects); cough (1.8% HibMenCY-TT subjects and 2.0% Hib subjects); nasal congestion (1.4% and 1.7% in Hib-MenCY-TT and Hib recipients, respectively); allergic rhinitis (0.5% HibMenCY-TT subjects and 1.0% Hib subjects); diaper dermatitis (1.2% HibMenCY-TT and 1.2% Hib); and

eczema (3.5% and 3.1% in Hib-MenCY-TT and Hib participants, respectively); rash (2.1% HibMenCY-TT subjects and 1.7% Hib subjects).

The applicant notes the lower incidence of events identified for extended follow-up among Mexican subjects as compared with Australian and U.S. subjects but offers no explanation. It is possible that these differences are related to differences in availability of medical facilities and medical care-seeking behaviors.

Analyses of solicited local and systemic adverse events during days 0 -3 post-vaccination according to co-vaccination status over doses 1 - 3:
The analysis per full co-vaccination status for these vaccines was performed for U.S. subjects only since all Australian and Mexican subjects were fully co-vaccinated with respect to DTaP-HBV-IPV and PCV7. In the U.S., 98.5% of subjects were fully co-vaccinated with DTaP-HBV-IPV and PCV7 at all 3 doses, and the sample of U.S. subjects not fully co-vaccinated was too small for meaningful conclusions (n = 29 in the HibMenCY-TT group, n = 12 in the Hib group). Analysis of concomitant influenza vaccination was performed for U.S. and Mexican subjects because 99.7% of Australian subjects did not receive a concomitant influenza vaccination. Concomitant influenza vaccination was reported in 27.8% of U.S. subjects and 33.9% of Mexican subjects. The overall/subject proportions of subjects with any symptom, general symptoms, and/or local symptoms (solicited and unsolicited) were similar, regardless of concomitant influenza vaccination. Analysis of co-administration of rotavirus vaccine was provided for U.S. subjects only since 100% and 96.9% of Mexican and Australian subjects, respectively, had not received any rotavirus vaccine. In the U.S., 11.8% of subjects were completely co-vaccinated, and 6.3% of subjects were partially co-vaccinated with rotavirus vaccine. Proportions of HibMenCY-TT subjects reporting any, general, or local symptoms were similar across these 3 groups, with overlapping 95% CIs; similar trends were observed for Hib study group comparisons.

Analysis of subjects from Hib-MenCY-TT-009/-010 who did not participate in evaluation of the fourth dose
A total of 558 subjects (including 72 subjects from the dropped U.S. study center) from study Hib-MenCY-TT-009/-010 did not participate in evaluation of the fourth dose. Comparison of the incidence of adverse events in the subjects who did not continue to Hib-MenCY-TT-010 with the incidence of adverse events in the subjects who continued in Hib-MenCY-TT-010 suggested that the incidence of adverse events had no apparent adverse impact on enrollment in the 4^{th} dose study. Generally, the rates of adverse events during study Hib-MenCY-TT-009 tended to be higher in subjects who continued into the HibMenCY-TT-010 extension.

Dose 4:

Adverse events: Days 0 – 30 post-4th vaccination

Table 13: Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through 31 days post-4th dose vaccination (Fourth dose Total Vaccinated Cohort)

	HibMenCY N = 2769				Hib N = 923			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one symptom	647	23.4	21.8	25.0	205	22.2	19.6	25.0
SAE	12	0.4	0.2	0.8	8	0.9	0.4	1.7
New onset chronic disease(s)	32	1.2	0.8	1.6	11	1.2	0.6	2.1
Rash	186	6.7	5.8	7.7	57	6.2	4.7	7.9
ER visit	48	1.7	1.3	2.3	22	2.4	1.5	3.6
Physician office visit	521	18.8	17.4	20.3	159	17.2	14.8	19.8

Source: Modified from applicant's Tables 63, 75, Hib-MenCY-TT-010 CSR

Hib-MenCY-TT = Hib-MenCY-TT + MMRII + V + Prevnar in subjects previously given 3 doses of Hib-MenCY-TT + *Prevnar*® + *DTaP-HBV-IPV*®

Hib = PedvaxHIB + MMRII + V + *Prevnar*® in subjects previously given 3 doses of *ActHIB*® + *Prevnar*® + *DTaP-HBV-IPV*®

N= number of subjects with administered dose

n/% = number/percentage of subjects reporting the symptom at least once

95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

During the follow-up period of one month post-fourth dose, 25 serious adverse events occurred in 20 subjects, 12 in the Hib-MenCY-TT group and 8 in the Hib group. Among these SAEs, 3 subjects in the Hib-MenCY-TT group had gastroenteritis, and 2 subjects in this group had dehydration. There were 5 reported episodes of gastroenteritis, 2 in the Hib-MenCY-TT group, and 3 in the Hib group. There were 3 reports of dehydration, 1 in the Hib-MenCY-TT group and 2 in the Hib group. The 2 reports of viral infection occurred in the Hib-MenCY-TT group. Other events during Days 0 – 30 post-4th vaccination included one each of idiopathic thrombocytopenic purpura (Hib-MenCY-TT), ventricular septal defect (Hib), abscess (Hib-MenCY-TT), adenoviral upper respiratory infection (Hib), cellulitis (Hib-MenCY-TT), lower respiratory tract infection (Hib), otitis media (Hib), viral pneumonia (Hib-MenCY-TT), staphylococcal infection (Hib-MenCY-TT), second degree burns (Hib-MenCY-TT), head injury (Hib), multiple injuries (Hib-MenCY-TT), skin laceration (Hib-MenCY-TT), respiratory distress (Hib), papular rash (Hib-MenCY-TT). In the 12 month old male Hib-MenCY-TT recipient with idiopathic thrombocytopenic purpura, onset was 14 days post-4th vaccination, required hospitalization and immunoglobulin administration for platelet count of 2300 – 16000 mm^3, and resolved 53 days later. While no description of concurrent viral infection is given, the SAE narrative does mention that he was febrile for 2 days prior to ITP onset.

Adverse events: Extended Safety Follow-up (ESFU) post-dose 4:

Table 14: Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through the Extended Safety Follow Up (ESFU) period – post-4th dose, Fourth dose Total Vaccinated Cohort

	HibMenCY N = 2769				Hib N = 923			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one symptom	860	31.1	29.3	32.8	274	29.7	26.8	32.7
SAE	47	1.7	1.2	2.3	18	2.0	1.2	3.1
New onset chronic disease(s)	85	3.1	2.5	3.8	33	3.6	2.5	5.0
Rash	265	9.6	8.5	10.7	94	10.2	8.3	12.3
ER visit	137	4.9	4.2	5.8	54	5.9	4.4	7.6
Physician office visit	668	24.1	22.5	25.8	205	22.2	19.6	25.0

Source: Modified from applicant's Table 63, Hib-MenCY-TT-010 CSR

Differences across the 3 countries in rates of these events reported through the ESFU period following dose 4 were similar to those differences observed in the reported rates of these events through the ESFU following dose 3. These differences are presented in the table below. Generally, observed rates of all pre-specified adverse events for the ESFU were similar in both treatment groups in the U.S. and Australia but comparatively lower in Mexico, perhaps due to differences in health care utilization. Despite these differences, additional description of the safety data reported for the ESFU after dose 4 is presented for these data across all 3 countries, to ensure capture of the most complete safety data. The description is in the text following the table.

Table 15: Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through the Extended Safety Follow Up (ESFU) period – post-4th dose, by country, Fourth dose Total Vaccinated Cohort

	Australia						Mexico						United States					
	HibMenCY N = 446			Hib N = 146			HibMenCY N = 567			Hib N = 193			HibMenCY N = 1756			Hib N = 584		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
SAE	13	2.9	1.6, 4.9	2	1.4	0.2, 4.9	6	1.1	0.4, 2.3	3	1.6	0.3, 4.5	28	1.6	1.1, 2.3	13	2.2	1.2, 3.8
New onset chronic disease	16	3.6	2.1, 5.8	7	4.8	1.9, 9.6	--	--	--	--	--	--	69	3.9	3.1, 4.9	26	4.5	2.9, 6.5
Rash	88	19.7	16.1, 23.7	30	20.5	14.3, 28.0	3	0.5	0.1, 1.5	0	0.0	0.0, 1.9	174	9.9	8.6, 11.4	64	11.0	8.5, 13.8
ER visits	23	5.2	3.3, 7.6	10	6.8	3.3, 12.2	3	0.5	0.1, 1.5	1	0.5	0.0, 2.9	111	6.3	5.2, 7.6	43	7.4	5.4, 9.8
Physician office visits	111	24.9	20.9, 29.2	41	28.1	21.0, 36.1	38	6.7	4.8, 9.1	5	2.6	0.8 5.9	519	29.6	27.4, 31.8	159	27.2	23.7, 31.0

Source: Modified from applicant's Supplements 357 – 370, Hib-MenCY-TT-010 CSR
N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

During the period between fourth vaccination through the end of the ESFU, a total of 83 non-fatal serious adverse events were reported for 65 subjects, 47 in the Hib-MenCY-TT group and 18 in the Hib group. There was one reported case of thrombocytopenia of grade 2 intensity which occurred in a Hib-MenCY-TT participant 91 days post-vaccination and lasted 10 days; the subject was reported as recovered. He had a history of 4 days of fever, diarrhea, and rash on admission, otitis media during hospitalization, with concurrent neutropenia and a normal hemoglobin. Another Hib-MenCY-TT recipient developed idiopathic thrombocytopenic purpura (ITP) 58 days post-4th vaccination; initially, the grade 2 ITP in this 14 month old male was classified as NOCD since he was not hospitalized but treated in the ER and the most recent platelet count was still thrombocytopenic, in the 80,000 mm^3 range (normal range: 140,000 – 400,000 mm^3). Among the reported SAEs, 35/47 in the Hib-MenCY-TT group were acute infections (abscess, bronchiolitis, cellulitis, croup, gastroenteritis, pneumonia, otitis media, respiratory tract infection, staphylococcal infection, upper respiratory tract infection, urinary tract infection, viral infection); while 13/18 SAEs reported in Hib participants were acute infections (upper respiratory tract infection, gastroenteritis, lower respiratory tract infection, abscess, osteomyelitis, otitis media, pneumonia). There were 3 reports of convulsions in the Hib-MenCY-TT group and 1 report of convulsion in the Hib group. One of these convulsions occurred 79 days post-4th Hib vaccination in a 15 month old female with past medical history of developmental delay and microcephaly who had concurrent croup, diarrhea, and fever. She presented to clinic with fever and report of seizure 45 minutes prior. She was diagnosed with otitis media. Two hours later, the subject had a second convulsion and was hospitalized subsequently. An EEG was abnormal, compatible with diffuse cerebral dysfunction without convincing epileptiform activity. Genetic testing was performed and prompted a diagnosis of Angelman's syndrome. One 13 month old male Hib-MenCY-TT recipient had a convulsion 32 days post-4th vaccination following a fall episode in which he hit his head on a wall, cried immediately and continued crying for some time. There was a family history of breath holding episodes. He was hospitalized, received no anti-seizure medications and had an outpatient EEG scheduled at the time of the report. A 16 month old male had a convulsion 4 months post-4th dose vaccination of Hib-MenCY-TT. He had rhinorrhea and congestion for 36 hours prior to the event, then developed fever and was brought to the hospital. En route, the child began to seize and continued to seize in the ER following Ativan. He received fosphenytoin and was admitted to the pediatric intensive care unit (PICU). He was discharged 2 days later. A 17 month old Mexican male Hib-MenCY-TT recipient had a seizure 5 months post-4th vaccination. He seized again 2 days later and again 14 days after that, and his work-up was ongoing at the time of the report. His family history was significant for his sister's diagnosis of febrile seizure at age 3 months. A 19 month old male Hib-MenCY-TT participant experienced convulsion 5 months post-4th vaccination and was hospitalized for 3 – 4 days; the admitting temperature was 104.9°F. There was 1 report of urticaria in a 15 month old Mexican female Hib-MenCY-TT recipient occurring 95 days post-4th vaccination, which presented with erythematous papules in both hands and legs with itching, progressing to rhinorrhea, cough, fever, periorbital swelling, erythematous plaques surrounded by an urticarial flare in the face, trunk, extremities, and buttocks, sore throat, and tonsillar swelling, and required hospitalization; the child reportedly recovered fully.

All non-fatal serious adverse events were reported as recovered/resolved except for the following: acute allergic reaction to tomato 35 days post-4th vaccination in a Hib-MenCY-TT recipient, asthma with onset 140 days post-4th vaccination in a Hib participant, and idiopathic thrombocytopenic purpura with onset 58 days post-4th vaccination in a Hib-MenCY-TT subject. One death occurred during the ESFU period, a 13 month old female group who died in a motor vehicle accident 29 days after the 4th Hib-MenCY-TT vaccination.

There were 106 occurrences of new onset of chronic diseases (NOCD) in 85 Hib-MenCY-TT subjects and 37 occurrences in 33 Hib recipients (3.1% and 3.6% of HibMenCY-TT and Hib subjects, respectively). The most frequently reported NOCD was asthma, occurring in 16/2769 HibMenCY-TT participants and 8/923 Hib subjects (0.6% in the HibMenCY-TT group and 0.9% in the Hib group). Bronchial hyperreactivity was reported in 9/2769 (0.3%) and 2/923 (0.2%) of Hib-MenCY-TT and Hib subjects, respectively. All other NOCD events were reported in < 0.5% of subjects. There was one report each of idiopathic thrombocytopenic purpura (ITP), petechiae and urticaria among Hib-MenCY-TT recipients. The occurrence of petechiae was 81 days after 4th dose, was rated as intensity grade 1, and lasted 64 days. The case of grade 1 urticaria occurred at 17 days post-4th vaccination and lasted for 2 days. The one report of ITP occurred in the 14 month old male described in the SAE section above. There was one report of autoimmune disease described as pauci-articular juvenile rheumatoid arthritis in a Hib participant. The onset of disease was 130 days post-4th vaccination.

Rash occurred in 9.6% and 10.2%, respectively, of Hib-MenCY-TT and Hib recipients. The most common rash in both groups was "rash" (4.1 – 5.1% overall). Urticaria was reported in 1.2% and 1.1% of Hib-MenCY-TT participants, respectively. All other rashes were reported in < 1% of subjects in either group. Within the Hib-MenCY-TT group, there were 2 reported occurrences of petechiae (one of which was chronic), 1 of ecchymosis, 1 of purpura, 1 of papular urticaria, and 34 of urticaria, one of which was chronic. In the Hib group, there were no corresponding occurrences of these specific events, other than 13 reports of urticaria. The Hib-MenCY-TT participant with purpura experienced onset 103 days post-4th vaccination; intensity was graded 1, and the episode lasted for 7 days with full recovery.

Emergency Room visits for at least one symptom occurred in 137 Hib-MenCY-TT and 54 Hib participants. The range was similar across groups (4.9% in the HibMenCY-TT groups and 5.9% in the Hib group). Acute infections (bronchiolitis, bronchitis, cellulitis, croup, otitis media, gastroenteritis, abscess, herpangina, influenza, pneumonia, lower respiratory tract infection, nasopharyngitis, oral herpes, pertussis, pharyngitis, rhinitis, roseola, scarlet fever, sinusitis, staphylococcal infection, tonsillitis, upper respiratory tract infection, varicella, viral infections, wound infection) comprised 95/193 ER diagnoses in the Hib-MenCY-TT group and 30/72 ER diagnoses in the Hib group. All diagnoses were reported in < 1% of subjects. The most frequently reported event was otitis media in 0.6% of HibMenCY-TT subjects and 0.4% of Hib subjects. The subject with idiopathic thrombocytopenic purpura who was reported in this section has been described above. There was one report each of erythema multiforme and urticaria among Hib-MenCY-TT recipients.

There were 668 subjects visiting physicians' offices for 1121 symptoms in the Hib-MenCY-TT group, and 205 subjects visiting physicians' offices for 357 symptoms in the Hib group. The rate of visits to a physician's office was similar between groups (24.1% of HibMenCY-TT subjects and 22.2% in the Hib group). Physician office visits were prompted most frequently by otitis media infection in both groups (4.8% in Hib-MenCY-TT and 4.7% in Hib). Other symptoms occurring in at least 1% of subjects which prompted physician office visits included: conjunctivitis (1.7% in Hib-MenCY-TT subjects, 0.9% in Hib subjects); pyrexia (2.0% in HibMenCY-TT subjects, 2.8% in Hib subjects); gastroenteritis (1.0% in HibMenCY-TT recipients and 1.1% in Hib participants); pharyngitis (1.5% in HibMenCY-TT subjects and 1.2% in Hib subjects); upper respiratory tract infection (2.7% HibMenCY-TT subjects and 3.6% Hib subjects); viral infection (1.0% HibMenCY-TT subjects and 0.5% Hib subjects); viral skin infection (1.0% in Hib-MenCY-TT participants, 0.7% in Hib participants); rash (1.4% HibMenCY-TT subjects and 1.2% Hib subjects). There were 2 reported cases of urticaria, one of which was reported as an NOCD, and one case of petechiae reported as a NOCD. Additionally,

there was one reported case of purpura in the Hib-MenCY-TT group. Grade 2 thrombocytopenia of 2 day duration was reported in 1 Hib-MenCY-TT recipient with onset 27 days post-4th vaccination.

Integrated summary of adverse events over doses 1 – 4 through the end of the ESFU after dose 4:
At least one SAE was reported in 5.2% of Hib-MenCY-TT and 6.2% of Hib subjects. With the exception of gastroenteritis, these SAEs were reported in < 1.0% of both groups. Gastroenteritis was reported in 0.8% of Hib-MenCY-TT recipients and 1.1% of Hib vaccine participants.

At least one NOCD was reported in 7.3% of Hib-MenCY-TT subjects and 7.6% of Hib subjects. These NOCDs were reported in < 1% of subjects in both groups with the exception of the following: eczema (2.8% Hib-MenCY-TT subjects and 2.2% Hib subjects), asthma (1.1% of Hib-MenCY-TT recipients and 1.3% of Hib participants), and bronchial hyperreactivity (0.5% of Hib-MenCY-TT and 1.1% of Hib subjects).

At least one rash event was reported in 21.1% of Hib-MenCY-TT and Hib subjects. Of these rashes, "rash" (not otherwise specified) was the most frequently reported rash. The other rashes were reported in < 1% of subjects in both groups, except for the following: eczema (5.4% Hib-MenCY-TT recipients and 5.0% Hib subjects), diaper dermatitis (3.0% Hib-MenCY-TT subjects and 3.1% Hib participants), urticaria (1.7% Hib-MenCY-TT participants and 1.8% Hib subjects), dermatitis (0.8% of Hib-MenCY-TT and 1.2% of Hib subjects, respectively), and atopic dermatitis (0.9% Hib-MenCY-TT and 1.1% Hib recipients).

At least one AE prompting an ER visit was reported in 10.3% of Hib-MenCY-TT recipients and 11.0% of Hib participants. These occurred in < 1.0% of subjects in both groups except the following: otitis media (1.5% of Hib-MenCY-TT and 0.8% of Hib subjects), upper respiratory tract infections (1.2% of Hib-MenCY-TT and 1.1% of Hib recipients), pyrexia (1.1% of Hib-MenCY-TT and 1.0% of Hib participants), bronchiolitis (1.0% of Hib-MenCY-TT and 0.8% of Hib subjects), and viral infection (0.9% and 1.1% of Hib-MenCY-TT and Hib recipients, respectively).

Analysis of solicited local and systemic adverse events during days 0-3 post-vaccination according to co-vaccination status during evaluation of the fourth dose:
There were 2076 Hib-MenCY-TT and 691 Hib subjects fully co-vaccinated with Hib-MenCY-TT or Hib, PCV7, MMR, and V and 247 Hib-MenCY-TT and 86 Hib recipients not fully co-vaccinated. In general, proportions of subjects with at least one symptom of interest during the ESFU, SAE, NOCD, rash, ER visit, and physician office visit were higher among fully co-vaccinated subjects as compared with not fully co-vaccinated subjects. Pain, drowsiness, and irritability tended to be reported more often in fully co-vaccinated Hib-MenCY-TT subjects when compared with Hib-MenCY-TT subjects who were not fully co-vaccinated. Irritability tended to be reported more often in fully co-vaccinated Hib subjects when compared with Hib subjects who were not fully co-vaccinated. For the other solicited local and systemic adverse events, 95% CIs overlapped for within treatment group comparisons of proportions by co-vaccination status.

Immunogenicity:

Lot to lot consistency:
The non-inferiority criteria for evaluation of lot to lot consistency were that the 95% CIs for the hSBA-MenC and hSBA-MenY GMT ratios and anti-PRP GMC ratios were within the pre-specified interval of [0.5, 2.0]. These criteria were met for 8 of 9 pairwise comparisons. The

comparison of Lot B over Lot A for hSBA-MenY GMTs had an interval of [1.14, 2.27], exceeding the pre-defined upper limit.

Meningococcal responses: Post-dose 3, the lower limit of the exact 95% CI for the percentage of Hib-MenCY-TT participants with hSBA ≥ 1:8 was above the pre-specified criterion of ≥ 90.0% for serogroup C and ≥ 85.0% for serogroup Y.

Table 16. Percentages of subjects with hSBA titer ≥ 1:8 and GMTs one month after 3rd vaccination, Primary ATP cohort for immunogenicity, Cohort 1

			≥ 1:8				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
hSBA-MenC	HibMenCY	491	485	98.8	97.4	99.6	967.6	864.0	1083.5
	HibMenCY Lot A	158	156	98.7	95.5	99.8	910.0	754.6	1097.3
	HibMenCY Lot B	168	167	99.4	96.7	100	1118.0	931.1	1342.5
	HibMenCY Lot C	165	162	98.2	94.8	99.6	885.7	712.4	1101.2
	Hib	164	11	6.7	3.4	11.7	2.5	2.2	2.9
hSBA-MenY	HibMenCY	481	461	95.8	93.7	97.4	236.6	205.7	272.1
	HibMenCY Lot A	150	140	93.3	88.1	96.8	178.9	136.4	234.6
	HibMenCY Lot B	168	165	98.2	94.9	99.6	288.1	232.8	356.6
	HibMenCY Lot C	163	156	95.7	91.4	98.3	249.6	195.6	318.7
	Hib	162	3	1.9	0.4	5.3	2.2	2.0	2.4

Source: Modified from Table 27, Hib-MenCY-TT-009 CSR
HibMenCY = Hib-MenCY-TT + DTaP-HBV-IPV + PCV7
Hib = *ActHIB*® + DTaP-HBV-IPV + PCV7
GMT = geometric mean antibody titer calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval
LL = lower limit, UL = upper limit

The exploratory analysis of meningococcal responses among subjects in Cohort 3 suggested that the proportion of HibMenCY-TT subjects with hSBA-MenC and hSBA-MenY titers ≥ 1:8 ranged from 97.9% and 98.0%, respectively, in Lot A to 100% in Lots B and C. In the Hib group, 4.3% and 2.2% had hSBA-MenC and hSBA-MenY titers ≥ 1:8, respectively. Observed hSBA-MenC and hSBA-MenY GMTs were approximately 3-fold higher than GMTs observed in Cohort 1.

Regarding the secondary objective of evaluation of hSBA antibody persistence for MenC and MenY, 96.0% and 92.8% of Hib-MenCY-TT subjects had hSBA-MenC and hSBA-MenY titers ≥ 1:8, respectively, pre-4th dose. Of the subjects who had received 3 Hib doses at 2, 4, and 6 months of age, 10.0% and 5.1%, respectively, met this criterion. Compared with the post-3rd vaccination titers, the GMTs for hSBA-MenC decreased 5.3-fold for the Hib-MenCY-TT group. The exploratory evaluation of antibody persistence in Cohort 3 suggested that the percentages of subjects retaining hSBA-MenC and hSBA-MenY antibody titers ≥ 1:8 were 96.7% and 97.5%, respectively.

Table 17. Percentage of subjects with hSBA-MenC titers ≥ 1:4 and ≥ 1:8 and GMTs, post-3rd dose and pre-4th dose, Primary ATP Cohort for Immunogenicity for Post dose 3 and Fourth dose ATP Cohort for Safety, Cohort 1 for Pre-dose 4:

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenC	HibMenCY Lots A, B, C combined	Post 3	446	441	98.9	97.4	99.6	441	98.9	97.4	99.6	935.6	834.7	1048.6
		Pre 4	420	403	96.0	93.6	97.6	403	96.0	93.6	97.6	176.5	153.9	202.4
	Hib	Post 3	155	10	6.5	3.1	11.5	10	6.5	3.1	11.5	2.5	2.1	2.9
		Pre 4	140	15	10.7	6.1	17.1	14	10.0	5.6	16.2	2.8	2.3	3.3
	HibMenCY Lot A	Post 3	158	156	98.7	95.5	99.8	156	98.7	95.5	99.8	910.0	754.6	1097.3
		Pre 4	134	127	94.8	89.5	97.9	127	94.8	89.5	97.9	158.9	123.3	204.6
	HibMenCY Lot B	Post 3	168	167	99.4	96.7	100	167	99.4	96.7	100	1118.0	931.1	1342.5
		Pre 4	147	140	95.2	90.4	98.1	140	95.2	90.4	98.1	179.2	140.9	227.9
	HibMenCY Lot C	Post 3	165	162	98.2	94.8	99.6	162	98.2	94.8	99.6	885.7	712.4	1101.2
		Pre 4	139	136	97.8	93.8	99.6	136	97.8	93.8	99.6	192.2	153.7	240.2
	HibMenCY Lots B and C combined	Post 3	333	329	98.8	97.0	99.7	329	98.8	97.0	99.7	996.1	864.4	1148.0
		Pre 4	286	276	96.5	93.7	98.3	276	96.5	93.7	98.3	185.4	157.4	218.3

Source: Modified from Tables 22, 24 Hib-MenCY-TT-009 CSR
HibMenCY = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses of Hib-MenCY-TT + PCV7 + DTaP-HBV-IPV in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMR + V + PCV7 in subjects primed with *ActHIB*® + PCV7 + DTaP-HBV-IPV
GMT = geometric mean antibody titer
N = number of subjects with available results at both time points for the specified antigen
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Post3 = post-3rd dose vaccination blood sample
Pre4 = pre-4th dose vaccination blood sample

Table 18. Percentage of subjects with hSBA-MenY titers ≥ 1:4 and ≥ 1:8 and GMTs, post-3rd dose and pre-fourth dose, Primary ATP Cohort for Immunogenicity for Post dose 3 and Fourth dose ATP Cohort for Safety, Cohort 1 for Pre-dose 4:

				≥ 1:4				≥ 1:8				GMT		
						95% CI				95% CI			95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenY	HibMenCY	Post 3	437	425	97.3	95.3	98.6	423	96.8	94.7	98.2	233.7	203.1	269.0
		Pre 4	419	392	93.6	90.8	95.7	389	92.8	89.9	95.1	117.5	101.3	136.2
	Hib	Post 3	152	3	2.0	0.4	5.7	3	2.0	0.4	5.7	2.2	2.0	2.4
		Pre 4	138	7	5.1	2.1	10.2	7	5.1	2.1	10.2	2.4	2.1	2.7
	HibMenCY Lot A	Post 3	150	141	94.0	88.9	97.2	140	93.3	88.1	96.8	178.9	136.4	234.6
		Pre 4	131	122	93.1	87.4	96.8	122	93.1	87.4	96.8	105.8	81.4	137.5
	HibMenCY Lot B	Post 3	168	165	98.2	94.9	99.6	165	98.2	94.9	99.6	288.1	232.8	356.6
		Pre 4	146	138	94.5	89.5	97.6	137	93.8	88.6	97.1	119.0	93.3	151.7
	HibMenCY Lot C	Post 3	163	157	96.3	92.2	98.6	156	95.7	91.4	98.3	249.6	195.6	318.7
		Pre 4	142	132	93.0	87.4	96.6	130	91.5	85.7	95.6	127.8	97.7	167.1
	HibMenCY Lots B and C combined	Post 3	331	322	97.3	94.9	98.7	321	97.0	94.5	98.5	268.5	228.5	315.4
		Pre 4	288	270	93.8	90.3	96.3	267	92.7	89.1	95.4	123.2	103.0	147.5

Source: Modified from Tables 22, 24 Hib-MenCY-TT-009 CSR
HibMenCY = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses of Hib-MenCY-TT + PCV7 + DTaP-HBV-IPV in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMR + V + PCV7 in subjects primed with *ActHIB*® + PCV7 + DTaP-HBV-IPV
GMT = geometric mean antibody titer
N = number of subjects with available results at both time points for the specified antigen
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Post3 = post-3rd dose vaccination blood sample
Pre4 = pre-4th dose vaccination blood sample

Post-4th vaccination, the percentages (95% CI) of Hib-MenCY-TT and Hib participants with hSBA $\geq$ 1:8 were 98.5% (96.5, 99.5) and 21.8% (14.8, 30.4), respectively, for serogroup C. For serogroup Y, the percentages of Hib-MenCY-TT and Hib participants with hSBA $\geq$ 1:8 were 98.8% (97.0, 99.7), and 72.5% (63.6, 80.3), respectively. GMTs in the group that received 4 doses of Hib-MenCY-TT increased by 12-fold for hSBA-MenC and 11.8-fold for hSBA-MenY as compared to the pre-4th dose time point.

Table 19. Geometric mean ratios post-fourth dose/pre-fourth dose vaccination of hSBA titers (Fourth dose ATP Cohort for Immunogenicity, Cohort 1)

					GMT ratio Post-fourth dose/Pre-fourth dose		
						95% CI	
		N	GMT Post-fourth dose	GMT Pre-fourth dose	Value	LL	UL
hSBA-MenC (1/dil)	HibMenCY	287	2175.73	181.50	12.0	10.4	13.8
	Hib	92	4.21	2.97	1.4	NA	NA
hSBA-MenY (1/dil)	HibMenCY	299	1430.58	120.76	11.8	10.2	13.8
	Hib	92	53.41	2.53	21.1	NA	NA

Source: Table 25 of the Hib-MenCY-TT-010 CSR
HibMenCY = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses of Hib-MenCY-TT + PCV7 + DTaP-HBV-IPV in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMR + V + PCV7 in subjects primed with *ActHIB*® + PCV7 + DTaP-HBV-IPV
GMT = geometric mean antibody titer
N = number of subjects with available results at both time points for the specified antigen
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre-fourth dose = pre-4th dose vaccination blood sample
Post-fourth dose = post-4th dose vaccination blood sample
NA = Not available due to departure from lognormal distribution (large number of imputed values)

Post-4th dose, the proportions of subjects with hSBA-MenC and hSBA-MenY titers $\geq$ 1:8 were 98.5% and 99.7% among Hib-MenCY-TT recipients and 21.8% and 72.5% among Hib recipients. The observed hSBA-MenC and hSBA-MenY GMTs, respectively, increased 11.3-fold and 11.7-fold for Hib-MenCY-TT participants. The proportions of Hib subjects with hSBA titers $\geq$ 1:8 was higher than expected and inconsistent with earlier studies in U.S. subjects. One possible explanation, suggested by the applicant, is that the *N. meningitidis* serogroup B outer membrane protein (GBOMP), which is the carrier protein for *PedvaxHIB*®, may generate cross-reactivity to other meningococcal serogroups in the SBA assay. The ELISA for the meningococcal polysaccharides anti-PSY and anti-PSC levels were not correspondingly high in the Hib control group. *ActHIB*®, which does not use GBOMP as the carrier protein, was used in study Hib-MenCY-TT-005/-006. Another potential cause of generation of hSBA response may be exposure to meningococcal serogroups C and Y.

Table 20. Percentage of subjects with hSBA-MenC and hSBA-MenY titers $\geq$ 1:4 and $\geq$ 1:8 and GMTs post-4th dose vaccination (Fourth dose ATP Cohort for Immunogenicity, Cohort 1)

			$\geq$ 1:4				$\geq$ 1:8				GMT		
					95% CI				95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
hSBA-MenC	HibMenCY	331	326	98.5	96.5	99.5	326	98.5	96.5	99.5	2039.8	1746.3	2382.6
	Hib	119	26	21.8	14.8	30.4	26	21.8	14.8	30.4	4.3	3.2	5.8
hSBA-MenY	HibMenCY	342	338	98.8	97.0	99.7	338	98.8	97.0	99.7	1389.5	1205.0	1602.2
	Hib	120	87	72.5	63.6	80.3	87	72.5	63.6	80.3	48.6	31.9	74.0

Source: Modified from Table 37, Hib-MenCY-TT-010 CSR
HibMenCY = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses of Hib-MenCY-TT + PCV7 + DTaP-HBV-IPV in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMR + V + PCV7 in subjects primed with *ActHIB*® + PCV7 + DTaP-HBV-IPV
GMT = geometric mean antibody titer
N = number of subjects with available results at both time points for the specified antigen
n/% = number/percentage of subjects with titer within the specified range
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

Approximately 30% of subjects in the Primary ATP Immunogenicity Cohort were excluded from the ATP analyses of response to doses 1 - 3; approximately 47% of subjects in the Primary ATP Immunogenicity Cohort were excluded from the ATP analyses of the 4th dose. However, the number of subjects for whom immunogenicity results are available is fairly robust. Further, the applicant provided additional analyses to support the representativeness of the subjects included in the ATP analyses with respect to the full cohort intended for immunogenicity analyses, i.e., Cohort 1. A selection of these additional analyses is summarized below.

Although the primary analysis of immunogenicity post-dose 3 was based on the Primary ATP immunogenicity cohort (Cohort 1), the protocol specified that a secondary analysis based on the Primary Total Vaccinated cohort (Cohort 1) would be performed since more than 5% of enrolled subjects were excluded from the Primary ATP cohort for immunogenicity post-dose 3.

Table 21. Comparison of Meningococcal Immune Responses Post-dose 3 Based on the Primary ATP Immunogenicity Cohort with Those Based on the Primary Total Vaccinated Cohort

			≥ 1:8				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
hSBA-MenC	ATP Immuno (Cohort 1), post-dose 3								
	HibMenCY	491	485	98.8	97.4	99.6	967.6	864.0	1083.5
	Hib	164	11	6.7	3.4	11.7	2.5	2.2	2.9
	Total Vaccinated (Cohort 1), post-dose 3								
	HibMenCY	582	576	99.0	97.8	99.6	965.9	871.7	1070.3
	Hib	190	14	7.4	4.1	12.1	2.6	2.2	3.1
hSBA-MenY	ATP Immuno (Cohort 1), post-dose 3								
	HibMenCY	481	461	95.8	93.7	97.4	236.6	205.7	272.1
	Hib	162	3	1.9	0.4	5.3	2.2	2.0	2.4
	Total Vaccinated (Cohort 1), post-dose 3								
	HibMenCY	570	549	96.3	94.4	97.7	245.0	215.7	278.3
	Hib	188	4	2.1	0.6	5.4	2.2	2.0	2.4

Source: Modified from Table 27 and Supplement 60, Hib-MenCY-TT-009 CSR

According to information presented in Tables 16 and 18 in the Hib-MenCY-TT-009 CSR, the age, gender, and ethnic/racial distribution of subjects who were eligible for inclusion in the Primary ATP cohort for immunogenicity, Cohort 1 was similar to that of subjects in the Primary Total Vaccinated cohort (Cohorts 1, 2, 3), except that the proportion of subjects who were Hispanic was higher in the Primary Total Vaccinated cohort, which included subjects enrolled in Mexico, as compared with the Primary ATP cohort for immunogenicity, Cohort 1, which included only subjects enrolled in the U.S. Based on information presented in Tables 21 and 22 of the Hib-MenCY-TT-010 CSR, demographics of the Fourth dose Total Vaccinated cohort were similar to demographics of the Primary Total Vaccinated Cohort in race/ethnicity, as were demographics of the Fourth dose ATP cohort for immunogenicity and the Primary ATP cohort for immunogenicity.

Subjects who received the 4th dose were similar to subjects who received doses 1 – 3 but did not receive the 4th dose in terms of demographics, immune responses post-dose 3 (Cohort 1), and safety profile. The applicant provided results of analyses of anti-PRP, hSBA-MenC, and hSBA-MenY responses post-dose 3 based on the Fourth dose ATP Cohort for Safety, Cohort 1, which were similar to those results post-dose 3 in the Primary ATP Cohort for immunogenicity, Cohort

1. Based on the data presented in Tables 33 and 34 of the Hib-MenCY-TT-010 CSR, the proportion of Hib-MenCY-TT recipients [95% CI] in the Fourth dose ATP Cohort for Safety, Cohort 1 with post-dose 3 hSBA titers $\geq$ 1:8 was 98.9% [97.4, 99.6] and 96.8% [94.7, 98.2] for MenC and MenY, respectively. GMTs were also similar (935.6 and 233.7 for MenC and MenY, respectively). Analyses of the pre-4th dose titers and GMTs were similar based on the Fourth dose ATP Safety Cohort and the Fourth dose ATP cohort for Immunogenicity, with the proportion of subjects with pre-4th dose hSBA-MenC titers $\geq$ 1:8 96.0% [93.6, 97.6] and GMT 176.5 [153.9, 202.4] based on the Fourth dose ATP Cohort for Safety, Cohort 1 and 96.7% [94.1, 98.3] and GMT 180.3 [155.6, 208.8] based on the Fourth dose ATP Immunogenicity Cohort, Cohort 1; the proportion of Hib-MenCY-TT recipients with pre-4th dose hSBA-MenY titers $\geq$ 1:8 and GMTs were 92.8% [89.9, 95.1] and 117.5 [101.3, 136.2] in the Fourth dose ATP cohort for safety, Cohort 1 and 93.0% [89.7, 95.5] and GMTs 119.1 [101.1, 140.3] in the Fourth dose ATP Immunogenicity Cohort, Cohort 1. Based on the results of analyses based on the Fourth dose Total Vaccinated Cohort, Cohort 1 presented in Supplement 156 to the Hib-MenCY-TT-010 CSR, pre-4th dose hSBA-MenC titers were $\geq$ 1:8 in 96.0% [93.9, 97.5] of Hib-MenCY-TT recipients, and GMTs were 177.1 [156.2, 200.9]; for hSBA-MenY, these results were 92.4% [89.7, 94.6] and GMTs were 118.3 [103.0, 135.8].

Although the primary analysis of immunogenicity post-dose 4 was based on the Fourth dose ATP immunogenicity cohort (Cohort 1), the protocol specified that a secondary analysis based on the Fourth dose Total Vaccinated cohort (Cohort 1) would be performed since more than 5% of enrolled subjects were excluded from the Fourth dose ATP cohort for immunogenicity post-dose 4.

Table 22. Proportions of subjects with MenC and MenY hSBA > 1:8 and GMTs post-dose 4, Fourth dose ATP immunogenicity cohort (Cohort 1) compared with Fourth dose Total Vaccinated cohort (Cohort 1):

			$\geq$ 1:8				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
hSBA-MenC	ATP Immuno (Cohort 1), post-dose 4								
	HibMenCY	331	326	98.5	96.5	99.5	2039.8	1746.3	2382.6
	Hib	119	26	21.8	14.8	30.4	4.3	3.2	5.8
	Total Vaccinated (Cohort 1), post-dose 4								
	HibMenCY	460	455	98.9	97.5	99.6	1843.8	1619.1	2099.7
	Hib	156	33	21.2	15.0	28.4	4.1	3.2	5.3
hSBA-MenY	ATP Immuno (Cohort 1), post-dose 4								
	HibMenCY	342	338	98.8	97.0	99.7	1389.5	1205.0	1602.2
	Hib	120	87	72.5	63.6	80.3	48.6	31.9	74.0
	Total Vaccinated (Cohort 1), post-dose 4								
	HibMenCY	474	469	98.9	97.6	99.7	1288.0	1137.0	1457.8
	Hib	155	107	69.0	61.1	76.2	40.8	28.2	59.0

Source: Modified from Tables 37, 38 and Supplement 156 in the Hib-MenCY-TT-010 CSR

The applicant also performed an additional analysis on a larger sample size based on an Enlarged ATP Cohort for immunogenicity (blood draw window of 35 to 77 days post-4th dose) for anti-PRP, hSBA-MenC, and hSBA-MenY. Results were similar to those obtained based on the Fourth dose ATP cohort for immunogenicity, with the proportion of subjects having post-frouth dose hSBA titers for MenC and MenY [95% CI] 98.6% [96.8, 99.5] and 98.9% [97.3, 99.7], respectively.

Additionally, the applicant provided analyses using a last observation carried forward (LOCF) strategy (Supplements 117, 118 of the Hib-MenCY-TT-010 CSR). The method was based on imputing either the post-dose 3 or the pre-4th dose value for the subject post-4th dose if the post-4th dose value was missing. Specifically, for subjects who did not participate in the evaluation of the 4th dose, the post-dose 3 value was imputed. For subjects that did participate but did not have a post-4th dose value, the pre-4th dose was imputed. Carrying forward the post-dose 3 immunogenicity results likely underestimates the post-dose 4 response, as it would be reasonable to assume that titers would increase further after an additional dose. The applicant's analyses based on the Fourth dose ATP Cohort for Immunogenicity, Cohort 1, with LOCF imputation gave a point estimate for the proportion of subjects with anti-PRP of at least 1.0 mcg/mL of 97.1% among Hib-MenCY-TT recipients and 97.2% of Hib recipients. Similar analyses were provided for the proportion of subjects with hSBA titers > 1:8 [95% CI] and GMTs. For MenC, these results were 98.1% [96.2, 99.2] and GMTs 1420.4 [1209.9, 1667.5] for Hib-MenCY-TT recipients and 20.4% [14.1, 28.0] and GMTs 4.0 [3.1, 5.2] for Hib recipients. For MenY, these results were 97.1% [95.0, 98.5] and GMTs 940.4 [800.0, 1105.5] for Hib-MenCY-TT recipients and 61.3% [52.7, 69.3] and GMTs 29.7 [19.8, 44.4] for Hib recipients.

Exploratory analysis of post-dose 4 meningococcal response based on Cohort 3 indicated that 100% of Hib-MenCY-TT recipients had hSBA-MenC and hSBA-Men Y $\geq$ 1:8; 7.7% and 53.8% of Hib recipients had hSBA-MenC and hSBA-Men Y $\geq$ 1:8, respectively. The higher than expected proportion of Hib control recipients with hSBA titers $\geq$ 1:8 may be related to the OMP carrier protein used in the Hib vaccine used as the control for the 4th dose, as described previously in this review. The observed hSBA-MenC GMTs increased 20.1-fold, and the observed hSBA-MenY GMTs increased 12.9-fold.

Anti-PRP response:

Percentages of subjects with anti-PRP concentration equal to or above the cut-off values of 0.15 and 1.0 mcg/mL and GMCs one month post-dose 3:

Table 23: Percentages of subjects with anti-PRP concentration equal to or above the cut-off values of 0.15 and 1.0 mcg/mL and GMCs, post-3rd vaccination and pre-fourth dose (Primary ATP Cohort for Immunogenicity for Post-dose 3 and Fourth dose ATP Cohort for Safety, Cohort 1 for Pre-dose 4)

				≥ 0.15 mcg/mL				≥ 1.0 mcg/mL				GMC		
						95% CI				95% CI			95% CI	
Antibody anti-PRP	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
	HibMenCY Lots A, B, C combined	Post 3	518	518	100	99.3	100	499	96.3	94.3	97.8	11.021	10.027	12.114
		Pre 4	441	423	95.9	93.6	97.6	298	67.6	63.0	71.9	1.615	1.439	1.812
	Hib	Post 3	171	168	98.2	95.0	99.6	156	91.2	85.9	95.0	6.463	5.288	7.900
		Pre 4	147	129	87.8	81.3	92.6	75	51.0	42.7	59.3	0.832	0.664	1.042
	HibMenCY Lot A	Post 3	162	162	100	97.7	100	158	97.5	93.8	99.3	10.170	8.855	11.681
		Pre 4	140	138	98.6	94.9	99.8	94	67.1	58.7	74.8	1.561	1.298	1.877
	HibMenCY Lot B	Post 3	180	180	100	98.0	100	175	97.2	93.6	99.1	11.424	9.710	13.441
		Pre 4	155	148	95.5	90.9	98.2	104	67.1	59.1	74.4	1.510	1.249	1.825
	HibMenCY Lot C	Post 3	176	176	100	97.9	100	166	94.3	89.8	97.2	11.438	9.503	13.768
		Pre 4	146	137	93.8	88.6	97.1	100	68.5	60.3	75.9	1.791	1.427	2.246
	HibMenCY Lots B and C combined	Post 3	356	356	100	99.0	100	341	95.8	93.1	97.6	11.431	10.113	12.921
		Pre 4	301	285	94.7	91.5	96.9	204	67.8	62.2	73.0	1.640	1.417	1.899

Source: Modified from applicant's Tables 32, Hib-MenCY-TT-010 CSR; Table 26, Hib-MenCY-TT-009 CSR; and Tables 1, 2 of the Effectiveness Information Amendment of January 8, 2010)
HibMenCY = Hib-MenCY-TT + MMR + V + PCV7 in subjects who received 3 doses Hib-MenCY-TT + DTaP-HBV-IPV + PCV7 in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMRII + V + PCV7 in subjects who received 3 doses *ActHIB*® + DTaP-HBV-IPV + PCV7 in study Hib-MenCY-TT-009
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
HibMenCY Lots A – C = subjects who received 3 doses of Hib-MenCY-TT Lots A – C + DTaP-HBV-IPV (+ PCV7)
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit
Post 3 = post dose 3 blood sample at month 5 (study Hib-MenCY-TT-009)
Pre 4 = pre-fourth dose vaccination blood sample

One month after the third vaccination, the percentage of subjects with anti-PRP concentration ≥ 1 mcg/mL was 96.3% for pooled Hib-MenCY-TT recipients [N=518] and 91.2% for Hib participants [N=171]. The rate difference in the proportions of Hib-MenCY-TT and Hib control recipients with this anti-PRP concentration (*p* Hib-MenCY-TT – *p* Hib) was 5.10% (1.20, 10.49), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration ≥1.0 µg/mL. For Hib-MenCY-TT Lot A, the rate difference (*p* Hib-MenCY-TT Lot A – *p* Hib) was 6.30% (1.46, 11.82), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration ≥1.0 µg/mL. For Hib-MenCY-TT Lots B and C combined, the rate difference (*p* Hib-MenCY-TT Lots B and C – *p* Hib) was 4.56% (0.31, 10.05), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration ≥1.0 µg/mL. These analyses were based on the Primary ATP Cohort for Immunogenicity, Cohort 1. Additionally, one month after the fourth vaccination, in the Fourth dose ATP Cohort for Immunogenicity, Cohort 1, the percentage of subjects with anti-PRP concentration ≥ 1 mcg/mL was 99.2% for Hib-MenCY-TT [N=361] and Hib [N=126] recipients. The rate difference (*p* Hib-MenCY-TT – *p*Hib) was -0.04% (-1.78, 3.57), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration ≥1.0 µg/mL. These PRP-related primary hypotheses were achieved. Also of interest, the percentage of subjects achieving anti-PRP concentration ≥ 0.15 mcg/mL one month post-3rd dose was 100% and 98.2% for Hib-MenCY-TT and Hib subjects, respectively. The corresponding GMCs and 95% CIs were 11.021 (10.027, 12.114) for Hib-MenCY-TT recipients and 6.463 (5.288, 7.900) for Hib participants.

Table 24: Percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL and GMCs post-4th dose vaccination

Percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL and GMCs post-4th dose vaccination (Fourth dose ATP Cohort for Immunogenicity, Cohort 1)													
			≥ 0.15 mcg/mL				≥ 1.0 mcg/mL				GMC		
					95% CI				95%CI			95% CI	
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
Anti-PRP	HibMenCY	361	361	100	99.0	100	358	99.2	97.6	99.8	34.851	30.664	39.610
	Hib	126	126	100	97.1	100	125	99.2	95.7	100	20.200	16.373	24.920

Source: applicant's Table 36, Hib-MenCY-TT-010 CSR
HibMenCY = Hib-MenCY-TT + *MMR$_{II}$*® + *V*® + *Prevnar*® in subjects who received 3 doses Hib-MenCY-TT + DTaP-HBV-IPV + PCV7 in study Hib-MenCY-TT-009
Hib = *PedvaxHIB*® + MMRII + V + Prevnar in subjects who received 3 doses *ActHIB*® + DTaP-HBV-IPV + PCV7in study Hib-MenCY-TT-009
GMC = geometric mean antibody concentration calculated on all subjects
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

Post-fourth dose, the proportions of subjects achieving anti-PRP antibody concentration ≥ 0.15 and ≥ 1.0 mcg/mL were 100 and 99.2%, respectively, in both groups. Regarding secondary objectives related to antibody persistence, exploratory evaluation of differences between groups indicated a statistically significant higher persistence of anti-PRP in subjects who received 3 doses of Hib-MenCY-TT compared with subjects who received 3 doses of Hib in study Hib-MenCY-TT-009.

Exploratory analyses of Cohort 3 suggested that 100% of subjects in all treatment groups had anti-PRP concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL one month post-dose 3. Compared with Cohort 1, Cohort 3 subjects had 4.6-fold and 2.1-fold higher GMCs in the Hib and pooled HibMenCY-TT groups, respectively, with point estimates of 29.759 [22.729, 38.965] in the Hib group and 23.165 [20.012, 26.815] in the pooled HibMenCY-TT group. Additionally, the

percentage of subjects in Cohort 3 who retained anti-PRP $\geq$ 0.15 mcg/mL prior to the fourth dose vaccination was 100% for both the HibMenCY-TT and Hib groups. The percentage retaining anti-PRP $\geq$ 1.0 mcg/mL was similar for both groups (88.0% for the HibMenCY-TT group and 88.6% for the Hib group). The GMCs in Cohort 3 had decreased 7.5-fold in the HibMenCY-TT group and 6.6-fold in the Hib group compared to the post-3rd vaccination concentrations.

Anti-PT, anti-FHA, and anti-PRN responses:

One month after the third vaccination, the lower limit of the two-sided 95% CI of the GMC ratio ($GMC_{Hib\text{-}MenCY\text{-}TT}$ /GMC_{Hib}) was $\geq$ 0.67 for PT, FHA, and PRN, achieving the criteria for non-inferiority of pertussis response to *DTaP-HBV-IPV* when co-administered with Hib-MenCY-TT vs. Hib, if one could pool the 3 HibMenCY-TT lots. However, given the failure to meet lot to lot consistency criteria necessary for pooling the 3 HibMenCY-TT lots for the MenY component, an evaluation of lot-specific percentages of subjects achieving anti-PT, anti-FHA, and anti-PRN $\geq$ 5 EL.U/mL and GMCs was provided, as seen in the below table:

Table 25. Percentage of subjects with anti-PT, anti-FHA, and anti-PRN concentrations ≥ 5 EL.U/mL and GMCs one month post-dose 3 (Primary ATP Cohort for Immunogenicity, Cohort 1)

			≥ 5 EL.U/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-PT	Hib	100	100	100	96.4	100	65.6	58.3	73.9
	HibMenCY	327	327	100	98.9	100	57.7	54.0	61.7
	Hib MenCY Lot A	99	99	100	96.3	100	54.4	47.9	61.8
	HibMenCY Lot B	110	110	100	96.7	100	64.1	57.3	71.7
	HibMenCY Lot C	118	118	100	96.9	100	55.1	49.2	61.6
Anti-FHA	Hib	97	97	100	96.3	100	293.6	261.4	329.8
	HibMenCY	324	324	100	98.9	100	243.8	227.9	260.9
	Hib MenCY Lot A	96	96	100	96.2	100	231.6	202.7	264.5
	HibMenCY Lot B	110	110	100	96.7	100	265.1	237.6	295.8
	HibMenCY Lot C	118	118	100	96.9	100	235.2	210.2	263.2
Anti-PRN	Hib	101	99	98.0	93.0	99.8	103.1	82.8	128.4
	HibMenCY	322	321	99.7	98.3	100	98.6	89.5	108.6
	Hib MenCY Lot A	97	97	100	96.3	100	90.8	74.7	110.4
	HibMenCY Lot B	108	107	99.1	94.9	100	114.1	98.1	132.8
	HibMenCY Lot C	117	117	100	96.9	100	92.2	78.7	108.0

Source: Table 31, Hib-MenCY-TT-009 CSR
GMC = geometric mean concentration calculated on all subjects
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

Table 26. Ratios of the anti-PT, anti-FHA, and anti-PRN GMCs between HibMenCY-TT and Hib regimens one month post-dose 3 (Primary ATP Cohort for Immunogenicity, Cohort 1):

					GMC ratio (Hib-MenCY-TT/Hib)		
	HibMenCY-TT		Hib			95% CI	
Antibody	N	GMC	N	GMC	Value	LL	UL
Anti-PT (EL.U/mL)	327	57.7	100	65.6	0.88	0.77	1.01
Anti-FHA (EL.U/mL)	324	243.8	97	293.6	0.83	0.72	0.95
Anti-PRN (EL.U/mL)	322	98.6	101	103.1	0.96	0.77	1.18

Source: Table 30, Hib-MenCY-TT-009 CSR
GMC = geometric mean concentration
N = number of subjects with post-vaccination results available
95% CI = 95% confidence interval for the GMC ratio; LL = lower limit; UL = upper limit

Hepatitis B (HBs) response:

Anti-HBs response to concomitantly administered DTaP-HBV-IPV was similar between Hib-MenCY-TT and Hib participants who had received a birth dose of hepatitis B vaccine, with at least 98.4% of subjects achieving anti-HBs concentrations ≥ 10 mIU/. In the small group of infants who had not received hepatitis B vaccine at birth (N= 26 total), the percentages of Hib-MenCY-TT recipients (94.4%) and Hib participants (100%) who achieved anti-HBs concentrations ≥ 10 mIU/mL was influenced by 1 subject in the Hib-MenCY-TT Lot A group who did not meet the seroprotective level.

Table 27. Percentage of subjects who received a birth dose of hepatitis B vaccine with anti-HBs concentrations ≥ 10 mIU/mL and GMCs one month post-dose 3, Primary ATP Cohort for Immunogenicity, Cohort 1:

		≥ 10 mIU/mL				GMC		
				95% CI			95% CI	
Group	N	n	%	LL	UL	Value	LL	UL
Hib	47	47	100	92.5	100	2187.6	1551.4	3084.5
HibMenCY	194	103	99.5	97.2	100	1963.2	1684.8	2287.7
HibMenCY Lot A	60	60	100	94.0	100	1949.3	1522.8	2495.4
HibMenCY Lot B	64	63	98.4	91.6	100	2176.6	1590.0	2979.7
HibMenCY Lot C	70	70	100	94.9	100	1797.4	1412.7	2286.9

Source: Modified from Table 34, Hib-MenCY-TT-009 CSR
GMC = geometric mean antibody concentration calculated on all subjects
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

Anti-polio response:

Anti-poliovirus types 1, 2, and 3 antibody titers were assessed 1 month post-3rd dose. All subjects in the pooled HibMenCY-TT group and in the Hib group had anti-poliovirus titers ≥ 1:8, with the lower limit of the 95% CI for the rate difference (*p* Hib-MenCY-TT – *p* Hib) of -1.33 for all poliovirus types, achieving the criteria of LL ≥ -10% for non-inferiority of pertussis response to *DTaP-HBV-IPV* when co-administered with Hib-MenCY-TT vs. Hib, if one could pool the 3 HibMenCY-TT lots. However, given the failure to meet lot to lot consistency criteria necessary for pooling the 3 Hib-MenCY-TT lots, the lot-specific percentages of subjects achieving anti-poliovirus titers ≥ 1:8 and GMTs were also provided, as shown below:

Table 28. Percentage of subjects with anti-poliovirus types 1, 2, and 3 titers ≥ 1:8 and GMTs one month post-dose 3, Primary ATP Cohort for Immunogenicity, Cohort 1:

			≥ 1:8				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-poliovirus 1	Hib	90	90	100	96.0	100	590.7	462.7	754.1
	HibMenCY	285	285	100	98.7	100	591.8	525.0	667.0
	Hib MenCY Lot A	87	87	100	95.8	100	652.8	522.8	815.3
	HibMenCY Lot B	97	97	100	96.3	100	616.6	508.6	747.5
	HibMenCY Lot C	101	101	100	96.4	100	522.8	422.9	646.2
Anti-poliovirus 2	Hib	90	90	100	96.0	100	452.7	360.3	568.8
	HibMenCY	285	285	100	98.7	100	496.7	435.9	566.0
	Hib MenCY Lot A	87	87	100	95.8	100	461.8	361.5	590.1
	HibMenCY Lot B	97	97	100	96.3	100	497.5	393.7	628.6
	HibMenCY Lot C	101	101	100	96.4	100	528.1	428.5	650.9
Anti-poliovirus 3	Hib	89	89	100	95.9	100	1239.2	973.5	1577.6
	HibMenCY	285	285	100	98.7	100	1367.7	1209.9	1546.0
	Hib MenCY Lot A	87	87	100	95.8	100	1501.0	1206.5	1867.4
	HibMenCY Lot B	97	97	100	96.3	100	1333.8	1087.3	1636.3
	HibMenCY Lot C	101	101	100	96.4	100	1293.1	1038.1	1610.6

Source: Modified from Table 33, Hib-MenCY-TT-009 CSR
GMT = geometric mean antibody titer calculated on all subjects
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

Anti-tetanus and anti-diphtheria responses:

Seroprotection rates for tetanus and diphtheria were assessed 1 month post-3rd dose. Following 3 doses of concomitantly administered DTaP-HBV-IPV, 100% of subjects who received any of 3 Hib-MenCY-TT lots or Hib had seroprotective levels for tetanus and diphtheria. The protocol-defined criteria for meeting the powered secondary objective of non-inferiority of DTaP-HBV-IPV co-administered with Hib-MenCY-TT to DTaP-HBV-IPV co-administered with Hib was a 95% CI lower limit of ≥ -10.0%. If criteria for pooling the 3 HibMenCY-TT lots had been met, this criteria would have been met for anti-diphtheria (anti-D) and anti-tetanus (anti-T), as the difference [95% CI] for *p* Hib-MenCY-TT – *p* Hib was 0.00% [-1.04, 3.11]. However, as criteria for lot pooling were not met, evaluation of the anti-T and anti-D data from the various HibMenCY-TT lots is described. Anti-T and anti-D GMCs were similar across HibMenCY-TT lots. Anti-D GMCs were similar between HibMenCY-TT groups and the Hib groups. However, anti-T GMCs were higher in the HibMenCY-TT groups when compared to the Hib group, with non-overlapping 95% CIs, likely due to the carrier protein used in HibMenCY-TT.

Table 29. Percentage of subjects with anti-D and anti-T concentrations ≥ 0.1 IU/mL and GMCs one month post-dose 3, Primary ATP Cohort for Immunogenicity, Cohort 1:

			≥ 0.1 IU/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-Diphtheria	Hib	120	120	100	97.0	100	2.2	2.0	2.5
	HibMenCY	365	365	100	99.0	100	2.0	1.9	2.2
	HibMenCY Lot A	114	114	100	96.8	100	2.0	1.7	2.3
	HibMenCY Lot B	121	121	100	97.0	100	2.2	1.9	2.5
	HibMenCY Lot C	130	130	100	97.2	100	1.9	1.7	2.2
Anti-Tetanus	Hib	120	120	100	97.0	100	1.9	1.7	2.2
	HibMenCY	365	365	100	99.0	100	3.9	3.7	4.1
	HibMenCY Lot A	114	114	100	96.8	100	3.8	3.4	4.1
	HibMenCY Lot B	121	121	100	97.0	100	4.1	3.6	4.5
	HibMenCY Lot C	130	130	100	97.2	100	3.8	3.5	4.2

Source: Modified from Table 29, Hib-MenCY-TT-009 CSR
GMC = geometric mean antibody concentration calculated on all subjects
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

Measles, mumps, and rubella (MMR) and varicella (V) co-administration:

Non-pooled analysis:
Analyses of MMR and V immune responses observed in Hib-MenCY-TT-010 are based on the Fourth dose ATP Cohort for Immunogenicity and presented in the below tables, for subjects with initial antibody concentrations or titers as follows: measles: <150 mIU/mL, mumps: <28ED50, rubella: < 4IU/mL, varicella: < 1:5. Although post-vaccination anti-measles concentrations ≥ 150 mIU/mL, anti-mumps titers ≥ 28 ED50, and anti-varicella titers ≥ 1:5 were specified endpoints, CBER assay reviewers determined that cut-off levels of ≥ 200 mIU/mL, ≥ 51 ED50, and ≥ 1:40 for evaluation of immune interference were supported by assay characteristics. Therefore, only these results are presented in the tables below. The percentage of subjects with anti-measles concentrations ≥ 150 mIU/mL and ≥ 200 mIU/mL 42 days post-4th vaccination was 98.6% and 96.5% for the HibMenCY-TT and Hib groups, respectively, for subjects seronegative prior to vaccination (in study Hib-MenCY-TT-010, all subjects). The percentages of subjects with anti-mumps titers ≥ 28 ED50 and ≥ 51 ED50 were 98.5% and 92.6% for HibMenCY-TT recipients and 100% and 90.1% for Hib recipients. Approximately one-third of participants in both treatment groups had pre-4th vaccination anti-mumps titers ≥ 24ED50. The percentage of subjects with anti-rubella concentrations ≥ 4 mIU/mL and ≥ 10 mIU/mL 42 days post-4th vaccination was 100% for the HibMenCY-TT participants and 100% and 99.1% for Hib recipients, respectively, for subjects seronegative prior to vaccination (in Hib-MenCY-TT-010, all subjects). All subjects had post-4th vaccination anti-varicella titers ≥ 1:5 and ≥ 1:40. Approximately 10.2% of HibMenCY-TT recipients and 7.6% of Hib recipients had pre-4th vaccination anti-varicella titers ≥ 1:5. The pre-specified criteria for the pooled analysis (i.e., the lower boundary of the 95% CI

for between group differences above -5% for measles, mumps, and rubella and above -10% for varicella), were met independently in study Hib-MenCY-TT-010.

Table 30. Immune responses to MMR and V concomitantly administered with Hib-MenCY-TT or Hib, Fourth dose ATP Cohort for Immunogenicity Cohort 1, for initially seronegative subjects:

			≥ 200 mIU/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-measles	HibMenCY	351	346	98.6	96.7	99.5	2651.5	2427.3	2896.4
	Hib	115	111	96.5	91.3	99.0	2335.1	1954.1	2790.3
			≥ 51 ED50				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-mumps	HibMenCY	269	249	92.6	88.8	95.4	127.6	117.3	138.9
	Hib	81	73	90.1	81.5	95.6	111.0	95.5	129.1
			≥ 10 IU/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-rubella	HibMenCY	350	350	100	99.0	100	85.3	79.1	91.9
	Hib	114	113	99.1	95.2	100	72.3	63.0	83.0
			≥ 1:40				GMT		
					95% CI			95% CI	
Antibody	Group	N	n	%	LL	UL	Value	LL	UL
Anti-varicella	HibMenCY	319	319	100	98.9	100	397.7	371.1	426.1
	Hib	104	104	100	96.5	100	349.0	311.9	390.4

Source: Modified from Tables 39, 41, 43, 45, Hib-MenCY-TT-010 CSR
HibMenCY-TT = HibMenCY-TT + MMR + V + PCV primed with HibMenCY-TT + DTaP-HBV-IPV + PCV7
Hib = PedvaxHIB + MMR + V + PCV7 primed with ActHIB + DTaP-HBV-IPV + PCV7
GMC = geometric mean concentration calculated on all subjects
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

Table 31. Between group seroconversion rate differences, Fourth dose ATP Cohort for Immunogenicity Cohort 1, for initially seronegative subjects:

Difference between groups in anti-measles concentrations ≥ 200 mIU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-measles	≥ 200 mIU/mL	351	346	98.6	115	111	96.5	2.05	-0.73	7.27
Difference between groups in anti-mumps titers ≥ 51 ED50 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-mumps	≥ 51 ED50	269	249	92.6	81	73	90.1	2.44	-3.71	11.27
Difference between groups in anti-rubella concentrations ≥ 10 IU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-rubella	≥ 10 IU/mL	350	350	100	114	113	99.1	0.88	-0.22	4.81
Difference between groups in anti-varicella titers ≥ 1:40 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-varicella	≥ 1:40	319	319	100	104	104	100	0.00	-1.19	3.57

Source: Modified from Tables 40, 42, 44, 46, Hib-MenCY-TT-010 CSR
HibMenCY-TT = HibMenCY-TT + MMR + V + PCV7 primed with HibMenCY-TT + DTaP-HBV-IPV + PCV7
Hib = PedvaxHIB + MMR + V + PCV7 primed with ActHIB + DTaP-HBV-IPV + PCV7
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = standardized asymptotic 95% confidence interval; LL = lower limit; UL = upper limit

Pooled analysis

GSK planned a pooled analysis with results from Hib-MenCY-TT-008 and -010 to ensure sufficient power to evaluate immune response endpoints for co-administration of measles, mumps, rubella, and varicella vaccines with the fourth dose of Hib-MenCY-TT or the Hib control vaccine. The pre-specified criteria for pooling of the measles, mumps, and rubella and varicella co-vaccination results from study Hib-MenCY-TT-010 and study Hib-MenCY-TT-008 were that the point estimates within each study met the pre-specified criteria for pooling.

Table 32. Between group seroconversion rate differences, Fourth dose ATP Cohort for Immunogenicity, Hib-MenCY-TT-008 and Fourth dose ATP Cohort for Immunogenicity Cohort 1, Hib-MenCY-TT-010 (Pooled analysis):

Difference between groups in anti-measles concentrations ≥ 200 mIU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-measles	≥ 200 mIU/mL	852	812	95.3	286	273	95.5	-0.15	-2.66	3.15
Difference between groups in anti-mumps titers ≥ 51 ED50 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-mumps	≥ 51 ED50	601	551	91.7	191	174	91.1	-0.58	-3.56	5.84
Difference between groups in anti-rubella concentrations ≥ 10 IU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-rubella	≥ 10 IU/mL	850	848	99.8	285	284	99.6	0.12	-0.57	1.73
Difference between groups in anti-varicella titers ≥ 1:40 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-varicella	≥ 1:40	723	722	99.9	223	223	100	-0.14	-0.78	1.56

Source: Tables 6, 7, Supplement 12, Hib-MenCY-TT-008-010 Annex
HibMenCY-TT = HibMenCY-TT + MMR + V + PCV7 primed with HibMenCY-TT + DTaP-HBV-IPV + PCV7
Hib = PedvaxHIB + MMR + V + PCV7 primed with ActHIB + DTaP-HBV-IPV + PCV7
GMC = geometric mean concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration within the specified range
95% CI = standardized asymptotic 95% confidence interval; LL = lower limit; UL = upper limit

Acceptance criteria (lower bound of the 95% CI for the between group difference > -5% for measles, mumps, rubella and > -10% for varicella) were met based on the pooled MMR and V immune response data from Hib-MenCY-TT-008 and Hib-MenCY-TT-010. However, the protocols for Hib-MenCY-TT-008 and -010 included different primary endpoints (seroconversion

criteria) for the non-inferiority evaluation. Therefore, the pooled analysis data are considered secondary support for evaluation of non-interference.

Influenza vaccine co-administration:

An exploratory analysis of the primary endpoints stratified according to whether or not subjects in Cohort 1 received co-administered influenza vaccine was performed. In Cohort 1 in study Hib-MenCY-TT, 773/2776 (27.8%) of subjects received concomitant influenza vaccine. The number of subjects from Cohort 1 who received concomitant inactivated influenza vaccine in the Primary ATP Cohort for Immunogenicity ranged from 48 – 52 per HibMenCY-TT lot. Among the 110 - 133 subjects per HibMenCY-TT lot from Cohort 1 who did not receive concomitant inactivated influenza vaccine in the Primary ATP Cohort for Immunogenicity, lot-to-lot consistency was not met for the hSBA-MenY immune response for Lot B/Lot A and Lot C/Lot A. This sample size was also reduced compared to the cohort on which the primary analysis was based. The applicant concludes that these observations support the hypothesis that failure to achieve success on all lot-to-lot comparisons was the result of marginally inadequate study power. However, the clinical reviewer believes it is important to note that the apparent failure of lot A on hSBA-MenY GMT criteria is consistent with the results of the primary analysis.

If subjects were stratified according to influenza co-administration, criteria for non-inferiority of post-dose 3 anti-PRP antibody concentration $\geq$ 1.0 mcg/mL used in the primary analysis were met, regardless of influenza co-vaccination status. Among the 3136 Hib-MenCY-TT recipients in study Hib-MenCY-TT-009, 771 (24.6%) received concomitant influenza vaccine, while 275/1044 Hib participants (26.3%) received concomitant influenza vaccine. Percentages of subjects reporting any adverse event, any systemic adverse event, any local adverse event, any SAE, any NOCD, any rash, any ER vist, and any physician office visit were fairly comparable between those who had and had not received concomitant influenza vaccine. However, in study Hib-MenCY-TT-010, the vast majority of subjects did not receive a concomitant influenza vaccination with the fourth dose study vaccines (i.e., 8 subjects in the Hib-MenCY-TT group and 5 subjects in the Hib group received concomitant influenza vaccinations). Conclusions cannot be drawn from the few subjects who were co-vaccinated with influenza vaccine with the 4th dose of Hib-MenCY-TT or Hib vaccine. The proportion of subjects achieving post-4th dose vaccination anti-PRP antibody concentration $\geq$ 1.0 mcg/mL and hSBA-MenC and hSBA-MenY $\geq$ 1:8 was comparable to that presented for the full Fourth dose ATP Cohort for Immunogenicity, Cohort 1.

Analyses of influenza antibody persistence according to influenza co-vaccination were done only on subjects in the Fourth dose ATP Cohort for Safety for Cohort 1 and only on those subjects that were compliant with the current U.S. seasonal influenza vaccination recommendations, i.e., subjects who had received 2 influenza vaccinations in the same influenza season with one concomitant with one of the first 3 doses of study vaccine and none with the fourth dose. Only 33 Hib-MenCY-TT recipients and 18 Hib recipients met these criteria, so the data should be interpreted with caution, and no conclusions can be made from them. The proportions of HibMenCY-TT subjects who had anti-H1N1, anti-H3N2, and anti-B titers $\geq$ 1:40 pre-fourth dose were 18.2%, 27.3%, and 6.1%, respectively. For Hib subjects, these corresponding proportions were 0.0%, 22.2%, and 0.0%. Among the 8 Hib-MenCY-TT recipients and 5 Hib recipients in the Fourth dose ATP Cohort for Immunogenicity Cohort 1 who had concomitant influenza vaccine and hSBA results, the percentages of subjects with hSBA-MenC titers $\geq$ 1:8 were 100% [59.0, 100] and 0.0 [0.0, 52.2], respectively, while the percentages of subjects with hSBA-MenY titers $\geq$ 1:8 were 100% [63.1, 100] and 100% [47.8, 100]. Again, given the small numbers of subjects, no conclusions can be regarding the comparability of responses to meningococcal

antigens and influenza antigens when influenza vaccine is co-administered with the 4th dose of Hib-MenCY-TT..

Similarly, analyses of influenza immune response were performed on subjects of the Fourth dose ATP Cohort for Immunogenicity, Cohort 1 who had received 2 influenza vaccines with one concomitant with the fourth dose of study vaccines, there were very few subjects ($N \leq 5$ per group) included, so no conclusions can be drawn from the results.

Rotavirus vaccine co-administration:
Among the 3136 Hib-MenCY-TT subjects evaluated over doses 1 - 3, 256 (8.2%) were completely co-vaccinated with rotavirus vaccine, while 137 (4.4%) were partly co-vaccinated. Among the 1044 Hib subjects, 82 (7.9%) were completely co-vaccinated with rotavirus vaccine, while 46 (4.4%) were partly co-vaccinated. In Australia and Mexico, > 95% of the subjects did not receive co-administered rotavirus vaccine. Based on the Primary Total Vaccinated cohort: United States, proportions of subjects reporting any adverse event, any systemic adverse event, and any local adverse event, were fairly similar, regardless of rotavirus co-vaccination status. Within treatment groups, the 95% CIs around the point estimates for proportions of subjects with any SAE, any NOCD, any rash, any ER visit, and any physician office visit by rotavirus co-vaccination status overlapped.

Hepatitis A vaccine co-administration:
Among the 1756 Hib-MenCY-TT recipients in the Fourth dose Total Vaccinated cohort, US subjects, 80 (4.6%) were co-vaccinated with hepatitis A vaccine. Among the 584 Hib participants in this same group, 26 (4.5%) were hepatitis A co-vaccinated. With the exception of "at least one symptom" and physician office visits, events of special interest during the ESFU had similar occurrences within treatment groups, with overlapping 95% CIs. For the 2 excepted categories, the proportions were higher in the Hib-MenCY-TT subjects who had not received concomitant hepatitis A vaccination when compared with the Hib-MenCY-TT subjects who did not receive it. Within treatment groups, proportions of subjects reporting any symptom, any general symptom, and any local symptoms tended to be higher among subjects who had not received concomitant hepatitis A vaccination. Again, given the limited number of subjects co-vaccinated for hepatitis A no conclusions can be drawn from the results.

Summary:
This study was a phase 3 lot consistency, safety and pivotal immunogenicity trial to support licensure of Hib-MenCY-TT in infants and toddlers. Hib-MenCY-TT was administered at 2, 4, 6 and 12-15 months of age. Criteria for lot consistency were based on ratios of pairwise comparisons of lots (A, B, C) for anti-PRP GMTs and Men C and MenY hSBA GMTs. Success criteria for lot consistency were met for all three antigens with the single exception of Men Y in the comparisons of lots A and B, for which lot the upper limit of the 95% CI for the ratio of hSBA MenY GMT in Lot B/hSBA MenY GMT in Lot A exceeded the pre-defined limit of 2.0. The primary endpoints related to immune responses to the Hib and meningococcal vaccine components were met for each of the 3 lots individually, even though these endpoints were not powered individually by lot. The hSBA assay, as a functional assay, is inherently more variable than certain other assays. Safety was comparable in all 3 lots. Additionally, the CMC review did not identify important differences between lots that would suggest manufacturing inconsistency. For these reasons, pooling of the 3 Hib-MenCY-TT lots in analyses of the safety and immunogenicity data were justified.

Most subjects reported solicited adverse events, and the percentages were fairly similar between study groups. Most adverse events were mild or moderate in severity.

In evaluation of doses 1 - 3, 258 SAEs were reported for 176 individuals [Hib-MenCY-TT n=126 of 3136 vaccinated subjects, 194 events; Hib n=50 of 1044 vaccinated subjects, 64 events]. Four deaths occurred during the ESFU, 3 in the HibMenCY-TT group and 1 in the Hib group. Given the timing and nature of the infants' deaths, it is reasonable to assess these deaths as unrelated to vaccination with Hib-MenCY-TT, Hib, DTaP-HBV-IPV , or PCV7. During the period from 4th vaccination through the end of the ESFU, 83 non-fatal SAEs were reported for 65 subjects, 47 in the Hib-MenCY-TT group and 18 in the Hib group. One child died from injuries sustained in a motor vehicle accident. Acute infection or management of other acute medical conditions accounted for the majority of SAEs.

One month after the third vaccination, the lower limit of the standardized asymptotic 95% CI on the difference in the percentage of subjects with anti-PRP concentration $\geq$ 1.0 mcg/mL was 1.20%, above the pre-specified lower limit of the 95% CI of $\geq$ -10.0%.

The protocol-defined criteria for post-dose 4 immune response to meningococcal serogroups C and Y were met: the lower limits of the exact 95% CIs for the percentages of Hib-MenCY-TT participants with hSBA-MenC titers $\geq$ 1:8 was 98.8%, above the pre-specified criterion of $\geq$ 90.0%; with hSBA-MenY titers $\geq$ 1:8 was 95.8%, above the pre-specified criterion of $\geq$ 90.0%. Analysis of the powered secondary immunogenicity endpoints suggested that the protocol-defined criteria for post-dose 3 immune response to meningococcal serogroups C and Y were met: the lower limits of the exact 95% CIs for the percentages of subjects in the HibMenCY-TT regimen (3 pooled lots) with hSBA-MenC titers $\geq$ 1:8 was 97.4%, above the pre-specified criterion of $\geq$ 90.0%; with hSBA-MenY titers $\geq$ 1:8 was 93.7%, above the pre-specified criterion of $\geq$ 85.0%. Criteria were also met for each of the 3 lots individually, although the endpoints were not powered accordingly. Likewise, analysis of the secondary endpoint of persistence of antibodies to meningococcal serogroup C induced by 3 doses of Hib-MenCY-TT at the pre-4th dose timepoint of 12 to 15 months met the pre-specified criteria of a lower limit of the 95% CI of $\geq$ 70% for the percentage of subjects with hSBA-MenC titers $\geq$ 1:8 [96.0% (93.6, 97.6)].

Pre-specified criteria for seroprotection from diphtheria and tetanus were also met, with the lower limit of the standardized 95% CI on the difference in the percentages of subjects with antibody concentrations $\geq$ 0.1 IU/mL -1.04% for both diphtheria and tetanus, above the pre-specified lower limit of the 95% CI of $\geq$ -10.0%.

The lower limits of the 95% CI on the GMC ratio (pooled HibMenCY-TT lots group/Hib group) were 0.77 for both anti-PT and anti-PRN and 0.72 for anti-FHA, each above the pre-specified limit of $\geq$ 0.67. The lower limits of the standardized asymptotic 95% CI on the difference between the pooled HibMenCY-TT group and the Hib group in the percentages of subjects with seroprotective titers ($\geq$ 1:8) of antibodies for each of the 3 poliovirus types was 1.33, above the pre-specified lower limit of the 95% CI of $\geq$ -10.0%.

The applicant met pre-specified criteria to allow pooling of MMR and V data from subjects in Hib-MenCY-TT-008 and Hib-MenCY-TT-010. However, the endpoints (seroconversion criteria) specified in the study protocols were different in the two studies, with the exception of those for rubella. Therefore, the clinical reviewer considered the MMR and V data from Hib-MenCY-TT--008 and Hib-MenCY-TT-010 separately, in addition to evaluating the pooled data. In Hib-MenCY-TT-010, acceptance criteria were met for evaluating non-inferiority of co-administered MMR and V vaccines. The pooled analysis were considered secondary supportive data, but they were consistent with the observation of non-interference in the immune responses to MMR and V vaccines co-administered with Hib-MenCY-TT observed in study Hib-MenCY-TT-010 alone.

The data from this trial support Hib-MenCY-TT vaccine's safety and reactogenicity profile, immunogenicity, and non-inferiority in terms of PRP and co-administered vaccine responses, and safety profile to Hib vaccine. The numbers of subjects who received concomitant influenza, hepatitis A, and rotavirus vaccines were too small to formulate conclusions regarding safety and immunogenicity of co-administration of these vaccines with Hib-MenCY-TT.

8.1.2 Study 102370 Hib-MenCY-TT-007 (Primary vaccination)/ Study 102371 Hib-MenCY-TT-008 (Booster vaccination)

A phase II, open, randomised, controlled, multicentre primary and booster vaccination study of GSK Biologicals' Hib-MenCY-TT conjugate vaccine versus ActHIB® and MenC conjugate licensed vaccine when given according to the 2-4-6 month schedule to healthy infants with a booster dose at 12 to 15 months of age.

This trial was an open-label, randomized (3:1:1), parallel group study. At 2, 4 and 6 months of age, infants received: (a) Hib-MenCY-TT group [n=660]: Hib-MenCY-TT, (b) Lic MenC group [n=200]: monvalent meningococcal C CRM_{197} vaccine (*Meningitec)* + *ActHIB*, or (c) Hib group [n=220]: *ActHIB*. *Infanrix penta* (DTaP-IPV-HBV) + *Prevnar* (PCV7) were administered to all subjects. At 12-15 months of age, subjects in the Hib-MenCY-TT and Lic MenC groups received Hib-MenCY-TT and subjects in the Hib group received *PedVaxHIB*. *MMRII* (MMR) and *Varivax* (V) were administered to all 3 study groups. The primary vaccination study period is the timeframe that includes data collected from the day of 1st vaccination to the time of 4th vaccination. The 4th dose vaccination study period is the timeframe that pertains to data collected just prior to the 4th Hib-MenCY-TT dose to 6 months afterwards.

The study results relevant to U.S. licensure are the safety and immunogenicity evaluations of MMR and V vaccines when co-administered with Hib-MenCY-TT (Hib-MenCY-TT and Hib study groups), and serious adverse events (all subjects) through 30 days after the 4th vaccination. Only the objectives germaine to evaluations are included below. Thereafter, subjects received a monovalent meningococcal C vaccine. Safety assessment of solicited adverse events for Hib-MenCY-TT, when co-administered with routine infant vaccines, was mainly supported by data evaluating doses 1 – 3 in study Hib-MenCY-TT -009/-010.

Co-Primary Objectives:
Fourth dose Vaccination:

- To demonstrate that in toddlers previously primed with 3 doses of Hib-MenCY-TT vaccine who are then given a 4th dose of Hib-MenCY-TT co-administered with *MMR®II* (MMR) and *Varivax®* (V) at 12-15 months of age, the immune response to M, M, R and V components is non-inferior to the corresponding immune response in the group previously primed with 3 doses of *ActHIB®* followed by a 4th dose of monovalent Hib vaccine (*PedvaxHIB®)*, when co-administered with MMR and V.

Safety Objective:
In all participants:

- To evaluate the safety and reactogenicity of each vaccine, when co-administered with (MMR) and (V)

Study Period: Hib-MenCY-TT-007: April 11, 2005 – July 24, 2006 (dates for the ESFU not provided). Hib-MenCY-TT-008: March 6, 2006 – February 21, 2007 (active phase)/July 16, 2007 (ESFU).

Population

The study was conducted at 3 centers in Australia.

Inclusion criteria

- Subjects for whom the investigator believes that their parents/guardians could and would comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).
- A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.
- Born after a gestation period between 36 and 42 weeks.
- For the fourth dose vaccination phase: Subjects who participated in the primary vaccination study Hib-MenCY-TT 007

Exclusion criteria

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs since birth. (For corticosteroids, this meant prednisone, or equivalent, $\geq$ 0.5 mg/kg/day. Inhaled and topical steroids were allowed.)
- Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of vaccine(s).
- Previous vaccination against *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, poliovirus, and/or *Streptococcus pneumoniae*; more than one previous dose of hepatitis B vaccine. Vaccination with hepatitis B at birth was accepted (although not mandatory). Influenza (Flu) vaccination was allowed 30 days after the administration of the 3rd vaccine dose to 30 days preceding the booster dose.
- History of *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, hepatitis B, poliovirus, *Streptococcus pneumoniae* and/or varicella invasive disease.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing was required).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s), including dry natural latex rubber, tetanus toxoid, diphtheria toxoid, neomycin, polymyxin.
- Major congenital defects or serious chronic illness.
- History of any neurologic disorders or seizures.
- Acute disease at the time of enrollment. (Acute disease was defined as the presence of a moderate or severe illness with or without fever. All vaccines could be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. rectal temperature <38°C, axillary <37.5°C).

Vaccination was deferred for presence of acute disease or temperature greater than or equal to these cut-offs, pending recovery of the subject.

- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

Additional specific exclusion criteria checked at visit 5:

- History of measles, mumps, rubella, or varicella
- Previous vaccination against measles, mumps, rubella, or varicella
- Previous booster vaccination with Hib or meningococcal serogroup C vaccine since the last visit of the primary phase.

Vaccine composition and administration

Please see study Hib-MenCY-TT -009/-010 for descriptions of vaccine composition. The first 3 doses of Hib-MenCY-TT or Hib vaccine (ActHIB) were administered at 2, 4, and 6 months of age. A 4th dose of Hib-MenCY-TT or a monovalent Hib vaccine (*PedvaxHIB*®) at 12 to 15 months of age.

DTaP-HBV-IPV combination vaccine and PCV7 were mandated as concomitant vaccines with the first 3 vaccinations and MMR and varicella, and were mandated as concomitant vaccines with the 4th dose of study vaccines. These vaccines were supplied.

Endpoints

4th dose primary endpoints

Forty-two days after 4th vaccination:

- Measles, mumps, varicella seroconversion, according to the protocol. Although not defined in the study protocol, seroconversion was defined by the applicant in a revised analysis plan as*:
  - Anti-measles seroconversion: appearance of antibodies (i.e., concentration greater than or equal to the cut-off value of 150 mIU/mL) in the serum of subjects seronegative (< 150 mIU/mL) before the vaccination
  - Anti-mumps seroconversion: titer $\geq$ 28 ED_{50} in subjects with titer < 28 ED_{50} before vaccination
  - Anti-varicella seroconversion: post-vaccination titers $\geq$ 1:5 in subjects seronegative (<1:5) before vaccination
- Rubella seroresponse, which is defined as post-vaccination concentration $\geq$ 10 IU/mL (ELISA, ---(b)(4)---- in subject who are seronegative (< 4 IU/mL) before vaccination.

*CBER viewed the following endpoints, measured by assays designated by the applicant, to be defined as:

- Anti-measles seroconversion: anti-measles virus antibody concentration $\geq$ 200 mIU/mL in subject with a pre-vaccination antibody concentration of < 150 mIU/mL
- Anti-mumps seroconversion: anti-mumps virus neutralizing antibody titer $\geq$ 1:51 in subjects with a pre-vaccination antibody titer of < 1:28
- Anti-rubella seroresponse: anti-rubella virus antibody concentration of $\geq$ 10 IU/mL (ELISA, ---(b)(4)----) in subjects seronegative (< 4 IU/mL) before vaccination.
- Anti-varicella assay seroconversion: anti-varicella antibody titer $\geq$ 1:40

Secondary Endpoints:
Immunogenicity endpoints:
Fourth dose vaccination:

- Anti-measles concentration and seroconversion (defined by an alternative antibody concentration)
- Anti-mumps titer and seroconversion (defined by an alternative antibody titer)
- Anti-rubella concentration and seroresponse (defined by an alternative antibody concentration)
- Anti-varicella concentration and seroconversion (defined by an alternative antibody titer)

Safety endpoints:
Incidence of SAEs and new onset of chronic illness, rash, ER (emergency room) visits or physician office visits

Randomization

Treatment allocation at the investigator site was performed using a central randomization call-in system on Internet (SBIR).

Surveillance

Safety
Study participants were observed for 30 minutes post-vaccination. Information about MMR and V specific solicited symptoms occurring through day 42 post-4th dose vaccination was collected on a diary card. When a solicited or unsolicited symptom was reported, parents/guardians were asked if the subject received medical attention defined as hospitalization, an emergency room visit, or a visit to or from medical personnel.

New onset of chronic illness, rash, ER (emergency room) visits or physician office visits unrelated to well-child care, vaccination, injury, or common acute illnesses.that occurred since the last visit, data were collected via daily diary cards for days 0 - 30, study visits, and telephone contact at 18 – 21 months of age.

Serious adverse events were collected during the time period from Day 0 to Month 6 via diary cards days 0 – 30, study visits, and telephone contact at 18 – 21 months of age.

Immunogenicity:
Blood drawn just prior to the 4th vaccination in all subjects, and 42 days after the 4th vaccination

Statistical plan
Sample size calculations
Sample size calculations for the 4th vaccination phase were based on MMRV non-inferiority hypotheses for the applicant's stated primary objectives and endpoints.

For MMRV non-inferiority hypotheses that are common to primary objectives in both studies Hib-MenCY-TT -008 and -010, a sample size of 820 subjects in this study (Hib-MenCY-TT

n=660, Hib n=220) and 1280 subjects from the immunogenicity cohort from study Hib-MenCY-TT-010 in total would enable at least 80% global power to meet the stated objectives.

Populations analyzed

Fourth dose vaccination phase:

Post-4th dose vaccination immunogenicity analyses for the stated primary objectives would be performed on data from studies Hib-MenCY-TT-008 and -010, if conditions for pooling were met, based on the according-to-protocol (ATP) for immunogenicity population. Within study analyses were also performed.

Total 4th dose vaccinated cohort for safety and immunogenicity:

Included all vaccinated subjects during the 4th dose vaccination phase. For the analysis of safety, this included all subjects with at least one vaccine administration documented during the 4th dose vaccination phase and for the analysis of immunogenicity, this included vaccinated subjects during the 4th dose vaccination phase for whom data for immunogenicity endpoint measures were available. The total vaccinated cohort analysis was performed per treatment actually administered.

According-to-Protocol (ATP) 4th dose cohort for immunogenicity:

Included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with procedures defined in the protocol, with no elimination criteria during the study) from the 4th dose ATP cohort for safety for whom assay results are available for antibodies against at least 1 study vaccine antigen for the blood sample taken 42 days after the administration of the 4th vaccination.

Primary 4th dose hypotheses

To demonstrate that, following a 4th vaccination, the immune response to MMR and V in the group that received 3 primary vaccine doses of Hib-MenCY-TT vaccine and a 4th dose of Hib-MenCY-TT vaccine co-administered with MMR and V is non-inferior to the corresponding immune response in the group that received 3 primary vaccine doses of *ActHIB*® and a booster dose of *PedvaxHIB*® co-administered with MMR and V. The hypothesis was based on pooling of data from Hib-MenCY-TT-008 and Hib-MenCY-TT-010.

This hypothesis would be supported by the data if the lower limit of the two-sided 95% CI for the difference in two proportions (pHib-MenCY-TT – pHib) were:

- $\geq$ - 5%, where p is the percentage of subjects with anti-measles, anti-mumps seroconversion and anti-rubella seroresponse; and
- $\geq$ - 10% where p is the percentage of subjects with anti-varicella seroconversion.

Relevant protocol amendments:

Protocol amendment 3 (January 24, 2006) extended the pooling of data from Hib-MenCY-TT-008 with Hib-MenCY-TT-010 to additional endpoints: persistence of the Hib-MenCY-TT immune response pre-4th dose and immune response to the 4th dose of Hib-MenCY-TT. Laboratory procedures and statistical analyses were aligned with Hib-MenCY-TT-009/-010. Amended the serology plan to allow for hSBA, in addition to rSBA. After finalization of this protocol amendment, the pooling of the databases was restricted to the primary endpoints related to MMR and V at CBER's request (specified in the RAP for Hib-MenCY-TT-008).

Results:

Population

A total of 1104 subjects were enrolled in study Hib-MenCY-TT -007, and 1103 subjects were vaccinated (661 Hib-MenCY-TT, 221 Lic MenC, 221 Hib), and 1038 were enrolled in the ESFU (626 Hib-MenCY-TT, 206 in group Lic MenC , and 206 in group Hib). Twenty-five subjects withdrew from the study (14 Hib-MenCY-TT recipients, 6 Lic MenC subjects, and 5 Hib participants): 3 Hib-MenCY-TT subjects withdrew due to a SAE: (hypotonic-hyporesponsive episode on the day of the first vaccination; epilepsy 18 days post-2nd dose; and skull fracture, respectively). One subject withdrew because of a non-serious AE (fever in a Hib-MenCY-TT subject). Twenty subjects voluntarily withdrew consent, lost to follow-up/moved from the study area or non-compliance with study procedures (9 Hib-MenCY-TT, 6 Lic MenC, 5 Hib).

There were 1038 subjects from study Hib-MenCY-TT-007 that enrolled in Hib-MenCY-TT-008. Thirty-six subjects (22 in group Hib-MenCY-TT, 7 in group Lic MenC, and 7 in group Hib) were lost to follow-up or did not participate for reasons such as migration from study area or voluntary withdrawal of consent. Three subjects had a subject number allocated but were not vaccinated in study Hib-MenCY-TT-008: voluntarily withdrew consent (1 Hib), ineligible (1Hib-MenCY-TT, 1Hib). The parents/guardians or investigator of 6 subjects (5 in group Hib-MenCY-TT and 1 in group Lic MenC) withdrew due to an AE or SAE. See Serious Adverse Events section for details.

Of the 1035 subjects who were vaccinated during Hib-MenCY-TT-008 (625 in group Hib-MenCY-TT, 206 in group Lic MenC-primed, and 204 in group Hib), 1029 subjects completed the 4th dose vaccination study (623 in group Hib-MenCY-TT, 203 in groups Lic MenC-primed and Hib). A total of 6 subjects were withdrawn from the study during the 4th dose active phase: 3 subjects (1 in group Hib-MenCY-TT and 2 in group Lic MenC-primed) migrated from the study area; 2 subjects (1 in group Lic MenC-primed and 1 in group Hib) were lost-to-follow up after receiving the complete vaccination course; 1 subject in group Hib-MenCY-TT was classified as other because the mother had delivered a new baby and was not available.

Of 1038 subjects in the study Hib-MenCY-TT-008 ESFU phase, 13 subjects withdrew before the end of the ESFU phase: 2 subjects (1 in group Hib-MenCY-TT and 1 in group Hib) due to voluntarily withdrew consent; 6 subjects (4 in group Hib-MenCY-TT, 1 in group Hib, and 1 in group Lic MenC-primed) were lost to follow-up.

Of the total vaccinated cohort of 1035 subjects in study Hib-MenCY-TT-008, 37 subjects were excluded from the 4th dose ATP cohort for safety: 17 subjects did not receive vaccine according to protocol; 20 subjects did not receive the study vaccine according to protocol, met ineligibility criteria, or were previously excluded in study Hib-MenCY-TT due to non-compliance with trial procedures; an additional 77 subjects were excluded from the Booster ATP cohort for immunogenicity: 39 subjects had non-compliance with the blood sampling schedule; 37 subjects were missing essential serological data.

4th dose safety population:

The 4th dose Total Vaccinated cohort included 1035 subjects (Hib-MenCY-TT n=625, Lic MenC-primed n=206, Hib n=204). There were 1035 subjects in the ESFU period in study Hib-MenCY-TT-008, and 1025 of them completed that phase of the study (620 in group Hib-MenCY-TT, 204 in group Lic MenC-primed, and 201 in group Hib).

4th dose immunogenicity population:
The 4th dose ATP cohort for immunogenicity included 921 participants (Hib-MenCY-TT n=554, Lic MenC-primed n=185, Hib n=182). The demographics of the Hib-MenCY-TT and Hib atudy groups were comparable with respect to mean age, gender, and racial distributions. For group Hib-MenCY-TT, the mean age at Visit 5 was 53.2 weeks, the distribution of females and males was 49.3% and 50.7%, respectively, and the population was predominantly White/Caucasian (95.7% of subjects). Similarly, for group Hib, the mean age at Visit 5 was 53.1 weeks, 45.6% of subjects were female, and 94.5% were White/Caucasian.

Hib-MenCY-TT -007/008 SAEs
Serious adverse events during the 31 days post-vaccination period following each of the 4 Hib-MenCY-TT doses:
A total of 41 SAEs were reported in 40 subjects. For time periods after doses 1-3, 15 SAEs were reported in 14 Hib-MenCY-TT subjects (cyanosis, respiratory tract malformation, anal fistula, bronchiolitis, urinary tract infection, gastroenteritis, sepsis, upper respiratory tract infection, hemangioma, epilepsy, hypotonic-hyporesponsive episode, aspiration pneumonia), 5 SAEs were reported in 5 Lic MenC (cryptorchidism, bronchiolitis, gastroenteritis, respiratory syncytial virus bronchiolitis, sepsis) subjects, and 7 SAEs were reported in 7 Hib subjects (bronchiolitis, gastroenteritis, viral infection, infantile spasms). All SAEs resolved without sequelae except 2 events which resolved with sequelae: 1 case of congenital vitreous anomaly in the Lic MenC group and 1 case of infantile spasms in the Hib group. After the 4th dose, SAEs were reported by 10 Hib-MenCY-TT subjects (croup, gastroenteritis, otitis media, viral tonsillitis, upper respiratory tract infection, asthma, sleep apnea syndrome, wheezing), 2 Lic MenC primed subjects (otitis media, viral pneumonia), and 2 Hib subjects (otorrhea, urinary tract infection). All SAEs during this time period resolved without sequelae. One SAE, hypertrophic cardiomyopathy, in a Hib participant, was diagnosed during the ESFU over doses 1 – 3, but the child died during the ESFU following the fourth dose of Hib.

MMR and V solicited symptoms for study Hib-MenCY-008:
Fever was reported similarly across groups (52.1% Hib-MenCY-TT, 55.7% Hib) during the 42 day follow-up period. Fever peaked at approximately day 9 post-vaccination in all groups, and fever > 40.0°C was reported in $\leq$ 3.5% of subjects per group. Parotid/salivary gland swelling was reported in 4 Hib-MenCY-TT recipients. Rashes with more than 200 lesions were reported in 5.0%, and 3.5% of Hib-MenCY-TT and Hib participants, respectively. Measles/rubella-like or varicella-like rashes were reported in 8.5% and 15.2% of Hib-MenCY-TT subjects and 10.3% and 11.3% of Hib subjects, respectively.

Immune responses to MMR and V vaccine components:
Due to the differences in endpoints specified in the protocols for evaluation of the immune responses to measles, mumps, and varicella in studies Hib-MenCY-TT-008 and Hib-MenCY-TT-010, the data from Hib-MenCY-TT-008 are presented separately, as previously done for study Hib-MenCY-TT-010.

Table 33: Immune responses to measles, mumps, rubella, and varicella vaccines concomitantly administered with Hib-MenCY-TT or Hib control vaccine (Fourth dose ATP Cohort for immunogenicity)

			≥ 200 mIU/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	N	%	LL	UL	Value	LL	UL
Anti-measles	HibMenCY	501	466	93.0	90.4	95.1	1627.5	1470	1801.9
	Hib	171	163	95.3	91.0	98.0	1786.4	1523.1	2095.3
			≥ 51 ED50				GMT		
					95% CI			95% CI	
Antibody	Group	N	N	%	LL	UL	Value	LL	UL
Anti-mumps	HibMenCY	293	265	90.4	86.5	93.6	120.8	112	130.3
	Hib	102	93	91.2	83.9	95.9	115.3	101.8	130.5
			≥ 10 IU/mL				GMC		
					95% CI			95% CI	
Antibody	Group	N	N	%	LL	UL	Value	LL	UL
Anti-rubella	HibMenCY	500	498	99.6	98.6	100	78.8	73.9	83.9
	Hib	171	171	100	97.9	100	76.7	69.0	85.2
			≥ 1:40				GMT		
					95% CI			95% CI	
Antibody	Group	N	N	%	LL	UL	Value	LL	UL
Anti-varicella	HibMenCY	404	403	99.8	98.6	100	414.6	391.4	439.3
	Hib	119	119	100	96.9	100	438.3	394.3	487.2

Source: Modified from Tables 7, 30, 32, 33, 34 in Hib-MenCY-TT-008 CSR, Tables 30, 32, 33, 34 in Hib-MenCY-TT-010 CSR
Hib-MenCY: Hib-MenCY-TT + MMR + V in subjects who received doses 1 -3 of Hib-MenCY-TT + DTaP-IPV-HBV + PCV7
Hib: PRP-OMP + MMR + V in subjects who received doses 1 – 3 of PRP-T + DTaP-IPV-HBV + PCV7
Subjects who received Lic MenC are not included

Table 34. Seroconversion rate differences between groups (Fourth dose ATP Cohort for immunogenicity)

Difference between groups in anti-measles concentrations ≥ 200 mIU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-measles	≥ 200 mIU/mL	501	466	93.0	171	162	94.7	-1.72	-5.36	3.08
Difference between groups in anti-mumps titers ≥ 51 ED50 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-mumps	≥ 51 ED50	293	265	90.4	102	93	91.2	-0.73	-6.5	6.92
Difference between groups in anti-rubella concentrations ≥ 10 IU/mL post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-rubella	≥ 10 IU/mL	500	498	99.6	171	171	100	-0.40	-1.45	1.80
Difference between groups in anti-varicella titers ≥ 1:40 post-4th dose vaccination										
								Difference in percentage (HibMenCY – Hib)		
		HibMenCY			Hib				95% CI	
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-varicella	≥ 1:40	404	403	99.8	119	119	100	-0.25	-1.39	2.89

Source: Modified from Supplement 52 in Hib-MenCY-TT-008 CSR
Hib-MenCY: Hib-MenCY-TT + MMR + V in subjects who received doses 1 -3 of Hib-MenCY-TT + DTaP-IPV-HBV + PCV7
Hib: PRP-OMP + MMR + V in subjects who received doses 1 – 3 of PRP-T + DTaP-IPV-HBV + PCV7
Subjects who received Lic MenC are not included

Summary and Conclusions:
For purposes of U.S. licensure, this study provided safety and immunogenicity data to support concomitant use of Hib-MenCY-TT with MMR and varicella vaccines in 12 month old toddlers.

Due to use of a vaccine which is not licensed in the U.S. in the evaluation of doses 1 – 3, only safety data related to MMR and V administered concomitantly with either Hib-MenCY-TT or Hib is relevant for the purposes of U.S. licensure. Following the 4th dose, fever was reported

similarly across groups (52.1% Hib-MenCY-TT, 55.7% Hib) during the 42 day follow-up period. Fever peaked at approximately day 9 post-vaccination in all groups, and fever > 40.0°C was reported in ≤ 3.5% of subjects per group. Parotid/salivary gland swelling was reported in 4 Hib-MenCY-TT recipients. Rashes with more than 200 lesions were reported in 5.0%, and 3.5% of Hib-MenCY-TT and Hib participants, respectively. Measles/rubella-like or varicella-like rashes were reported in 8.5% and 15.2% of Hib-MenCY-TT subjects and 10.3% and 11.3% of Hib subjects, respectively. Given the randomization ratio, the numbers of SAEs reported across groups appear greater among Hib-MenCY-TT recipients; the proportion of subjects reporting SAEs was similar across groups. The nature of the SAEs reported within 31 days of vaccination is not unexpected during a pediatric trial.

Due to the differences in endpoints (seroconversion criteria) specified in the protocols for evaluation of the immune responses to measles, mumps, and varicella in Hib-MenCY-TT-008 and Hib-MenCY-TT-010, the data from Hib-MenCY-TT-008 are presented separately, although the pooled data are presented as well in Section 8.1.1. Although in Hib-MenCY-TT-008, the lower limit of the 95% CI for between group difference in percentages of participants with relevant immune responses was > -5% for anti-measles and anti-mumps, Hib-MenCY-TT-008 was not powered for non-inferiority acceptance criteria. The point estimates for the proportions of initially seronegative subjects achieving seroconversion post-vaccination did not raise concerns for immune interference of Hib-MenCY-TT when concomitantly administered with MMR and V. As noted in Section 8.1.1, evaluation of concomitantly administered MMR and V vaccines did not raise concern for immune interference of Hib-MenCY-TT in Hib-MenCY-TT-010. As such, results from these studies are consistent.

8.1.3 Study 101858 Hib-MenCY-TT-005 (Primary vaccination)/ Study 102015 Hib-MenCY-TT-006 (Booster vaccination)

A phase II, single-blinded, randomized, controlled, multicenter primary and booster vaccination study to evaluate the immunogenicity, reactogenicity and safety of GSK Biologicals' Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) compared to ActHIB®, each co-administered with DTaP-HBV-IPV® and Prevnar®, in healthy infants at 2, 4, and 6 months of age and in healthy toddlers at 12 to 15 months of age (booster dose), when co-administered with Prevnar®. An exploratory control group will receive licensed Menomune® at 3 to 5 years of age.

The primary vaccination study period is the timeframe that included data collected from the day of 1st vaccination to 6 months after the third dose. The 4th dose vaccination study period is the timeframe that pertained to data collected just prior to the 4th Hib-MenCY-TT dose to 6 months afterwards. Due to difficulties in the applicant's ability to provide PCV7 for the Hib-MenCY-TT clinical program, assessment of pneumococcal antibody responses was based on data from this trial.

Objectives

Co-Primary Objectives:

- To demonstrate that the proportion of participants with anti-PRP antibody concentration ≥ 1.0 mcg/ml one month after the 3rd Hib-MenCY-TT vaccination is non-inferior to the corresponding antibody concentration in infants given 3 doses of *ActHIB.*
- To demonstrate that the ratio of participants with pneumococcal IgG antibody concentrations to serotypes contained in PCV7 one month after the 3rd Hib-MenCY-TT vaccination is non-inferior to the corresponding antibody concentration in infants given 3 doses of *ActHIB*.

- To demonstrate that the ratio of participants with anti-PT, anti-FHA, and anti-PRN concentrations one month after the 3rd Hib-MenCY-TT vaccination is non-inferior to the corresponding antibody concentrations in infants given 3 doses of *ActHIB*.
- To demonstrate that the incidence of any grade 3 symptom which occurs during the 4 days after any of the three Hib-MenCY-TT vaccinations in infancy is non-inferior to the same parameter in infants given 3 doses of *ActHIB*.
- To demonstrate that the proportion of participants with anti-PRP antibody concentration $\geq$ 1.0 mcg/ml following a 4th dose of Hib-MenCY-TT is non-inferior to the corresponding antibody concentration in subjects given a 4th dose of *ActHIB*.

Secondary Objectives:

- To evaluate the MenC and MenY bactericidal antibody responses following the 3rd and 4th Hib-MenCY-TT vaccination compared to corresponding antibody responses after a single Menomune (MenACWY-PS) dose in children 3 to 5 years old, measured by hSBA and rSBA
- To evaluate immune responses after the 3rd Hib-MenCY-TT vaccination compared to that of *ActHIB*, each co-administered with DTaP-HBV-IPV and PCV7, with respect to the
    - % of subjects with anti-PRP concentration $\geq$0.15 μg/mL and GMCs
    - % of subjects with IgG antibody concentrations $\geq$ 0.05 μg/mL, $\geq$ 0.2 μg/mL, and $\geq$ 0.5 μg/mL for the 7 serotypes in PCV7
    - Immune responses to diphtheria, tetanus, hepatitis B, poliovirus types 1-3 antigens contained in DTaP-HBV-IPV
- To determine, prior to the administration of a fourth dose of Hib-MenCY-TT or Hib at 12 to 15 months of age, the persistence of PRP, Men C and Y (hSBA, rSBA) and tetanus antibodies induced by 3 doses of Hib-MenCY-TT vaccine or *ActHIB*
- To evaluate MenC and Y antibody responses following a 4th dose of Hib-MenCY-TT, measured by ELISA, hSBA and rSBA.
- To evaluate PRP and T antibody responses following a 4th dose of Hib-MenCY-TT in subjects who had previously received 3 doses of Hib-MenCY-TT vaccine compared to corresponding immune responses after a
  - 4th Hib vaccination with Hib-MenCY-TT in subjects who had previously received 3 doses of Hib;
  - 4th dose of Hib in subjects who had previously received 3 primary doses of Hib
- To evaluate the immunogenicity of PCV7 when co-administered as a 4th dose with Hib-MenCY-TT or Hib.
- To evaluate safety and reactogenicity after each dose and in each study group

Study Design

Primary vaccination: single-blinded (infants only), controlled, multi-center trial in the United States with 2 parallel randomized groups and 1 exploratory control group.

- Hib-MenCY-TT group: Hib-MenCY-TT + DTaP-HBV-IPV) + PCV7 [n=300 infants]
- *ActHIB* (PRP-T) group: *ActHIB* + DTaP-HBV-IPV + PCV7 [n=300 infants]
- *Menomune* group: *Menomune* A/C/Y/W135 (MenACWY-PS) [n=150 children 3 – 5 years old]

4th dose vaccination: infants in the Hib-MenCY-TT group in the primary phase were allocated to the Hib-MenCY-TT group, and subjects in the *ActHIB* group in the primary phase were re-randomized (1:1) to receive one dose of either Hib-MenCY-TT or *ActHIB* at 12 to 15 months of age.

Study Period: Hib-MenCY-TT-005: August 13, 2004 – March 29, 2006; Hib-MenCY-TT-006: July 1, 2005 – May 8, 2006

Population

Study Hib-MenCY-TT-005 was conducted at 29 centers in the U.S.; 27 of the 29 sites recruited and enrolled subjects in study Hib-MenCY-TT-006.

Inclusion criteria

Hib-MenCY-TT and *ActHIB* groups:

- Subjects for whom the investigator believes that parents/guardians can and will comply with the requirements of the protocol (e.g., completion of the memory aids, return for follow-up visits).
- A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parent or guardian of the subject.A healthy male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination
- Born after a gestation period between 36 and 42 weeks.
- Infants who have not received a previous dose of hepatitis B vaccine or those who have received only 1 dose of hepatitis B vaccine administered at least 30 days prior to enrollment.

Menomune group: same as above except for

- A male or female between, and including, 3 and 5 years of age at the time of the first vaccination.

Exclusion criteria

Hib-MenCY-TT and *ActHIB* groups:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose. (For corticosteroids, this will mean prednisone, or equivalent, ≥0.5 mg/kg/day. Inhaled and topical steroids are allowed.)
- Planned administration/ administration of a vaccine not foreseen by the study protocol within 30 days of the first dose of study vaccine(s).
- Previous vaccination against *Neisseria meningitidis, Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, poliovirus, and/or *Streptococcus pneumoniae*; more than one previous dose of hepatitis B vaccine.
- History of *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, hepatitis B, poliovirus, and/or *Streptococcus pneumoniae* disease.
- Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing is required).
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine(s), including dry natural latex rubber.
- Major congenital defects or serious chronic illness.
- History of any neurologic disorders or seizures.
- Acute disease at time of enrollment. (Acute disease is defined as the presence of moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection with or without low-grade febrile illness, i.e. rectal temperature <38.0°C (<100.4°F), axillary/oral

temperature <37.5°C (<99.5°F), tympanic temperature on oral setting <37.5°C (<99.5°F), or tympanic temperature on rectal setting <38.0°C (<100.4°F). A temperature greater than or equal to these cut-off warrants deferral of the vaccination pending recovery of the subject.

- Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

Menomune group: same as above except for

- Previous vaccination against *Neisseria meningitidis.*
- History of *Neisseria meningitidis* disease.

Vaccine composition

Hib-MenCY-TT, Hib (*ActHIB*), DTaP-HBV-IPV, PCV7: as described in Study Hib-MenCY-TT-009 in evaluation of doses 1 - 3. For evaluation of doses 1 - 3, Hib-MenCY-TT and the monovalent Hib vaccine were administered at two month intervals, at approximately 2, 4, and 6 months of age. Participants ages 3 – 5 years received one dose of MenACWY-PS.

Permitted: U.S. licensed influenza vaccine to subjects $\geq$ 6 months of age within a period of 14 days after the previous study vaccine dose and 14 days prior to next study vaccine dose.

Endpoints

Primary endpoints

As described in the stated objectives.

CBER viewed the primary outcomes of interest for serotypes contained in PCV7 to be the IgG GMCs for each serotype contained in PCV7 post-dose 3 and post-dose 4. Additionally, the proportions of subjects with IgG antibody levels $\geq$0.2ug/mL (based on the GSK assay) post-3rd vaccination were evaluated. These data are presented below. However, evaluation of immune interference to a 4th dose of PCV7 co-administered with Hib-MenCY-TT was based comparisons of antibody responses to PCV7 when administered concomitantly with a 4th dose of a Hib control vaccine that is not licensed for use as a 4th dose at 12 – 15 months of age in the U.S. Therefore, no conclusion can be made regarding immune interference in responses to the 4th dose of PCV7 when co-administered Hib-MenCY-TT , and the Package Insert should reflect this uncertainty.

Secondary Endpoints:

Immunogenicity endpoints:

Hib-MenCY-TT and ActHIB groups:

Pre-1st and one month after the 3rd vaccination:

- Endpoints for antibody responses to PRP and to vaccine antigens contained in DTaP-HBV-IPV are the same as described in study Hib-MenCY-TT -009/-010.
- hSBA-MenC titer and % with $\geq$1:4 and $\geq$1:8 in subjects with post-vaccination rSBA MenC antibody titers <1:128
- hSBA-MenC titer and % with $\geq$1:4 and $\geq$1:8 in subjects with post-vaccination rSBA MenC antibody titers <1:128

One month after the 3rd vaccination:

- Vaccine response to pertussis antigens (PT, FHA and PRN), defined the % of subjects with post-vaccination IgG antibody levels $\geq$5EL.U/mL to PT, FHA and PRN if pre-1st

vaccination pertussis antibody concentrations are <5EL.U/mL or at least maintenance of pre-vaccination antibody concentrations if pre-1st vaccination pertussis antibody concentrations are ≥5EL.U/mL

Pre-1st and one month after the 3rd vaccination; post-4th dose:

- % with pneumococcal IgG antibody concentrations ≥0.05, ≥0.2 µg/mL, and ≥0.5 µg/mL for each of the serotypes contained in PCV7

Pre-4th dose and one month post-4th dose:

- Anti-PRP concentration and concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL (except 1 month post-4th dose, see primary endpoint)
- Anti-T concentration and concentrations ≥ 0.1 IU/mL

Other endpoints:
MenC and Y antibody responses measured by ELISA and rSBA
MenC and Y hSBA seroresponses following Hib-MenCY-TT vaccination at age 12-15 months

Secondary safety endpoints:
Hib-MenCY-TT and ActHIB groups
Solicited local and systemic symptoms within 4 days and within 8 days following each vaccination; unsolicited symptoms from the 1st vaccination through 30 days following of the 3rd Hib-MenCY-TT vaccine or *ActHIB* vaccination and from the 4th vaccination through 30 days post-4th vaccination; SAEs and occurrence of new onset of chronic diseases rashes, and AEs resulting in ER or physician office visits during the entire study and from 4th vaccination through the end of the 6-month safety follow-up; large swelling reactions post-4th dose.
Menomune group

- Occurrence of medically attended visits, rashes, and SAEs during the 31-day follow-up period after vaccination

Randomization

Infants were randomized 1:1 (Hib-MenCY-TT: Hib) for the primary vaccination phase. The *Menomune* group was not randomized. For the 4th dose vaccination phase, subjects from the Hib group were re-randomized 1:1 to receive one dose of Hib-MenCY-TT or a monvalent Hib vaccine (*ActHIB*) at 12-15 months.

Surveillance

Safety
After each vaccination, participants were observed for 30 minutes post-vaccination. Solicited local and systemic adverse events were recorded daily by the parent for 8 days post-vaccination. Solicited adverse events included injection site pain, redness, and swelling and systemic symptoms (fever, irritability/fussiness, drowsiness, and loss of appetite). Unsolicited non-serious adverse events were recorded via diary card for Days 0 – 30 and telephone contact on Days 8-10.

Information about medically attended visits was collected by asking the parent if any medical attention was received for each reported adverse event. Medical attention was defined as hospitalization, emergency room visit or visit to or from medical personnel for any reason. Information was collected via diary cards for Days 0 - 30, telephone contacts on Days 8 – 10 and once during the interval occurring between Days 182 – 194 post-4th dose.

Serious adverse events were collected from Day 0 to Month 6: events were reported via diary cards on Days 0 – 30, telephone contact on Days 2 – 4 and Days 8 – 10, and once during the interval occurring between Days 182 – 194 post-4th dose.

Participants in the *Menomune*® group were monitored for SAEs, events that resulted in a hospitalization, an ER visit, a medical visit, and rash within 31 days of vaccination.

Immunogenicity:
Blood draws for the *Menomune*® group were pre-vaccination and day 31 – 48. For the Hib-MenCY-TT and *ActHIB*® groups, blood draws were pre-1st dose, 31 – 48 days post-3rd dose, pre-4th dose, and 31 – 48 days post-4th dose.

ELISAs to measure meningococcal, PRP, D, T, pertussis (PT,FHA,PRN) antibody responses and -----(b)(4)---------- assay to measure antibody responses to polio antigens were performed using GSK in-house assays. ELISA antibody responses to HepB surface antigen was performed using a commercial assay. All serum testing was performed at GSK Laboratories (Rixensart, Belgium).

Subjects in the Hib-MenCY-TT and Hib groups with anti-PRP antibody concentration <1.0 µg/mL and/or pneumococcal IgG antibody concentration <0.20 µg/mL to ≥ 1 PCV7 vaccine serotype after the 3rd vaccination would receive a 4th vaccination according to their treatment assignment as close to their 12-month birthday as possible. Subjects with anti-D or anti-T antibody concentration <0.1 IU/mL, and/or anti-pertussis (PT, FHA or PRN) antibody level <5 EL.U/mL after the 3rd vaccination would receive a booster dose of DTaP as close to the 15-month birthday as possible. Subjects with anti-HBs <10 mIU/mL and/or anti-polio titer <1:8 to types 1, 2 or 3 were offered an additional dose of the appropriate vaccine(s).

Statistical plan
Sample size calculations
The target sample size of 638 (Hib-MenCY-TT n=255, *ActHIB*® n=255, *Menomune*® n=128) enabled 80.1% overall power to acheive the primary objectives, using ---(b)(4)---- adjustment to adjust the type II error for the multiplicity of endpoints. A planned interim immunogenicity analysis was performed on available sera from the first 80 enrolled *Menomune*® recipients. The applicant reports that results were not shared with investigators before study conclusion. The type I error considered for the final analyses were not adjusted for the interim analysis.

Populations analyzed

The immunogenicity analyses for the primary objectives were based on the ATP cohort for immunogenicity (primary vaccination, 4th dose). The safety analyses were based on the Total vaccinated cohort.

Total vaccinated cohort:
Primary vaccination: included all participants who received at least one dose of the 3-dose primary vaccination series. 4th dose vaccination: included all participants who received a 4th dose of study vaccine. Analyses were performed according to the vaccine received.

According-to-Protocol (ATP) cohort for immunogenicity:
Primary ATP cohort for immunogenicity: Included subjects who met all eligibility criteria, complied with the procedures defined in the protocol, with no elimination criteria during the study from the Primary ATP cohort for safety, and for whom assay results were available for

antibodies against at least 1 study vaccine antigen for the blood sample taken one month after the third vaccine dose.
4th dose cohort for immunogenicity: All evaluable subjects from the 4th dose ATP cohort for safety for whom assay results were available for antibodies against at least 1 study vaccine antigen for the blood sample taken 1 month after the administration of the 4th vaccination.

ATP cohort for safety
Primary ATP cohort for safety: included all participants who met all inclusion criteria and no exclusion criteria, who received at least 1 dose of vaccine, according to the treatment assigned, during the primary vaccination, for whom the location of the injection site was known, and who did not receive a vaccine not specified in the protocol during the primary vaccination course.
4th dose cohort for immunogenicity: Included all eligible subjects who met all inclusion criteria, received 3 doses in the primary vaccination phase, received the 4th vaccination, for whom the injection site of study/control vaccine was known, and who did not receive a vaccine forbidden or not specified in the protocol.

Primary hypotheses

1. Immune response to *Haemophilus influenzae* type b (anti-PRP concentration $\geq$ 1.0 mcg/ml), pneumococcal antigens, and pertussis antigens following immunization with Hib-MenCY-TT, PCV7, and DTaP will be non-inferior to the immune response to these antigens following vaccination with *ActHIB*®, PCV7, and DTaP.
2. Incidence of any grade 3 adverse event within 4 days of any immunization in the 3 dose series of Hib-MenCY-TT is non-inferior to the incidence in the 3 dose series of *ActHIB*®.

Non-inferiority criteria
One month after 3rd vaccination:

- LL of the two-sided 95% CI of (*p* Hib-MenCY-TT – *p ActHIB*®) $\geq$ -10%, where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration $\geq$1.0 µg/mL.
- LL of the two-sided 95% CI of the GMC ratios $GMC_{Hib\text{-}MenCY\text{-}TT/}$ GMC *ActHIB*® for each of the 7 pneumococcal serotypes in PCV7 is $\geq$ 0.5.
- LL of the two-sided 95% CI of the GMC ratios ($GMC_{Hib\text{-}MenCY\text{-}TT/}$ GMC_{ActHIB}) for each of the pertussis antigens is $\geq$ 0.67.
- LL of the two-sided 95% CI of (*p ActHIB*® -*p*Hib-MenCY-TT) $\geq$ -10%, where *p* is the percentage of participants with any grade 3 symptom (solicited local and systemic, or unsolicited) occurring within 4 days following any of the 3 vaccinations.

One month after 4th vaccination:
(*p*Hib-MenCY-TT - *p ActHIB*®) $\geq$ -10%, where *p ActHIB*® and *p*Hib-MenCY-TT are the percentage of participants with anti-PRP concentration $\geq$1.0 µg/mL, who received 3 doses of *ActHIB* and Hib-MenCY-TT in study Hib-MenCY-TT-007, respectively

Pertinent secondary hypotheses
After the 4th PCV7 dose, the pneumococcal IgG antibody responses for each serotype are similar in children who received a 4-dose PCV7 series co-administered with 4 doses of Hib-MenCY-TT or ActHIB or 3 doses of ActHIB + Hib-MenCY-TT as a 4th Hib vaccination.

Other immunogenicity analyses
- % with post-vaccination hSBA-MenC and hSBA-MenY titers and titers $\geq$ 1:4 and $\geq$ 1:8 in all subjects in the Hib-MenCY-TT group (post-3rd dose) and a subset of subjects in the Menomune

group. Sera was tested for subjects for whom sera was available after the primary analysis was completed.

- % of subjects with hSBA ≥1:4 and ≥1:8 using the same sera from a subset of subjects with a post-vaccination rSBA-MenC titer <1:128 or an rSBA-MenY titer <1:128. Individual titers for each subject were also provided.

Protocol amendments and pertinent verbal communications

Telephone conference call, December 14, 2004: An error occurred in the computer code handling randomization such that all subjects in the primary vaccination phase were being assigned to the *ActHIB*® group until all the *ActHIB*® was administered at each site. At that point, enrollment was 177 in the *ActHIB*® group and 94 in the Hib-MenCY-TT group.

Amendment 1: revised rescue plan to give vaccine according to the treatment assignment as close as possible to the 12-month birthday; included other endpoints to assess bactericidal antibody responses by rSBA; randomization processes were updated to address imbalance, to specify separate randomization processes for each study phase, and use of a minimization algorithm for assignment in the 4th dose phase; clarified populations used for analyses of solicited symptoms and unsolicited adverse events.

Amendment 2: permitted influenza vaccine to be administered to subjects ≥ 6 months of age; performed an interim immunogenicity analysis on sera from the first 80 subjects in the *Menomune*® group as an estimate of serogroup Y immunogenicity to optimize the Hib-MenCY-TT formulation.

Amendment 3: updated pneumococcal objectives to include assessment of all pneumococcal vaccine antigens; co-primary objectives were assessed in a hierarchical manner; included additional evaluations of MenC and MenY bactericidal antibody response in the second year of life; included sensitivity analyses for solicited adverse events for which intensity scores are not reported.

Amendment 4: included an exploratory evaluation of differences between hSBA and rSBA responses in sera from a subset of subjects; included alternative definitions of hSBA-MenC and hSBA-MenY antibody responses following doses given in the second year of life.

Results:

The safety and immunogenicity data presented in this review focused mainly on data from infant study groups, hSBA antibody responses, and concomitant vaccine evaluations in participants who received 4 doses of Hib-MenCY-TT or Hib.

Population

A total of 759 (Hib-MenCY-TT n=288, *ActHIB*® n=321, *Menomune*® n=150) subjects were enrolled in -005, and 706 (Hib-MenCY-TT n=262, *ActHIB*® n=294, *Menomune*® n=150) individuals completed study -005. A total of 500 (Hib-MenCY-TT n=236, ActHIB_ActHIB n=130, ActHIB_Hib-MenCY-TT n = 132) toddlers were enrolled, and 484 (Hib-MenCY-TT n=232, ActHIB_ActHIB n=124, ActHIB_Hib-MenCY-TT n=128) individuals completed study -006. A total of 523 subjects (Hib-MenCY-TT n = 244, ActHIB n = 279) completed the ESFU

following dose 3. A total of 483 subjects (Hib-MenCY-TT n = 230, ActHIB_ActHIB n = 124, ActHIB_Hib-MenCY-TT n = 129) completed the ESFU post dose 4.

Safety population:
The Primary Total Vaccinated cohort population for safety included 756 participants (Hib-MenCY-TT n=287, *ActHIB*® n=319, *Menomune*® n=150) for study -005. The 4th dose Total Vaccinated cohort for safety included 498 subjects (Hib-MenCY-TT n=236, ActHIB_ActHIB n=130, ActHIB_Hib-MenCY-TT n=132).

Immunogenicity population:
The Primary vaccination ATP cohort for immunogenicity included 576 participants (Hib-MenCY-TT n=205, *ActHIB*® n=229, *Menomune*® n=142). The most common reasons for exclusion from the immunogenicity population after dose 3 were essential serological data missing, non-compliance with the blood sampling schedule, and non-compliance with the vaccination schedule. The demographic profile of this cohort was similar to that of the Primary Total Vaccinated cohort. While primary analyses of immune responses after dose 3 were based on the Primary ATP Cohort for immunogenicity, secondary analyses were performed based on the Primary Total Vaccinated cohort. Analysis of antibody persistence was based on the 4th dose ATP cohort for safety, which included 460 subjects (Hib-MenCY-TT n=216, ActHIB_ActHIB n=118, ActHIB_Hib-MenCY-TT n=126). The 4th dose ATP cohort for immunogenicity included 377 participants (Hib-MenCY-TT n=178, ActHIB_ActHIB n=95, ActHIB_Hib-MenCY-TT n=104). The most frequent reasons for exclusion from the 4th dose ATP cohort for immunogenicity were missing essential serological data and non-compliance with the blood sampling schedule.

Safety:
Evaluation of the incidence of any grade 3 reaction during the 4 day follow-up following each of the first 3 doses was a primary objective. All other safety evaluations were performed as secondary objectives.

Overall safety profile:
During the primary vaccination phase, the incidence of adverse events was 88.9% [255/287] in the Hib-MenCY-TT group and 92.2% [294/319] in the *ActHIB*® group. The confidence intervals were overlapping. The incidence of grade 3 adverse events overall/subject was 11.5% [33/287] in the Hib-MenCY-TT group and 24.8% [79/319] in the *ActHIB*® group. The confidence intervals were not overlapping. The difference in percentage was 13.27% [7.22, 19.29], satisfying the pre-specified criteria for non-inferiority of Hib-MenCY-TT to *ActHIB*® with respect to incidence of grade 3 adverse events.

Following the fourth dose, the overall incidence of adverse events during the 4-day post-vaccination period was 78.8% [186/236] in the Hib-MenCY-TT group, 71.2% [94/132] in ActHIB_Hib-MenCY-TT subjects, and 75.4% [98/130] in ActHIB_ActHIB recipients.

Immediate reactions:
None

Local reactions:

In the primary vaccination phase, the overall occurrence per subject of any grade 3 local reactions was reported as 5.2% [15/287] and 12.9% [41/319] of Hib-MenCY-TT and *ActHIB*® recipients, respectively. The 95% confidence intervals (CIs) did not overlap. Local reactions of any severity

were reported in 55.7% [160/287] and 67.1% [214/319] of Hib-MenCY-TT and *ActHIB*® participants, respectively. The respective 95% CIs were (49.8, 61.6) and (61.6, 72.2).

Most local reactions occurred during the first 4 days, and grade 3 redness and swelling occurred during the 4-day follow-up period. The most frequently reported solicited local reaction in all groups, pain, was reported in 45.1% of Hib-MenCY-TT participants and 53.9% of *ActHIB*® subjects. One subject experienced 180-190 mm swelling at all three injection sites (study vaccine, DTaP-HBV-IPV, and PCV7 after dose 1. The majority of local symptoms occurred during the first 4 days of the 8-day follow-up period.

Following the fourth dose, grade 3 reactions occurred in < 2.5% of participants. The most frequently reported grade 3 local reaction was redness (> 30 mm diameter), which was reported in 3 – 4 subjects per group. One local swelling event met the definition of large swelling, i.e. > 50 mm diameter. Redness and swelling with a maximum diameter of 70 mm were reported in one subject in the Hib-MenCY-TT group. Redness resolved on day 5, and swelling resolved on day 14. The event was accompanied by grade 2 pain.

During the 4-day post-4th vaccination period local reactions were reported in 60.6% [143/236] in the Hib-MenCY-TT group, 56.1% [74/132] in ActHIB_Hib-MenCY-TT subjects, and 63.1% [82/130] in ActHIB_ActHIB recipients. The most frequently reported solicited local reactions were redness in the Hib-MenCY-TT group (34.9%), increased arm circumference in the ActHIB_ActHIB group (34.9%), and pain in the ActHIB_Hib-MenCY-TT group (36.9%). All solicited local reactions occurred within the 4-day follow-up after vaccination except 4 reports of grade 1 increase in arm circumference (2 in the Hib-MenCY-TT group and 2 in the ActHIB_ActHIB group) and one report of injection site redness (> 30 mm diameter) in the ActHIB_Hib-MenCY-TT group. Events in 5 subjects were ongoing after the 8-day follow-up period: 1 Hib-MenCY-TT subject had swelling which resolved 7 days beyond the 8-day follow-up period; 1 ActHIB_ActHIB recipient had grade 1 swelling which resolved 5 days beyond the 8-day follow-up period; 2 ActHIB_Hib-MenCY-TT participants had grade 1 to 2 swelling which resolved 1 day beyond the 8-day follow-up period, with 1 of these subjects also reporting grade 1 to 2 redness which resolved 1 day beyond the 8-day follow-up period; 1 ActHIB_Hib-MenCY-TT subject had a 15 mm increase in arm circumference which resolved 85 days beyond the 8-day follow-up period.

Systemic reactions:
The overall per subject occurrence of grade 3 systemic reactions was 8.7% [25/287] for Hib-MenCY-TT and 18.2% [58/319] for *ActHIB*®. The confidence intervals did not overlap. The overall per subject occurrence of any systemic reaction was 87.5% [251/287] for Hib-MenCY-TT and 91.5% [292/319] for *ActHIB*®. The confidence intervals overlapped. The majority of solicited general symptoms occurred in the 4 day follow-up period.

In both groups, irritability was the most frequently solicited systemic reaction in the 4 day follow up period post-vaccination and occurred in 75.9% [217/286] of Hib-MenCY-TT participants and 84.5% [268/317] *ActHIB*® participants. Confidence intervals overlapped. Grade 3 irritability occurred in 7.7% and 15.1% of Hib-MenCY-TT and *ActHIB*® subjects, respectively. No subjects had fever > 40.0°C rectal temperature equivalent. Following each dose, most fevers occurred in the first 48 hours post-vaccination, and the median duration of fever was $\leq$ 2 days. Seven Hib-MenCY-TT recipients and 11 *ActHIB*® subjects had rectal equivalent $\geq$ 38°C after the last day of the 8-day follow-up period and ongoing at Day 7, with a median duration of 2 days beyond the follow-up period for both groups.

Unsolicited systemic reactions were reported in 74.2% and 72.1% of Hib-MenCY-TT and *ActHIB*® recipients, respectively. The most frequently reported unsolicited symptom in both groups was upper respiratory tract infection (26.8% and 22.3% in the Hib-MenCY-TT and *ActHIB*® groups, respectively). Other unsolicited symptoms reported in more than 10% of the subjects were otitis media and nasal congestion (23.3% and 10.1% of Hib-MenCY-TT recipients and 17.2% and 5.6% of *ActHIB*® participants). Among *Menomune*® recipients, 24.7% reported at least one unsolicited symptom, with the most frequently reported unsolicited symptoms nasopharyngitis (4.0%) and otitis media (4.0%). Findings of a safety analysis over the 4 dose series which were provided by the applicant at CBER's request were similar.

In Hib-MenCY-TT-006, the most frequently reported solicited general symptom in all 3 groups was irritability; it occurred in 49.1%, 44.3%, and 51.6% of Hib-MenCY-TT, *ActHIB*®_Hib-MenCY-TT, and ActHIB_ActHIB recipients, respectively. Grade 3 solicited general symptoms were reported rarely, occurring in two or fewer subjects per group, except grade 3 irritability, which was reported in 4.3%, 3.1%, and 0% of subjects in the Hib-MenCY-TT, ActHIB_Hib-MenCY-TT, and ActHIB_ActHIB groups, respectively. One Hib-MenCY-TT subject had an axillary temperature of 103.6°F on Day 0. Due to the applicant's use of a 0.5°C conversion factor for axillary temperatures, this subject is recorded as having a grade 3 fever (>40.0°C).

In Hib-MenCY-TT-006, at least one unsolicited systemic reaction was reported in 43.2% [102/236] Hib-MenCY-TT subjects, 43.9% [58/132] of ActHIB_Hib-MenCY-TT participants, and 30% [39/130] of ActHIB_ActHIB recipients. The most frequently reported unsolicited adverse event was otitis media, occurring in 11%, 9.1%, and 8.5% of Hib-MenCY-TT, ActHIB_Hib-MenCY-TT, and ActHIB_ActHIB recipients, respectively.

Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through the Extended Safety Follow Up (ESFU) period for doses 1 – 3 of Hib-MenCY-TT and *ActHIB*® or through 31 day follow-up for *Menomune*®:

Regarding doses 1 - 3:
Forty-nine SAEs were reported for 36 individuals reported serious adverse events [Hib-MenCY-TT n=16 subjects, 23 events; *ActHIB*® n=20 subjects, 26 events]. Acute infection (bronchiolitis, erythema infectiosum, influenza, otitis media, respiratory tract infection, streptococcal bacteremia, viral infection) or management of other acute medical conditions (intussusception, thermal burn, dehydration, hyperkalemia, bronchial hyperreactivity, respiratory distress) accounted for 20/23 SAEs in Hib-MenCY-TT participants. Acute infection (bronchiolitis, croup, gastroenteritis, otitis media, respiratory syncytial virus infection or pneumonjia, viral infection) or management of other acute medical conditions (burns, dehydration, hypoxia, dyskinesia) accounted for 23/26 SAEs in *ActHIB*® participants.

One death occurred; a Hib-MenCY-TT participant died of SIDS 30 days after the 2nd vaccination.

The 7 subjects with new onset of chronic diseases (NOCD) included 2 Hib-MenCY-TT recipients, 1 with a bone lesion and 1 subject with bronchial hyperreactivity; the 5 *ActHIB*® recipients with NOCD included 2 subjects with gastroesophageal reflux disease, 2 subjects with eczema, and 1 subject with atopic dermatitis.

Rash was reported in 17.4% and 17.2%, respectively, of Hib-MenCY-TT and *ActHIB*® recipients. The most common rash in both groups was eczema. Within the Hib-MenCY-TT group, 1 subject reported petechiae, 1 subject reported erythema multiforme, 1 subject reported exfoliative rash,

and 2 subjects reported urticaria. One *Menomune*® subject reported rash of unspecified etiology and morphology.

Emergency Room visits for at least one symptom occurred in 25 Hib-MenCY-TT and 31 *ActHIB*® participants. Acute infections (bronchiolitis, bronchitis, candidiasis, croup, gastroenteritis, groin abscess, influenza, otitis media, pneumonia, respiratory syncytial virus infection, salmonellosis, sinusitis, upper respiratory tract infection, urinary tract infection, viral infection) comprised 21/38 ER diagnoses in the Hib-MenCY-TT group and 23/43 ER diagnoses in the *ActHIB*® group. One *Menomune*® recipient visited the ER for eye swelling.

There were 181 subjects visiting physicians' offices for 407 symptoms in the Hib-MenCY-TT group, and 190 subjects visiting physicians' offices for 420 symptoms in the *ActHIB*® group. Physician office visits were prompted most frequently by upper respiratory tract infection in both groups (24.7% in Hib-MenCY-TT and 19.1% in *ActHIB*®). Otitis media was another frequently reported AE resulting in a physician visit (22.3% and 18.2% in the Hib-MenCY-TT and *ActHIB*® participants, respectively). Other symptoms occurring in at least 5% of subjects which prompted physician office visits included: conjunctivitis (1.7% in Hib-MenCY-TT subjects, 6.3% in *ActHIB*® subjects); bronchiolitis (5.9% in Hib-MenCY-TT participants, 6.6% in *ActHIB*® participants); nasal congestion (5.6% and 2.8% in Hib-MenCY-TT and *ActHIB*® recipients, respectively); and eczema (3.8% and 7.2% in Hib-MenCY-TT and *ActHIB*® participants, respectively). Otitis media was the most frequent reason for a physician office visit in the *Menomune*® recipients (4.0%).

Table 35. Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through the Extended Safety Follow Up (ESFU) period for Hib-MenCY-TT and *ActHIB*® or through 31 day follow-up for *Menomune*®

	Hib-MenCY-TT N = 287				*ActHIB*® N = 319				*Menomune*® N = 150			
			95% CI				95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom	195	67.9	62.2	73.3	207	64.9	59.4	70.1	20	13.3	8.3	19.8
SAE	16	5.6	3.2	8.9	20	6.3	3.9	9.5	0	0.0	0.0	2.4
New onset chronic disease(s)	2	0.7	0.1	2.5	5	1.6	0.5	3.6	0	0.0	0.0	2.4
Rash	50	17.4	13.2	22.3	55	17.2	13.3	21.8	1	0.7	0.0	3.7
ER visit	25	8.7	5.7	12.6	31	9.7	6.7	13.5	1	0.7	0.0	3.7
Physician office visit	181	63.1	57.2	68.7	190	59.6	54.0	65.0	18	12.0	7.3	18.3
Physician office visit not related to common illnesses	51	17.8	13.5	22.7	46	14.4	10.8	18.8	NR	NR	NR	NR

Source: Modified from Tables 46, 47, Hib-MenCY-TT-005 CSR
Hib-MenCY-TT = Hib-MenCY-TT + DTaP-HBV-IPV + PCV7
ActHIB® = *ActHIB*® + DTaP-HBV-IPV + PCV7
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n = number of subjects reporting a given symptom at least once
% = percentage of subjects reporting a given symptom at least once
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
NR: not reported

Regarding dose 4:
During the follow-up period from one month post-third dose to one month post-fourth dose, 15 non-fatal serious adverse events occurred in 11 subjects, 6 in the Hib-MenCY-TT group, 3 in the ActHIB_Hib-MenCY-TT group, and 2 in the ActHIB_ActHIB group. One fatal SAE occurred during the ESFU period, a child in the Hib-MenCY-TT group who died 4 months post-4th vaccination of sudden unexplained arrhythmogenic death. Three subjects in the Hib-MenCY-TT group had gastroenteritis, and 2 subjects in this group had dehydration. Two subjects reported bronchiolitis, one in the Hib-MenCY-TT group, and one in the ActHIB_Hib-MenCY-TT group. Other events included one each of limb abscess (ActHIB_ActHIB), cellulitis (ActHIB_ActHIB), respiratory syncytial virus infection (ActHIB_ActHIB), sepsis (ActHIB_ActHIB), hypoglycemic seizure (ActHIB_Hib-MenCY-TT), hypokalemia (Hib-MenCY-TT), febrile convulsion (Hib-MenCY-TT), and wheezing (ActHIB_Hib-MenCY-TT).

From the analysis over the 4 dose series, at least one SAE occurring from Day 0 after dose 1 through the end of the ESFU period of dose 4 was reported in 7.0% of Hib-MenCY-TT recipients and 6.9% of Hib participants. Those SAEs reported in > 1.0% in either group were dehydration (1.7% in Hib-MenCY-TT subjects and 1.9% in Hib subjects) and bronchiolitis (1.4% in Hib-MenCY-TT subjects and 0.9% in Hib subjects). The two reported deaths in this analysis were the one death in study Hib-MenCY-TT-005 and one in study Hib-MenCY-TT-006, described above.

The 3 subjects with new onset chronic disease included 2 subjects in the Hib-MenCY-TT group, one with diarrhea/celiac disease with onset day 166, graded 3 intensity, and attributed a causal relationship to vaccination by the investigator; and one subject with seasonal allergies with onset day 185, graded 1 intensity, and considered unrelated by the investigator. The third subject with NOCD was an ActHIB_ActHIB recipient with lactose intolerance, onset day 11, graded 2 intensity, and considered unrelated by the investigator.

Based on the provided analysis over the 4 dose series, NOCD events were reported in 1.4% of Hib-MenCY-TT subjects and 1.9% of Hib subjects. Those NOCDs reported in > 0.5% of subjects in either group were gastroesophageal reflux disease (0.0% Hib-MenCY-TT subjects and 0.6% Hib subjects) and eczema (0.0% in Hib-MenCY-TT recipients and 0.6% in Hib recipients).

Rash was reported in 4.2%, 7.7%, and 7.6% of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants, respectively. The most commonly reported rash was diaper dermatitis, occurring in 1.3%, 1.5%, and 3.0% of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants, respectively. One episode of petechiae was reported in a Hib-MenCY-TT recipient, with onset day 7 and accompanied by leukocytosis, mild bronchiolitis, and right ottorhea; it was grade 1 intensity and resolved in 6 days. Four subjects reported urticaria, 3 in the ActHIB_ActHIB group (onset days 10 - 180), and 1 in the ActHIB_Hib-MenCY-TT group (onset day 22).

From the analysis over the 4 dose series, rash was reportedi n 19.9% and 20.4% of Hib-MenCY-TT and Hib recipients, respectively. Eczema was the most frequently reported rash (5.6% and 7.8% of Hib-MenCY-TT and Hib participants, respectively). Other rashes reported in > 1.0% of subjects were “rash” (4.9% of Hib-MenCY-TT subjects and 2.5% of Hib subjects), diaper dermatitis (3.8% of Hib-MenCY-TT subjects and 3.8% of Hib subjects), atopic dermatitis (3.5% of Hib-MenCY-TT subjects and 1.3% of Hib subjects), and seborrheic dermatitis (1.0% of Hib-MenCY-TT recipients and 2.5% of Hib participants). Two subjects, both in the Hib-MenCY-TT group, reported petechiae. Five subjects reported urticaria (2 in the Hib-MenCY-TT group and 3 in the Hib group).

Emergency Room visits for at least one symptom occurred in 6 Hib-MenCY-TT, 1 ActHIB_ActHIB, and 7 ActHIB_Hib-MenCY-TT participants. Otitis media was the most common event, occurring in 1.3%, 0.8%, and 0.0% of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants, respectively. Acute infections (croup, gastroenteritis, otitis media, pharyngitis, pneumonia, upper respiratory tract infection, viral infection, and viral rash) comprised 8/11 ER diagnoses in the Hib-MenCY-TT group, 1/1 ER diagnoses in the ActHIB_ActHIB group, and 5/10 ER diagnoses in the ActHIB_Hib-MenCY-TT group.

Over the 4 dose series, AEs resulting in ER visits were reported in 10.1% of Hib-MenCY-TT and 10.0% of Hib subjects. Those events reported in > 1% of subjects in either group were otitis media (2.8% of Hib-MenCY-TT subjects and 2.5% of Hib subjects), upper respiratory infection (1.7% of Hib-MenCY-TT recipients and 1.6% of Hib participants), pyrexia (0.7% of Hib-MenCY-TT subjects and 1.6% of Hib subjects), conjuncitivitis (1.7% of Hib-MenCY-TT participants and 0.0% of Hib recipients), and gastroenteritis (1.4% of Hib-MenCY-TT subjects and 0.3% of Hib subjects).

There were 75 subjects visiting physicians' offices for 121 symptoms in the Hib-MenCY-TT group, 31 subjects visiting physicians' offices for 53 symptoms in the ActHIB_ActHIB group, and 43 subjects visiting physicians' offices for 63 symptoms in the ActHIB_Hib-MenCY-TT group. Physician office visits were prompted most frequently by otitis media in all groups (10.2% in Hib-MenCY-TT, 9.2% in ActHIB_ActHIB, and 9.1% in ActHIB_Hib-MenCY-TT). The other symptom occurring in at least 5% of subjects which prompted physician office visits included upper respiratory tract infection (8.9%, 7.7%, and 1.5% of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants, respectively.

Adverse events not related to common illness that prompted physician office visits occurred in 5.5%, 6.2%, and 9.8% of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT recipients, respectively. The most frequently reported of these events were bronchiolitis and croup in the Hib-MenCY-TT group (each reported in 3 subjects), urticaria in the ActHIB_ActHIB group (2 subjects), and croup, pneumonia, and viremia in the ActHIB_Hib-MenCY-TT group (each reported in 2 subjects).

Immunogenicity:

Anti-PRP response:
Primary Objectives: One month after the third vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 1 mcg/mL was 93.5% for Hib-MenCY-TT recipients [N=199] and 85.8% for *ActHIB*® participants [N=211]. The rate difference (*p* Hib-MenCY-TT – *p ActHIB*®) was 7.69% (1.83, 13.77), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration $\geq$1.0 µg/mL. The applicant provided similar results from analyses based on the Primary Total Vaccinated Cohort. One month after the fourth vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 1 mcg/mL was 98.9% for both Hib-MenCY-TT [N=176] and ActHIB_ActHIB [N=93] recipients. The rate difference (*p* Hib-MenCY-TT – *p ActHIB*®) was -0.06% (-3.14, 4.78), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration $\geq$1.0 µg/mL.

Secondary objectives: The percentage of subjects achieving anti-PRP concentration $\geq$ 0.15 mcg/mL one month post-3rd dose was 98.5% and 95.7% for Hib-MenCY-TT and *ActHIB*® subjects, respectively. The corresponding GMCs and 95% CIs were 7.99 (6.71, 9.46) for Hib-MenCY-TT recipients and 4.39 (3.56, 5.43) for *ActHIB*® participants.

The percentage of Hib-MenCY-TT and ActHib subjects with an anti-PRP concentration $\geq$ 0.15 mcg/mL, measured just prior to the 4th Hib vaccination, was 95.3% and 83.3%, respectively. Additionally, one month after the 4th Hib vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 1 mcg/mL was 98.1% [N=103] for ActHIB_Hib-MenCY-TT recipients. Anti-PRP GMCs values were among study groups receiving Hib-MenCY-TT (4 doses), ActHIB_ActHIB and ActHIB_Hib-MenCY-TT were 28.6, 19.0, and 10.7, respectively. Exploratory evaluation of differences between groups indicated statistically significantly higher anti-PRP GMCs in Hib-MenCY-TT primed subjects compared with *ActHIB*® primed subjects.

Pneumococcal IgG antibody responses:

The geometric mean concentrations (GMCs) following a 3rd dose of PCV7 administered with either Hib-MenCY-TT or ActHib control, are presented below for each of the serotypes contained in PCV7. The GMC ratios were within 2-fold (lower limit of 95% CI for the GMC ratio HibMenCY/ActHIB > 0.5) for all 7 serotypes.

Table 36. Anti-PCV7 adjusted geometric mean concentrations (GMCs) one month after dose 3 (Primary ATP cohort for immunogenicity)

Antibody	HibMenCY N	HibMenCY Adjusted GMC	ActHIB N	ActHIB Adjusted GMC	Adjusted GMC ratio (HibMenCY/ActHIB) Value	Adjusted GMC ratio (HibMenCY/ActHIB) Value LL of 95% CI	Adjusted GMC ratio (HibMenCY/ActHIB) UL of 95% CI
Anti-4	77	1.7	85	2.0	0.83	0.64	1.07
Anti-6B	73	1.3	77	1.7	0.77	0.54	1.11
Anti-9V	77	2.2	85	2.4	0.90	0.72	1.12
Anti-14	67	4.7	76	4.6	1.02	0.76	1.36
Anti-18C	75	2.5	77	2.8	0.87	0.68	1.11
Anti-19F	75	1.7	82	1.6	1.03	0.80	1.32
Anti-23F	77	2.3	88	2.5	0.92	0.67	1.26

Source: Table 18, Hib-MenCY-TT-005 CSR
HibMenCY = Hib-MenCY-TT + DTaP-HBV-IPV + PCV7
ActHIB = ActHIB + DTaP-HBV-IPV + PCV7
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit

After the 3rd PCV7 vaccination, 93.4% and 95.7% of subjects in the Hib-MenCY-TT and ActHib groups, respectively, achieved a serotype 6B IgG antibody concentration ≥0.2ug/mL. For the remaining 6 serotypes, the percentage of participants achieving the specified IgG antibody concentrations was >98% in both study groups. Based on a response rate difference of 10% between groups (lower bound of 95% confidence interval for the difference between HibMenCY – ActHIB >-10%), immune interference was not observed for any PCV7 serotype at the 0.2 mcg/mL reference level. Although not specified in the clinical protocol as a primary endpoint for evaluation of immune interference, these data provide additional support for lack of immune interference when PCV7 and Hib-MenCY-TT are administered concomitantly. The applicant provided similar results based on the Primary Total Vaccinated cohort, with at least 98.5% of subjects in both the Hib-MenCY-TT and Hib groups achieving the specified IgG antibody concentrations

Table 37. Difference between Hib-MenCY-TT and ActHIB groups in anti-pneumococcal antibody concentrations greater than or equal to 0.2 mcg/mL one month after the dose 3 (Primary ATP cohort for immunogenicity)

							Rate difference (Group 2 minus Group 1)			
									95 % CI	
Antibody	**Group 1**	**N**	**%**	**Group 2**	**N**	**%**	Difference	**%**	**LL**	**UL**
anti-4	*ActHIB*	177	100	HibMenCY	173	100	HibMenCY - ActHIB	0.00	-2.17	2.12
anti-6B	*ActHIB*	162	95.7	HibMenCY	166	93.4	HibMenCY - ActHIB	-2.31	-7.70	2.86
anti-9V	*ActHIB*	180	100	HibMenCY	174	99.4	HibMenCY - ActHIB	-0.57	-3.18	1.52
anti-14	*ActHIB*	172	99.4	HibMenCY	167	99.4	HibMenCY - ActHIB	-0.02	-2.78	2.67
anti-18C	*ActHIB*	169	98.8	HibMenCY	172	100	HibMenCY - ActHIB	1.18	-1.01	4.21
anti-19F	*ActHIB*	169	100	HibMenCY	167	99.4	HibMenCY - ActHIB	-0.60	-3.31	1.63
anti-23F	*ActHIB*	177	98.3	HibMenCY	174	98.3	HibMenCY - ActHIB	-0.03	-3.45	3.35

Source: Supplement 62, Hib-MenCY-TT-005 CSR
HibMenCY = Hib-MenCY-TT + DTPa-HBV-IPV + PCV7
ActHIB = ActHIB + DTPa-HBV-IPV + PCV7
N = number of subjects with available results
% = percentage of subjects with anti-pneumococcal antibody concentrations ≥ 0.2 µg/mL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit

Data presented based on the threshold of 0.2 mcg/mL in the applicant's 22F inhibition ELISA, which the applicant maintains is equivalent to 0.35 mcg/mL used in other ELISAs for evaluation of immune response to pneumococcal antigens.

The geometric mean concentrations (GMCs) following dose 4 of PCV7 administered concomitantly with Hib-MenCY-TT compared with ActHIB at 12 – 15 months are presented below for each of the serotypes contained in PCV7.

Table 38. Geometric Mean Concentrations (GMCs) for antigens contained in PCV7, one month after dose 4, Fourth dose ATP cohort for immunogenicity

Antibody	HibMenCY N	HibMenCY GMC	Hib N	Hib GMC	HibMenCY/Hib Value	HibMenCY/Hib 95% CI LL	HibMenCY/Hib 95% CI UL
Anti-4	174	2.4	89	2.7	0.88	0.71	1.09
Anti-6B	174	3.9	89	4.1	0.96	0.77	1.20
Anti-9V	175	3.8	90	3.8	1.00	0.82	1.22
Anti-14	174	6.1	87	7.0	0.87	0.71	1.08

Antibody	HibMenCY N	HibMenCY GMC	Hib N	Hib GMC	HibMenCY/Hib Value	HibMenCY/Hib 95% CI LL	HibMenCY/Hib 95% CI UL
Anti-18C	175	4.6	88	5.2	0.88	0.70	1.09
Anti-19F	173	1.8	89	1.9	0.94	0.73	1.20
Anti-23F	176	7.2	90	8.0	0.90	0.70	1.16

Source: Modfied from Supplement 93, HibMenCY-TT-006 CSR
HibMenCY = Hib-MenCY-TT + PCV7
ActHIB = ActHIB + PCV7
GMC = geometric mean concentration calculated on all subjects
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.

Based on criteria of a 2-fold GMC ratio (lower limit of 95% CI for the GMC ratio HibMenCY/ActHIB > 0.5), no evidence of immune interference was observed following the 4th dose of PCV7 administered concomitantly with Hib-MenCY-TT as compared with the 4th dose of PCV7 concomitantly administered with the Hib control vaccine at 12-15 months of age. However, the 4th dose of ActHIB control vaccine was administered on a schedule that is not licensed for use in the U.S. (i.e., at 12 – 15 months). Therefore, these data are insufficient to conclude that there is no immune interference in immune responses to the PCV7 serotypes when the 4th dose of PCV7 is administered concomitantly with Hib-MenCY-TT.

Responses based on the Primary and Fourth dose Total Vaccinated Cohorts were similar post-dose 3 and post-dose 4 to those based on the Primary ATP Immunogenicity Cohort and the Fourth dose ATP Immunogenicity Cohort, respectively.

Anti-PT, anti-FHA, and anti-PRN responses:
One month after the third concomitantly administered DTaP-HBV-IPV vaccination, the upper limit of the two-sided 95% CI of the GMC ratio (GMC_{ActHIB} / $GMC_{Hib\text{-}MenCY\text{-}TT}$) for each pertussis antigen (PT, FHA and PRN) was < 1.5. The anti-PT, anti-FHA and anti-PRN GMCs corresponding to subjects in the Hib-MenCY-TT [N=111-116] vs. ActHib groups [N=132-135], described in the same order, were 59.2 vs. 67.7, 216.3 vs. 251.7 and 82.5 vs. 94.7. The applicant had similar results based on the Primary Total Vaccinated Cohort.

Antibody responses to Hepatitis B, IPV, T and D vaccine antigens
Following the 3rd concomitantly administered DTaP-HBV-IPV vaccination:

Hep B: Except for Hib-MenCY-TT participants who did not receive hepatitis B vaccine at birth, at least 97.7% of subjects in both study groups achieved anti-HBs concentrations ≥ 10 mIU/mL. Of infants who had not received hepatitis B vaccine at birth, 91.7% and 100% of Hib-MenCY-TT recipients [N=22] and *ActHIB*® [N=28] participants, respectively, achieved an anti-HBs concentrations ≥ 10 mIU/mL.

IPV: For both study groups, the percentage of participants who achieved an anti-poliovirus antibody titer ≥ 1:8 ranged from 98.8% to 100% after dose 3. The applicant presented similar results based on the Primary Total Vaccinated cohort.

Tetanus, Diphtheria: For both study groups, 99.5% to 100% of subjects in study Hib-MenCY-TT -005 and -006 acheived an IgG antibody concentration >0.1 IU/mL to tetanus and diphtheria toxoid antigens. The applicant presented similar results based on the Primary Total Vaccinated cohort.

hSBA-Men C and hSBA-MenY antibody responses:

The percentage of infant participants with an hSBA titer $\geq$ 1:8 after the 3rd Hib-MenCY-TT dose was 95.9% (95%CI 90.6, 98.6) for serogroup C and 89.4% (95%CI 83.1, 93.9) for serogroup Y. After a single Menomune dose administered to children age 3-5 years 16 of 53 participants (30.2%) and 29 of 61 participants (47.5%), respectively, achieved an hSBA-MenC and hSBA-MenY titer $\geq$1:8.

Prior to 4th HibMenCY-TT dose: 90.5% and 50.0% of Hib-MenCY-TT subjects had an hSBA-MenC and hSBA-MenY titer $\geq$ 1:8, respectively.

Post-4th vaccination (Hib-MenCY-TT and ActHIB_ActHIB study groups): 96.9% (89.3, 99.6), and 0.0% (0.0, 9.5) of Hib-MenCY-TT [N=65] and ActHIB_ActHIB [N=38] participants, respectively, achieved an hSBA-MenC $\geq$ 1:8. The corresponding, listed in the same order, GMTs were 657 and 2, respectively. For serogroup Y, the percentages of Hib-MenCY-TT and ActHIB_ActHIB, participants with hSBA $\geq$ 1:8 were 95.4% (87.1, 99.0) and 2.7% (0.1, 14.2), respectively. The corresponding GMTs, listed in the same order, were 247 and 2, respectively.

Summary and Conclusions:
Due to difficulties in the applicant's ability to provide PCV7 for the Hib-MenCY-TT clinical program, assessment of pneumococcal antibody responses was based on data from this trial. Additionally, the trial provided data to support evaluation of the anti-PRP response following both the 3rd and 4th doses. Evaluation of the immune responses to the meningococcal components of the vaccine was based on the subset of subjects for whom sufficient sera were available to test with the hSBA assay. Solicited AE data were collected Day 0 to Day 7 after each vaccination, and based on the timing of solicited AE occurrence in this study, solicited AE data were collected Day 0 to Day 3 in the phase 3 trials.

Evaluation of the incidence of any grade 3 reaction during the 4 day follow-up period following each of the first 3 doses was a primary objective. The difference in percentage of subjects reporting any grade 3 reaction was 13.27% [7.22, 19.29], satisfying the pre-specified criteria for non-inferiority of Hib-MenCY-TT to *ActHIB*® with respect to incidence of grade 3 adverse events. All other safety evaluations were performed as secondary objectives. Most subjects reported solicited adverse events, and the percentages were fairly similar between study groups. Most adverse events were mild or moderate in severity, and most occurred within 4 days post-vaccination.

In study Hib-MenCY-TT-005, 49 SAEs were reported for 36 individuals reported serious adverse events [Hib-MenCY-TT n=16 subjects, 23 events; *ActHIB*® n=20 subjects, 26 events]. One death occurred; a Hib-MenCY-TT participant died of SIDS 30 days after the 2nd vaccination. During the follow-up period from one month post-third dose to one month post-fourth dose, 15 non-fatal serious adverse events occurred in 11 subjects, 6 in the Hib-MenCY-TT group, 3 in the ActHIB_Hib-MenCY-TT group, and 2 in the ActHIB_ActHIB group. One fatal SAE occurred during the ESFU period, a child in the Hib-MenCY-TT group who died 4 months post-4th vaccination of sudden unexplained arrhythmogenic death. Acute infection or management of other acute medical conditions accounted for the majority of SAEs.

One month after the third vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 1 mcg/mL was 93.5% for Hib-MenCY-TT recipients [N=199] and 85.8% for *ActHIB*® participants [N=211]. The rate difference (*p* Hib-MenCY-TT – *p ActHIB*®) was 7.69% (1.83, 13.77), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration $\geq$1.0 µg/mL. Additionally, one month after the fourth vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 1 mcg/mL was 98.9% for both Hib-MenCY-TT [N=176] and ActHIB_ActHIB

[N=93] recipients. The rate difference (*p* Hib-MenCY-TT – *p ActHIB*®) was -0.06% (-3.14, 4.78), where *p* is the percentage of subjects with antibody to PRP (anti-PRP) concentration ≥1.0 µg/mL. These primary hypotheses were achieved. Evaluation of anti-PRP responses among subjects who received 3 doses of Hib at 2, 4, and 6 months of age and 1 dose of Hib-MenCY-TT at 12 – 15 months of age demonstrated that 100% of subjects had anti-PRP ≥ 0.15 mcg/mL and 98.1% had anti-PRP ≥ 1.0 mcg/mL. However, anti-PRP GMCs were lower among these subjects (10.7) compared with subjects who received either 4 doses of Hib (GMC 19.0) or 4 doses of Hib-MenCY-TT (GMC 28.6).

All serum bactericidal antibody (SBA) evaluations were performed as secondary objectives.

Post-dose 3, the percentage of Hib-MenCY-TT participants with hSBA ≥ 1:8 was 95.9% (90.6, 98.6) for serogroup C and 89.4% (83.1, 93.9) for serogroup Y. Regarding the secondary objective of evaluation of hSBA antibody persistence for MenC and MenY, 90.5% and 50.0% of Hib-MenCY-TT subjects had hSBA-MenC and hSBA-MenY titers ≥ 1:8, respectively, pre-4th dose. No subjects who had received 3 *ActHIB*® doses met this criteria. Post-4th vaccination, the percentages of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants with hSBA ≥ 1:8 were 96.9% (89.3, 99.6), 0.0% (0.0, 9.5), and 94.3% (80.8, 99.3), respectively, for serogroup C. For serogroup Y, the percentages of Hib-MenCY-TT, ActHIB_ActHIB, and ActHIB_Hib-MenCY-TT participants with hSBA ≥ 1:8 were 95.4% (87.1, 99.0), 2.7% (0.1, 14.2), and 57.1% (39.4, 73.7), respectively. GMTs in the Hib-MenCY-TT primed group increased by 9.6-fold for hSBA-MenC and 21.8-fold for hSBA-MenY as compared to the pre-4th dose time point. Statistically significant higher GMTs of hSBA-MenC and hSBA-MenY were observed in the Hib-MenCY-TT group compared with the ActHIB_Hib-MenCY-TT group.

The data support Hib-MenCY-TT vaccine's safety and reactogenicity profile, immunogenicity, and non-inferiority in terms of PRP and co-administered vaccine responses, and safety profile to *ActHIB*®. The hSBA-MenC and hSBA-MenY GMTs were higher in subjects who had received 4 doses of Hib-MenCY-TT as compared with subjects who had received 3 doses of *ActHIB*® and 1 dose of Hib-MenCY-TT for their 4th vaccination.

After the 3rd PCV7 vaccination, 93.4% and 95.7% of subjects in the Hib-MenCY-TT and ActHib groups, respectively, achieved a serotype 6B IgG antibody concentration ≥0.2ug/mL. For the remaining 6 serotypes, the percentage of participants achieving the specified IgG antibody concentrations was >98% in both study groups. Based on a response rate difference of 10% between groups (lower bound of 95% confidence interval for the difference between HibMenCY – ActHIB >-10%), immune interference was not observed for any PCV7 serotype at the 0.2 mcg/mL reference level. Although not specified in the clinical protocol as a primary endpoint for evaluation of immune interference, these data provide additional support for lack of immune interference when PCV7 and Hib-MenCY-TT are administered concomitantly.

Based on criteria of a 2-fold GMC ratio (Lower limit of 95% CI for the GMC ratio HibMenCY/ActHIB > 0.5), no evidence of immune interference was observed following the 4th dose of PCV7 administered concomitantly with Hib-MenCY-TT as compared with the 4th dose of PCV7 concomitantly administered with the Hib control vaccine at 12-15 months of age. However, the 4th dose of ActHIB control vaccine was administered on a schedule that is not licensed for use in the U.S. (i.e., at 12 – 15 months). Therefore, these data are insufficient to conclude that there is no immune interference in immune responses to the PCV7 serotypes when the 4th dose of PCV7 is administered concomitantly with Hib-MenCY-TT.

Responses based on the Primary and Fourth dose Total Vaccinated Cohorts were similar post-dose 3 and post-dose 4 to those based on the Primary ATP Immunogenicity Cohort and the Fourth dose ATP Immunogenicity Cohort, respectively.

8.1.4 Study 105987: Hib-MenCY-TT-011 (Primary vaccination)/Study 105988: Hib-MenCY-TT-012 (Booster vaccination)

A phase III, single-blind, randomized, controlled, multinational study for the evaluation of safety of GSK Biologicals' *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) compared to monovalent *Haemophilus influenzae* type b (Hib) control vaccine in healthy infants at 2, 4, 6, and 12 to 15 months of age.

The study had 2 active phases and 2 extended follow-up phases. The active phases were from Day 0 through 1 month post-3rd vaccination and from administration of the 4th vaccination through day 31 post-4th vaccination. The extended follow-up phases were defined as interim time periods starting from one month post-vaccination 3 to the 4th vaccination and from one month post-4th vaccination through 5 months post-4th vaccination.

Objectives

Primary objective: evaluated in pooled set of subjects in Hib-MenCY-TT-009 and Hib-MenCY-TT-011:

- To evaluate occurrence of SAEs, new onset of chronic disease (NOCD), rash, and ER visits following Hib-MenCY-TT vaccine, compared to a monovalent Hib vaccine (PedvaxHIB or ActHIB). Timepoints: Day of vaccination (Day 0) to one month post-dose 3; Day 0 to pre-dose 4.

Secondary objective:

- To evaluate occurrence of serious adverse events (SAEs) and medically significant adverse events following Hib-MenCY-TT vaccine, compared to a monovalent Hib vaccine (PedvaxHIB or ActHIB), within 30 days and within 6 months after the 4th dose. Timepoints: Day of vaccination (Day 0) to one month post-dose 4; Day 0 to 6 months post-dose 4.

Study Design: This study was a randomized (3:1), single-blind, controlled, multi-national Phase 3 safety trial conducted at the same United States and Mexican sites as study Hib-MenCY-TT 009/010. Study personnel administering the vaccines were not blinded to the treatment assignment due to differences in vaccine packaging and appearance. Study personnel collecting the safety data were not blinded to the treatment assignment. Parents/guardians were blinded until the completion of Visit 6, outside the protocol's active phase. At that timepoint, for compliance with local recommendations, Australian subjects in study Hib-MenCY-TT-009 who had not received a meningococcal serogroup C conjugate vaccine were offered a licensed one, effectively unblinding Australian parents. For consistency with study Hib-MenCY-TT-009, parents of subjects enrolled in Hib-MenCY-TT-011 were unblinded upon completion of Visit 6.

Study Period for Hib-MenCY-TT-011: September 15, 2006 to March 28, 2008. Hib-MenCY-TT-012: July 13, 2007 to November 12, 2008.

Population

The study was conducted at 59 centers in the U.S. and 2 centers in Mexico.

Inclusion/Exclusion criteria

Same as for study Hib-MenCY-TT-009/010

Vaccine administration

Please see study Hib-MenCY-TT 009/010 for descriptions of vaccine composition. Participants received, intramuscularly, Hib-MenCY-TT or a monovalent Hib vaccine. For the primary vaccination phase, ActHIB was administered, while PedvaxHIB was administered for the fourth Hib vaccination. DTaP-HBV-IPV was administered concomitantly, and PCV7 was given concomitantly to all subjects receiving monovalent Hib and to subjects receiving Hib-MenCY-TT if Prevnar was available.

DTaP-HBV-IPV and Hib were provided by the applicant. It was anticipated that US subjects would have access to PCV7, so it was not provided as a study vaccine for doses 1- 3, although the applicant provided it outside the US. The applicant provided MMR, varicella, and the 4th dose of PCV7 vaccines. It was preferred that subjects received PCV7, MMR and V vaccines concomitantly at the 4th dose. Synagis, influenza, rotavirus, and hepatitis A vaccines were permitted to be co-administered with primary immunization according to local recommendations.

Endpoints

Primary endpoints: participants from studies Hib-MenCY-TT-011 and Hib-MenCY-TT-009

Primary vaccination - from dose 1 to day 30 post-dose 3 and from dose 1 through but excluding 4th dose vaccination:

- Occurrence of SAEs
- Occurrence of adverse events associated with emergency room visits, new onset of chronic illness (e.g. autoimmune disorders, asthma, type I diabetes) and rash (e.g. hives, idiopathic thrombocytopenia purpura, petechiae)

Secondary endpoints: participants from studies Hib-MenCY-TT-012 and Hib-MenCY-TT-010

Fourth dose vaccination – from dose 4 up to day 30 post-dose 4 and from dose 4 through end of 6-month safety follow-up:

- Occurrence of SAEs
- Occurrence of medically significant adverse events, which included emergency room visits, new onset of chronic illness (e.g. autoimmune disorders, asthma, type I diabetes) and rash (e.g. hives, idiopathic thrombocytopenia purpura, petechiae)

Randomization

Same as for study Hib-MenCY-TT-009/010

Surveillance

Safety parameters:
Monitoring and collection of immediate adverse events within a 30 day observation period, SAEs and medically significant adverse events was the same as described in study Hib-MenCY-TT 009/010.

Statistical plan
Sample size calculations
Sample size for the primary objective was based on a pooled dataset from all participants in studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011.

Number of planned enrolled (evaluable) participants:

Study #	Hib-MenCY-TT	Monovalent Hib
Hib-MenCY-TT 009	3300	1100
Hib-MenCY-TT 011	3264	1088
Total	6564	2188

The planned sample size enabled >80% power to detect a doubling in AE rate after Hib-MenCY-TT vaccination, assuming that the incidence of the SAE in the monovalent Hib group was >1%.

Populations analyzed

Total vaccinated cohort:

The total vaccinated cohort for the primary vaccination study period included all participants who received at least one dose of the 3-dose primary vaccination series. The total vaccinated cohort for the fourth dose vaccination study period included all participants who received a 4th dose of study vaccine. Analyses were performed according to the vaccine received.

Primary analyses of the primary and secondary objectives were based on the total vaccinated cohort for the primary vaccination and the fourth dose vaccination study periods, respectively.

Safety Analyses

Analyses include number and percentage of participants with occurrence of adverse events that are defined according to MedDRA terms, and categorized by study group and by country.

Changes in the conduct of the study or planned analyses:

PCV7 (4th dose), MMR, and V were provided as study vaccines and administered according to US labeling and Advisory Committee on Immunization Practices (ACIP) recommendations. Contraindications to MMRII and V immunization were added to the exclusion criteria for study enrollment.

Descriptive statistics of the incidence of unsolicited symptoms were performed per country and per co-administration of other vaccines (categorized as full co-vaccination, influenza co-vaccination, and hepatitis A co-administration). Differences in country effect were reported as differences in relative risk.

Due to temperature deviations noted for the shipment of PedvaxHIB to Mexican study sites, vaccination with commercially available PedvaxHIB was permitted to prevent a shortage of Hib supply. These subjects were noted as protocol deviations but were not excluded from the ATP cohorts.

Results:

There were 4432 subjects enrolled (3308 in the Hib-MenCY-TT group and 1123 in the Hib group). One enrolled subject was not assigned a group and was not vaccinated. The Primary Total Vaccinated cohort consisted of all vaccinated subjects enrolled except for the excluded subjects of center 35785: 3278 subjects in the Hib-MenCY-TT group and 1113 in the Hib group. The number of subjects completing study Hib-MenCY-TT-011 was 3114 in the Hib-MenCY-TT group and 1048 in the Hib group. The number of subjects withdrawn due to SAEs and AEs, respectively, was 9 and 0 in the Hib-MenCY-TT group and 5 and 1 in the Hib group.

There were 4048 subjects enrolled (3032 Hib-MenCY-TT subjects and 1016 Hib subjects) for evaluation of dose 4. The Fourth dose Total Vaccinated cohort consisted of 3010 subjects in the Hib-MenCY-TT group and 1010 subjects in the Hib group. The number of subjects completing

study Hib-MenCY-TT-012 was 2985 and 1001 in the Hib-MenCY-TT and Hib groups, respectively. Lost to follow-up was the most common reason for study withdrawal in both groups. Of the 4021 subjects enrolled in Hib-MenCY-TT-012, 136 did not attend the concluding visit/contact of the ESFU phase; 133 of these subjects were lost to follow up, and 3 withdrew consent.

The demographic characteristics of subjects in the Hib-MenCY-TT and Hib groups were similar in Hib-MenCY-TT-011 and -012. In both studies more than two-thirds of subjects were Hispanic, and approximately 25% of subjects were of Caucasian/European heritage.

Study Hib-MenCY-TT-011:

The majority (98.3%) of U.S. subjects and all Mexican subjects were fully co-vaccinated with either Hib-MenCY-TT or Hib given concomitantly with DTaP-HBV-IPV at doses 1 – 3. No Mexican subjects were co-vaccinated with influenza or rotavirus vaccine. Approximately 3.1% of all U.S. subjects were co-vaccinated with influenza vaccine; slightly more than half of U.S. subjects (53.2%) were completely co-vaccinated with rotavirus vaccine

Table 39: Percentage of subjects in study Hib-MenCY-TT-011 with at least one symptom, SAE, NOCD, rash, or ER visit after any of the first 3 doses in study Hib-MenCY-TT-011 from Day 0 through day 30 following dose 3 and from day 0 through the ESFU, Primary Total Vaccinated Cohort

AE category	Time period	HibMenCY N = 3278				Hib N = 1113				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI			95% CI	
		n	%	LL	UL	N	%	LL	UL	RR	LL	UL
≥ 1 AE	0 - 30	422	12.9	11.7	14.1	149	13.4	11.4	15.5	Not given		
	0 - ESFU	654	20.0	18.6	21.4	232	20.8	18.5	23.4	0.96	0.87	1.07
SAE	0 - 30	109	3.3	2.7	4.0	33	3.0	2.0	4.1	Not given		
	0 - ESFU	157	4.8	4.1	5.6	48	4.3	3.2	5.7	1.11	0.88	1.41
NOCD	0 - 30	50	1.5	1.1	2.0	18	1.6	1.0	2.5	Not given		
	0 - ESFU	66	2.0	1.6	2.6	25	2.2	1.5	3.3	0.91	0.65	1.29
Rash	0 - 30	243	7.4	6.5	8.4	81	7.3	5.8	9.0	Not given		
	0 - ESFU	386	11.8	10.7	12.9	134	12.0	10.2	14.1	0.98	0.85	1.13
ER visit	0 - 30	114	3.5	2.9	4.2	44	4.0	2.9	5.3	Not given		
	0 - ESFU	198	6.0	5.2	6.9	69	6.2	4.9	7.8	0.99	0.81	1.21

Source: Modified from Supplement 33, and Table 19, Hib-MenCY-TT-011 CSR

There were no statistically significant differences between groups in terms of the total number of adverse events reported, overall percentage of SAEs, NOCD, rash, and AEs leading to ER visits. The most common types of rash reported were “rash”, diaper rash, and eczema in both groups. Urticaria was reported by 0.8% and 0.9% of subjects in the Hib-MenCY-TT and Hib groups, respectively, and 1 case of petechiae was reported in group Hib-MenCY-TT. The most frequently reported AEs leading to an ER visit were pyrexia, bronchiolitis, gastroenteritis, and otitis media. The only AE and SAE with a statistically significantly higher incidence in the Hib-MenCY-TT group was bronchiolitis (1.2% vs. 0.5% in the Hib group). A few SAEs and AEs

occurred at a statistically significantly higher rate in the Hib group, with incidences ≤ 0.4%: viral infection, dehydration, milk allergy, abnormal feces, constipation, and hair-thread tourniquet syndrome.

In the Primary Total Vaccinated cohort, during the ESFU, 157 Hib-MenCY-TT subjects (4.8%) reported a combined total of 192 SAEs, and 48 Hib subjects (4.3%) reported a combined total of 68 SAEs. Infectious processes accounted for 133/192 SAEs in the Hib-MenCY-TT group and 42/68 SAEs in the Hib group and included abscess, bronchiolitis, bronchitis, pneumonia, cellulitis, croup, gastroenteritis, influenza, nasopharyngitis, otitis media, pharyngitis, pyelonephritis, septic shock, tonsillitis, tracheitis, varicella, viral infection, upper respiratory tract infection, and urinary tract infection. In this same cohort, during the period from day 0 after dose 1 through day 30 after dose 3, 109 Hib-MenCY-TT subjects (3.3%) reported 134 SAEs, and 33 Hib subjects (3.0%) reported 45 SAEs. Infectious processes accounted for 96/134 and 29/45 SAEs in the Hib-MenCY-TT and Hib groups, respectively.

In the Primary Total Vaccinated cohort, during the ESFU, 66 Hib-MenCY-TT subjects (2.0%) reported 80 NOCDs, and 25 Hib subjects (2.2%) reported 27 NOCDs. The most common NOCD was eczema in both groups (0.9%). Gastroenteritis was reported in 0.4% of Hib participants, and asthma and milk allergy were both reported in 0.3% of Hib recipients. All other NOCDs were reported in ≤ 0.2% of subjects. During the period from day 0 after dose 1 through day 30 after dose 3, 50 Hib-MenCY-TT subjects (1.5%) reported 59 NOCDs, and 18 Hib subjects (1.6%) reported 20 NOCDs. Eczema was the most commonly reported NOCD during this period, reported in 0.8% and 0.7% of Hib-MenCY-TT and Hib participants, respectively.

During the ESFU, in the Primary Total Vaccinated cohort, 386 Hib-MenCY-TT subjects (11.8%) reported 444 episodes of rash, while 134 Hib subjects (12.0%) reported 151 rash events. The majority of events were coded as “rash” (135/444 events in the Hib-MenCY-TT group and 44/151 events in the Hib group). The next most frequent rashes reported were diaper dermatitis and eczema, reported in 2.3% and 2.0% of Hib-MenCY-TT participants and in 2.3% and 2.5% of Hib recipients. All other rashes were reported in ≤ 1.9% of subjects. Urticaria was reported in 25 Hib-MenCY-TT recipients (0.8%), and 10 Hib participants (0.9%). Petechiae were reported once in the Hib-Men-CY-TT group. In the period from day 0 after dose 1 through day 30 after dose 3, 243 Hib-MenCY-TT subjects (7.4%) reported 271 episodes of rash, and 81 Hib subjects (7.3%) reported 89 episodes of rash. Atopic dermatitis, eczema, and “rash” were the most common rashes reported, occurring in 1.6%, 1.5%, and 1.4%, respectively, of Hib-MenCY-TT recipients and in 1.3%, 1.7%, and 1.3% of Hib participants, respectively.

In the Primary Total Vaccinated cohort, during the ESFU, 198 Hib-MenCY-TT subjects (6.0%) and 69 Hib subjects (6.2%) reported AEs resulting in ER visits. In both groups, pyrexia (0.9% of Hib-MenCY-TT participants and 0.8% of Hib subjects), bronchiolitis (0.8% in both groups), and gastroenteritis and otitis media (0.8% and 1.0%, Hib-MenCY-TT and Hib subjects, respectively for each AE) were the most frequently reported AEs resulting in an ER visit. All other AEs resulting in ER visits occurred in < 1% of subjects in both groups. During the period from day 0 after dose 1 through day 30 after dose 3, 114 Hib-MenCY-TT subjects (3.5%) reported 49 AEs resulting in ER visits, while 44 Hib subjects (4.0%) reported 19 AEs leading to ER visits. Nature of the AEs was similar to that during the ESFU.

Twelve deaths were reported, 7 in the Hib-MenCY-TT group (3 subjects with sudden infant death syndrome; 1 subject with hypovolemic shock; 1 subject with 3 events: bronchiolitis, dehydration, and gastroenteritis; 2 subjects with pneumonia); and 5 in the Hib group (2 with sudden infant death syndrome, 2 with pneumonia, one of whom had congestive heart failure, and 1 subject with

“bronchopneumonia” and pharyngitis). The investigator determined these deaths to be unrelated to study vaccines; number of days post-vaccination ranged from 10 to 77 days.

For pooled analyses of safety data across doses 1 – 3 from the pivotal studies, please see the Integrated Summary of Safety (ISS).

Study Hib-MenCY-TT-012:

Table 40: Percentage of subjects in study Hib-MenCY-TT-012 with at least one symptom, SAE, NOCD, rash, or ER visit post-dose 4 from Day 0 through Day 30 and from Day 0 through the ESFU, Fourth dose Total Vaccinated Cohort

AE category	Time period	HibMenCY N = 3010				Hib N = 1010				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI			95% CI	
		n	%	LL	UL	N	%	LL	UL	RR	LL	UL
≥ 1 AE	0 - 30	164	5.4	4.7	6.3	59	5.8	4.5	7.5	0.94	0.76	1.17
	0 - ESFU	395	13.1	11.9	14.4	137	13.6	11.5	15.8	0.98	0.85	1.13
SAE	0 - 30	12	0.4	0.2	0.7	1	0.1	0.0	0.6	4.03	1.00	35.18
	0 - ESFU	72	2.4	1.9	3.0	18	1.8	1.1	2.8	1.34	0.93	1.99
NOCD	0 - 30	12	0.4	0.2	0.7	6	0.6	0.2	1.3	0.69	0.33	1.51
	0 - ESFU	50	1.7	1.2	2.2	18	1.8	1.1	2.8	0.95	0.65	1.44
Rash	0 - 30	123	4.1	3.4	4.9	41	4.1	2.9	5.5	1.02	0.79	1.32
	0 - ESFU	227	7.5	6.6	8.5	82	8.1	6.5	10.0	0.94	0.79	1.13
ER visit	0 - 30	29	1.0	0.6	1.4	16	1.6	0.9	2.6	0.62	0.40	0.99
	0 - ESFU	129	4.3	3.6	5.1	48	4.8	3.5	6.3	0.92	0.73	1.18

Source: Modified from Synopsis Table 2, Supplement 42, Hib-MenCY-TT-012 CSR

During the period from day 0 through the end of the ESFU, there were no statistically significant differences between groups in terms of the total number of adverse events reported overall, percentage of SAEs, NOCD, rash, and AEs leading to ER visits. Rash was the most frequently reported AE category, 7.5% and 8.1% in the Hib-MenCY-TT and Hib groups, respectively. During the 31-day follow-up period, there was a statistical imbalance between the groups in terms of the percentage of SAEs, with these events occurring in a higher percentage of Hib-MenCY-TT subjects (p=0.0499). This 4-fold greater relative risk of SAEs in the Hib-MenCY-TT group, as well as the lower relative risk of AEs resulting in ER visits, were of borderline statistical significance. While similar trends were observed in the Fourth Dose ATP Cohort for Safety-based analyses, criteria for statistical significance were not met.

In the Fourth Dose Total Vaccinated cohort, during the ESFU, 72 Hib-MenCY-TT subjects (2.4%) reported a combined total of 90 SAEs, and 18 Hib subjects (1.8%) reported a combined total of 22 SAEs. Infectious processes accounted for 55/90 SAEs in the Hib-MenCY-TT group and 16/22 SAEs in the Hib group and included abscess, bronchiolitis, pneumonia, gastroenteritis, croup infection, erysipelas, folliculitis, influenza, otitis media, tracheitis, and upper respiratory tract infection. Among the SAEs were 1 occurrence of Henoch-Schonlein purpura and 1 occurrence of urticaria, both in the Hib-MenCY-TT group. The urticaria occurred approximately 98 days post-vaccination. In this same cohort, during the 31 day period post-4th dose, 12 Hib-MenCY-TT subjects (0.4%) reported 16 SAEs, and 1 Hib subject (0.1%) reported 1 SAE. Infectious processes accounted for 9/16 and 1/1 SAEs in the Hib-MenCY-TT and Hib groups, respectively.

In the Fourth Dose Total Vaccinated cohort, during the ESFU, 50 Hib-MenCY-TT subjects (1.7%) reported 59 NOCDs, and 18 Hib subjects (1.8%) reported 19 NOCDs. The most common NOCD was asthma in the Hib-MenCY-TT group (0.4%) and asthma and eczema in the Hib group

(0.3% each). Results were consistent with the results of analyses on the Fourth Dose ATP for safety cohort. During the 31 days post-4th dose, 12 Hib-MenCY-TT subjects (0.4%) reported 12 NOCDs, and 6 Hib subjects (0.6%) reported 6 NOCDs. Eczema was the most commonly reported NOCD during this period, reported in 2 subjects in each group or 0.1% of Hib-MenCY-TT recipients and 0.2% of Hib participants.

During the ESFU, in the Fourth Dose Total Vaccinated cohort, 227 Hib-MenCY-TT subjects (7.5%) reported 245 episodes of rash, while 82 Hib subjects (8.1%) reported 96 rash events. The majority of events were coded as "rash" (129/245 events in the Hib-MenCY-TT group and 55/96 events in the Hib group). Urticaria was reported in 15 Hib-MenCY-TT recipients (0.5%), and 6 Hib participants (0.6%). Henoch-Schonlein purpura and purpura were reported once each, and petechiae was reported twice in the Hib-Men-CY-TT group. The 2 episodes of petechiae occurred in 2 subjects, 26 days post-vaccination and 103 days post-vaccination, respectively. Purpura occurred 117 days post-vaccination, while the episode of Henoch-Schonlein purpura occurred 171 days post-vaccination. In the 31-day post-4th dose period, 123 Hib-MenCY-TT subjects (4.1%) reported 124 episodes of rash, and 41 Hib subjects (4.1%) reported 41 episodes of rash. Again, "rash" was the most common diagnosis.

In the Fourth Dose Total Vaccinated cohort, during the ESFU, 129 Hib-MenCY-TT subjects (4.3%) and 48 Hib subjects (4.8%) reported AEs resulting in ER visits. In both groups, otitis media was the most frequently reported AE requiring a visit to the ER (0.7% in the Hib-MenCY-TT group and 1.1% in the Hib group), followed by pyrexia (0.5% and 0.2% in the Hib-MenCY-TT and Hib groups, respectively), and upper respiratory tract infection (0.4% and 0.6% in the Hib-MenCY-TT and Hib groups, respectively). All other AEs resulting in ER visits occurred in $\leq$ 0.5% of subjects in both groups. During the 31 day post-4th vaccination period, 29 Hib-MenCY-TT subjects (1%) reported 38 AEs resulting in ER visits, while 16 Hib subjects (1.6%) reported 20 AEs leading to ER visits. Nature of the AEs was similar to that during the ESFU.

No deaths were reported in study Hib-MenCY-TT-012 from day of 4th dose vaccination through the end of the ESFU.

For pooled analyses of safety data after dose4 from the pivotal studies, please see the Integrated Summary of Safety (ISS).

Immunogenicity: Not applicable.

Summary:

Study Hib-MenCY-TT-011/-012 evaluated the safety of Hib-MenCY-TT in infants and toddlers compared with monovalent Hib vaccine. Safety comparisons were made with respect to occurrence of serious adverse events, new onset of chronic disease, rash, and adverse events resulting in emergency room visits.

Fewer than 5% of subjects experienced serious adverse events. Most serious adverse events were of infectious etiology. Occurrence of serious adverse events, new onset of chronic disease, rash, and adverse events resulting in emergency room visits was similar between groups.

The proportion of subjects reporting urinary tract infections and pyelonephritis as SAEs was greater in the Hib-MenCY-TT treatment group as compared with the monovalent Hib group. The reason for this case imbalance is unclear, and there does not seem to be a biologically plausible mechanism by which Hib-MenCY-TT vaccine could cause urinary tract infections and

pyelonephritis. However, it would be important to explore this issue further in post-marketing studies. Please see Section 10 for the overview of safety across all trials, as there was no case imbalance observed when all trials were considered.

Overall, the studies support the safety of the Hib-MenCY-TT vaccine.

8.2 Antibody Persistence Study

Study 107824: Hib-MenCY-TT-013/ Study 107826: Hib-MenCY-TT-014/ Study 107829: Hib-MenCY-TT-015: A phase II, open, controlled, multicenter study to evaluate the long-term antibody persistence at 1, 3, and 5 years after the administration of a booster dose of Hib-MenCY-TT vaccine compared to *ActHIB*® in subjects boosted in study Hib-MenCY-TT-006

CBER views the primary immunization series for Hib-MenCY-TT as a 4-dose regimen given at 2, 4, 6, and 12-15 months of age.

The 1 year antibody persistence evaluation was completed (Hib-MenCY-TT-013) and included in the BLA. Thus, only the sections relevant to the assessment of 1 year antibody persistence following the 4th Hib-MenCY-TT dose are presented in this review.

Objectives
The primary objectives were to evaluate the percentage of participants with hSBA-MenC and Y titers ≥1:8 and anti-PRP concentrations ≥ 0.15 mcg/mL. Other objectives included assessment of anti-PRP responses in participants who received 3 doses of monvalent Hib as infants, followed by HibMenCY-TT given as a 4th Hib vaccination.

Study Design: This study was an open, controlled multicenter study with three parallel groups in former Hib-MenCY-TT –005/-006 participants. Children were who were currently 22 through 36 months of age, had completed the assigned HibMenCY-TT or Hib regimen/had not withdrawn from Hib-MenCY-TT-006 were recruited to participate in Hib-MenCY-TT-013. Subjects from 22 of the 27 Hib-MenCY-006 sites participated in this study.

Randomization assignments were maintained from Hib-MenCY-TT -006 as follows

- Group Hib-MenCY: Hib-MenCY-TT was administered at 2, 4, 6 and 12-15 months of age
- Group ActHIB: ActHIB was administered at 2, 4, 6 and 12-15 months of age
- Group ActHIB_Hib-MenCY: ActHIB was administered at 2, 4, and 6 months of age and Hib-MenCY-TT was given at 12 to 15 months of age

Study Period for Hib-MenCY-TT-013: September 11, 2006 – November 28, 2007
Surveillance

Safety: SAEs related to study participation (e.g., protocol-mandated procedures, invasive tests, change from existing therapy) or were related to a concurrent medication from the applicant were collected and recorded from the time of consent to participate until the subject was discharged from the study.

Immunogenicity (methods): All assays were performed at GSK Biologicals.

Table 41. Intervals between study visit/contact for inclusion in the ATP cohort for persistence and the Enlarged ATP cohort for persistence

Interval	Length of interval (weeks)	Interval used for inclusion in ATP cohort for persistence Year 1	Interval used for inclusion in Enlarged ATP cohort for persistence Year 1
Dose 4 → Visit 1	1 year +/- 8 weeks	309 – 421 days	309 – 645 days

Source: Table 2, Hib-MenCY-TT CSR

Populations analyzed

ATP cohort for persistence Year 1

The ATP cohort for persistence Year 1 included all evaluable subjects who received the 4 doses of vaccines according to their random assignment during study Hib-MenCY-TT-005/-006; who had not received a previous administration of a 4th dose of Hib, meningococcal serogroup C/Y vaccines except study vaccines received during Hib-MenCY-TT-006; who had available assay results for at least one tested antigen; who did not have a history of *H. influenzae* type b, meningococcal serogroup C/Y diseases; who did not have an immunocompromising medical condition; who had not received any chronic immunosuppressant(s) or other immune-modifying drug(s) (> 14 days) within 6 months prior to the study visit; who had not received immunoglobulins or blood products within 6 months prior to the study visit; who had not received investigational drugs and/or investigational vaccines; and who complied with the blood sampling intervals defined in the protocol (309 to 421 days).

Protocol Amendments (Amendments to IND):

Amendment 1 (77): GSK extended the age windows for enrollment of subjects into the study. This was done to maximize the amount of antibody persistence data available for analysis. The upper limits of the age windows were changed as follows: from 29 to 36 months (Year 1), from 55 to 60 months (Year 3), and from 79 to 84 months (Year 5). Strict aherence to the intervals between visits/contacts defined in the protocol was important for inclusion in the ATP cohort for persistence; individuals with serum samples obtained outside of these intervals were to be included in a second analysis on the Total Cohort Year 1.

Amendment 2 (144): GSK removed secondary objectives and endpoints and references to rSBA and anti-PSC and anti-PSY ELISAs. Laboratory assays were re-prioritized for persistence years 3 and 5 to reflect higher prioritization of hSBA-MenC and hSBA-MenY over anti-PRP response. The amendment provided several age windows for enrollment of subjects into an Enlarged ATP Cohort for Persistence along with the originally defined ATP cohort. In addition to recording of SAEs related to studies Hib-MenCY-TT-005 and Hib-MenCY-TT-006 and SAEs related to study participation, SAEs were to be collected that were related to concurrent GSK medication from the time of consent to participation until the subject was discharged. For all antigens and for all analyses, the GMC and/or GMT ratio and its 95% CI were to be computed using an ANOVA model on the log10-transformed concentration/titer using the vaccine group as only covariate instead of using the pre-vaccination concentration/titer and the group effect as covariates (as planned in the protocol). This amendment was not submitted to CBER until the pre-BLA timepoint; as communicated to the applicant, CBER does not concur with use of the Enlarged ATP Cohort for Persistence.

Other significant changes:

Additional analyses included in the Report Analysis Plan (RAP) but not described in the protocol:

- After finalization of Protocol amendment 2, hSBA-MenC and hSBA-MenY antibody titers $\geq$ 1:8 were added as secondary endpoints based on a request from the FDA that the primary endpoint for hSBA-MenC and hSBA-MenY antibody persistence for the Phase 3 studies in the clinical development program be the percentage of subjects with antibody titers $\geq$ 1:8.
- A planned complementary exploratory analysis to evaluate the robustness of the results with respect to drop-out by using a repeated generalized linear model at each persistence timepoint (1, 3, and 5 years post-4th dose). However, the value at 1 month after administration of the 4th dose could not be taken into account in the repeated measurement model. This analysis will be performed when the results of Year 3 and Year 5 are available and will take into account the data of the previous timepoint.
- The following exploratory analyses were planned in the RAP at 1 year post-4th dose (on the Enlarged ATP cohort for persistence Year 1 and the ATP cohort for persistence Year 1):
    - Difference in the percentage of subjects with anti-PRP concentrations $\geq$ 1.0 mcg/mL, hSBA-MenC and hSBA-MenY titers $\geq$ 1:4 and $\geq$ 1:8 between the ActHIB group and HibMenCY group, the ActHIB group and ActHIB_HibMenCY group, and ActHIB_HibMenCY group and HibMenCY group, with standardized asymptotic 95% CI
    - Ratio of anti-PRP GMC between the ActHIB_HibMenCY group and the HibMenCY group with standardized asymptotic 95% CIs

Additional changes after completion of the RAP included the ratios of anti-PRP GMC, hSBA-MenC GMT, and hSBA-MenY GMT with 95% CIs for each treatment group on a subset of subjects who had results available at the 2 timepoints in a post-hoc analysis: a) at 1 month and at 1 year post-4th dose, and b) just before and at 1 year post-4th dose.

Results:

Safety:
No serious adverse events considered by the investigator to be possibly related to the vaccines administered during evaluation of doses 1 – 4 or possibly related to the procedures performed as part of study Hib-MenCY-TT-013 were reported at 1 year after the fourth dose.

Immunogenicity:
Of the 500 subjects enrolled in study Hib-MenCY-TT-006, 270 subjects (Hib-MenCY-TT: 138, ActHIB: 70, ActHIB_HibMenCY: 62) were enrolled for this persistence visit at 1 year post-4th dose, and all subjects who came for this persistence visit completed the study. Of the 270 subjects, 16 were not eligible for inclusion in the ATP cohort for safety: 12 subjects received a vaccine forbidden in the protocol (HibMenCY: 3, ActHIB: 5, ActHIB_HibMenCY: 4); 4 additional subjects (all in group HibMenCY) were excluded from the ATP cohort for safety because the vaccines were not administered according to the protocols of studies Hib-MenCY-TT-005/-006. Thus, 254 subjects were included in the ATP cohort for safety. Thirty-five additional subjects were excluded from the Enlarged ATP cohort for persistence Year 1: 3 subjects for protocol violations (HibMenCY: 2, ActHIB: 1); 23 subjects for non-compliance with blood sampling schedule (HibMenCY: 9, ActHIB: 8, ActHIB_HibMenCY: 6); 9 subjects (3 per group) for missing essential serological data. Therefore, 219 subjects (117 HibMenCY subjects, 53 ActHIB subjects, and 49 ActHIB_HibMenCY subjects) were included in the Enlarged ATP cohort for persistence Year 1. From the ATP cohort for safety, an additional 3 subjects were excluded for protocol violations and 129 subjects were excluded for having an interval > 421

days between the fourth dose and the persistence visit. Another 8 subjects were excluded from the ATP cohort for persistence year 1 because of missing essential serological data. Thus, **114 subjects (64 in group HibMenCY, 28 in group ActHIB, and 22 in group ActHIB_HibMenCY) were included in the ATP cohort for persistence Year 1.**

The mean age of the ATP Cohort for Persistence Year 1 was 24.8 months (range 23 to 28 months). The proportion of female and male subjects was 51.8% and 48.2%, respectively. The ActHIB group had a higher ratio of females to males (64.3% to 35.7%) compared to the other groups. Overall, 66.7% of subjects were White/Caucasian and 24.6% were African American. The ActHIB_Hib-MenCY group had a smaller percentage of African Americans (18.2%) compared to the other groups.

Meningococcal responses:
One year post-4th vaccination, the percentages of subjects with hSBA-MenC $\geq$ 1:8 were 98.4%, 21.4%, and 71.4% in the Hib-MenCY, ActHIB, and ActHIB_HibMenCY groups, respectively. For hSBA-MenY, the corresponding percentages were 88.3%, 0%, and 66.7%. The laboratory assays on the blood samples taken at 1 year post-4th vaccination were performed at a different timepoint than the assays on the blood samples just prior to and 1 month post-4th vaccination. Also, the hSBA-MenC assay was modified, and the methods of calculating titers were modified for both hSBA-MenC and hSBA-MenY during the period in which the serological testing was done for the different timepoints. Therefore, the comparisons of antibody decline kinetics should be interpreted cautiously. For the Enlarged ATP cohort for persistence, the hSBA-MenC GMTs ranged from 3.9 in the ActHIB group to 150.1 in the HibMenCY group. For the ATP cohort for persistence, the range was from 3.8 in the ActHIB group to 209.5 in the HibMenCY group. The hSBA-MenY GMTs ranged from 2.0 in the ActHIB group to 128.8 in the HibMenCY group and from 2.0 in the ActHIB group to 177.5 in the HibMenCY group for the Enlarged ATP cohort for persistence and ATP cohort for persistence, respectively.

Anti-PRP response:
One year after the fourth vaccination, the percentage of subjects with anti-PRP concentration $\geq$ 0.15 mcg/mL was 100% for Hib-MenCY-TT [N=116] and ActHIB_HibMenCY [N=46] recipients, and 96.1% of ActHIB [N=51] subjects based on the Enlarged ATP cohort for persistence. These percentages were 100% for all groups based on the ATP cohort for persistence (Hib-MenCY-TT N = 64, ActHIB_HibMenCY N = 22, and ActHIB N = 28). The percentage of subjects with anti-PRP concentration $\geq$ 1.0 mcg/mL decreased from 99.1% at 1 month post-4th dose to 75.9% at 1 year post-4th dose in the HibMenCY group, from 100% to 52.2% in group ActHIB_HibMenCY, and from 100% to 68.6% in group ActHIB (Enlarged ATP cohort for persistence). Based on the ATP cohort for persistence, these percentages decreased from 99.1% to 78.1% for Hib-MenCY subjects, from 100% to 85.7% for ActHIB subjects, and from 100% to 50.0% for ActHIB_HibMenCY subjects. Anti-PRP GMCs for each group were lower 1 year post-4th dose compared with 1 month post-4th dose, but these GMCs were still higher than before 4th dose. Comparisons of the kinetics of antibody decline should be interpreted cautiously. Since having serological data available at 1 month post-4th dose was not an entry requirement for this study, there are fewer subjects with results available for the previous timepoints. Also, the assays on the blood samples taken at 1 year post-4th dose were done at a different timepoint than the assays on the blood samples just prior to and 1 month post-4th dose. The percentage of subjects maintaining anti-PRP concentrations $\geq$ 1 mcg/mL and GMC ratios were significantly higher in the Hib-MenCY group compared with the ActHIB_HibMenCY group, based on the Enlarged ATP cohort for persistence.

Summary:

Study Hib-MenCY-TT-013 was an open, controlled multicenter study with three parallel groups in former Hib-MenCY-TT -006 participants. The primary objectives were to evaluate the percentage of participants with hSBA-MenC and Y titers >1:8 and anti-PRP concentrations ≥ 0.15 mcg/mL. Other objectives included assessment of anti-PRP responses in participants who received 3 doses of monvalent Hib as infants, followed by HibMenCY-TT given as a 4th Hib vaccination. One year post-4th vaccination, the percentages of subjects with hSBA-MenC ≥ 1:8 were 98.4%, 21.4%, and 71.4% in the Hib-MenCY, ActHIB, and ActHIB_HibMenCY groups, respectively. For hSBA-MenY, the corresponding percentages were 88.3%, 0%, and 66.7%. The laboratory assays on the blood samples taken at 1 year post-4th vaccination were performed at a different timepoint than the assays on the blood samples just prior to and 1 month post-4th vaccination. Also, the hSBA-MenC assay was modified, and the methods of calculating titers were modified for both hSBA-MenC and hSBA-MenY during the period in which the serological testing was done for the different timepoints. Therefore, the comparisons of antibody decline kinetics should be interpreted cautiously.

8.3 Supporting Clinical Studies

8.3.1 Study 001: 792014/001 (Hib-MenCY-TT-001)*

A phase II, open (partially double-blind), randomized, controlled, multicentric, primary vaccination study to evaluate the immunogenicity (including immune memory), reactogenicity and safety of three different formulations of the GSK Biologicals' combined Haemophilus influenzae type b-meningococcal serogroups CY conjugate vaccine given concomitantly with Infanrix® penta and Prevenar®, versus
ActHIB® and Meningitec®# given concomitantly with Infanrix® penta and Prevenar® in infants according to a 2-4-6 month schedule.

*Study 792014 was conducted in two parts: the primary vaccination phase (792014/001[Hib-MenCY-TT-001]) and the fourth dose vaccination phase (792014/002 [Hib-MenCY-TT-002]).
#Menjugate was used instead of Meningitec

Study Design: This study was an open (partially double-blind), randomized, dose-ranging, proof of concept trial at three study centers. 409 infants 6 – 12 weeks of age were enrolled. Infants were vaccinated, intramuscularly, at 2, 4, and 6 months of age with Hib-MenCY (2.5/5/5) + Infanrix® penta (DTaP-IPV-HBV) + Prevenar® (PCV7), Hib-MenCY (5/10/10) + DTaP-IPV-HBV penta + PCV7, Hib-MenCY (5/5/5) + DTaP-IPV-HBV + PCV7, Menjugate® + Act HIB® + DTaP-IPV-HBV, or ActHIB® + DTaP-IPV-HBV + PCV7.

Parent(s)/guardian(s) of the subjects reported solicited local (pain, redness and swelling) and general (drowsiness, fever, irritability, and loss of appetite) symptoms on diary cards for the 8-day post-vaccination period (Days 0 to 7). There was a 31-day (Days 0 to 30) follow-up period, after the 3rd vaccine dose, of unsolicited non-serious adverse events (AEs); recording of serious adverse events (SAEs) during the entire study period.

Sera collected pre- and 1 month-post vaccination for measurement of antibodies to the Hib polysaccharide PRP by ELISA, meningococcal polysaccharides C and Y specific IgGs by ELISA, IgG antibodies against pertussis components (PT, FHA, PRN) by ELISA, anti-diphtheria and anti-tetanus antibody concentrations by ELISA, antibodies against poliovirus types 1, 2, and 3 by a virus micro-neutralization test, antibodies to HBs by EIA, pneumococcal serotype specific total IgG antibodies (to 4, 6B, 9V, 14, 18C, 19F, and 23F) by ELISA, and functional anti-meningococcal serogroup C and Y activity (SBA-MenC and SBA-MenY) using rabbit complement.

Study Period: March 18, 2003 – February 12, 2004

Results:
Safety: Of 409 enrolled participants, 407 received vaccine (total vaccinated cohort); 4/407 did not receive vaccine according to protocol, yielding 403 as the ATP safety cohort.

Across study groups, redness was the most common solicited local reaction, peaking after dose 2, occurring in 342 subjects [Hib-MenCY ([(2.5µg/5 µg /5 µg n=67, 5 µg /10 µg /10 µg n=67, 5 µg /5 µg /5 µg n=64), Menjugate n=75, and ActHIB n=69]. Of the local reactions characterized as grade 3, pain defined as crying when limb is moved or spontaneously painful was most frequent, and occurred more often in the ActHIB group (n=6) than among Hib-MenCY subjects (2.5µg/5 µg /5 µg n=2, 5 µg /10 µg /10 µg n=1, 5 µg /5 µg /5 µg n=1). Irritability was most the most frequent systemic reaction and was slightly more common after the 1st and 2nd doses; it occurred in 391 subjects [(2.5µg/5 µg/5 µg n=76, 5 µg /10 µg /10 µg n=79, 5 µg /5 µg /5 µg n=76), Menjugate (n=80), and ActHIB (n=80)]. Irritability was the most frequent grade 3 systemic reaction. Fever occurring in the 2.5/5/5 group was most common after the 2nd dose; overall, it occurred in 327 subjects [(2.5µg/5 µg /5 µg n=65, 5 µg /10 µg /10 µg n=64, 5 µg /5 µg /5 µg n=64), Menjugate (n=64), and ActHIB (n=70)]. High fever (T >39 C) occurred in 34 subjects [(2.5µg/5 µg /5 µg n=5, 5 µg /10 µg /10 µg n=6, 5 µg /5 µg /5 µg n=6), Menjugate (n=5), and ActHIB (n=12)]. Most fevers in the vaccine candidate group occurred within 1 day of vaccination. Overall, there was no clear dose-dependent relationship between the doses of the Hib-MenCY-TT vaccines and solicited reactions.

Twenty-two serious adverse events in 22 subjects occurred among all study groups combined, 13 of which occurred within 30 days post-vaccination; 5 of these 13 were bronchiolitis and 3 of these 13 were gastroenteritis. One death occurred in a 6 month old infant due to SIDS ~ 3 months after the first vaccination with Hib-MenCY 5/5/5.

Immunogenicity: Of 409 enrolled participants, 378 participants had evaluable results. Following study dose 3, 100% of Hib 2.5/5/5 and ActHib subjects achieved anti-PRP antibody GMC $\geq$ 0.15 mcg/mL; 97.3% of Hib 2/5/5/5 subjects and 94.6% of ActHib subjects achieved anti-PRP antibody GMC $\geq$ 1.0 mcg/mL. CBER considers SBA results using ---(b)(4)----- complement to be an unreliable predictor of inferred efficacy in children younger than 2 years old.

Summary: Serum samples were analyzed with an SBA with ---(b)(4)----- complement and with ELISA for GMCs. CBER does not consider either of these analyses to be definitive evidence of seroprotection. The choice of selected dose and dosing regimen for further studies in infants was supported by the safety results.

8.3.2 Study 002: 792014/002 (Hib-MenCY-TT-002)

A phase II, open (partially double-blind), randomized, controlled, multicentre, primary vaccination study to evaluate the immunogenicity (including immune memory), reactogenicity and safety of three different formulations of the GSK Biologicals' combined Haemophilus influenzae type b meningococcal serogroups CY conjugate vaccine given concomitantly with Infanrix® penta and Prevenar®, versus ActHIB® and Meningitec®# given concomitantly with Infanrix® penta and Prevenar® in infants according to a 2-4-6 month schedule.

*Study 792014 was conducted in two parts: the primary vaccination phase (792014/001[Hib-MenCY-TT-001]) and the immune memory, antibody persistence vaccination phase (792014/002 [Hib-MenCY-TT-002]).
#Menjugate was used instead of Meningitec for infant immunization

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Study Design: This study was an open (partially double-blind), randomized, active-controlled extension trial of the primary vaccination study to evaluate persistence of immune response and immune memory induced by a 3-dose primary vaccination schedule (at 2, 4, and 6 months) with three Hib-MenCY formulations (given concomitantly with DTaP-IPV-HBV + PCV7) at three study centers in Australia. 394 participants 11-14 months of age were enrolled. Children who had been vaccinated in Study 001 with DTaP-IPV-HBV and one of the three Hib-MenCY formulations or Menjugate® + ActHIB® or PCV7 + ActHIB® were vaccinated, intramuscularly, at ~12 months (range 11-14 months) with one dose of 10 µg plain PRP and 1/5 of a dose of polysaccharide ACWY (Mencevax®).

Parent(s)/guardian(s) of the subjects reported solicited local (pain, redness and swelling) and general (drowsiness, fever, irritability, and loss of appetite) symptoms on diary cards for the 8-day post-vaccination period (Days 0 to 7). There was a 31-day (Days 0 to 30) follow-up period, after the 4th vaccine dose, of unsolicited non-serious adverse events (AEs); recording of serious adverse events (SAEs) during the entire study period.

Sera was collected pre- and 1 month-post 4th vaccination for measurement of antibodies to PRP, meningococcal IgG antibody to C and Y polysaccharides, and serogroup-specific serum bactericidal antibody (SBA-MenC and SBA-MenY) with an assay using (b)(4) complement. A subset of sera was tested for bactericidal antibodies using an assay with human complement. Antibody persistence, measured prior to the 4th study vaccination, was described for antigens contained in routinely recommended childhood vaccines. Safety and reactogenicity of one dose of 10 µg plain PRP and 1/5 of a dose of polysaccharide ACWY (Mencevax®) were evaluated, as well.

Study Period: December 19, 2003 – August 23, 2004

Results:
Safety: Of 394 enrolled participants, 394 received vaccine (total vaccinated cohort), and 393 were included in the ATP cohort for safety. Overall, symptoms occurred in 334 subjects ([(2.5µg/5 µg /5 µg n=68, 5 µg /10 µg /10 µg n=65, 5 µg /5 µg /5 µg n=62), Menjugate n=74, and ActHIB n=65]. Across study groups, redness was the most frequent local reaction, occurring in 166 subjects [Hib-MenCY ([(2.5µg/5 µg /5 µg n=39, 5 µg /10 µg /10 µg n=27, 5 µg /5 µg /5 µg n=27), Menjugate n=44, and ActHIB n=29]. Of the local reactions, one subject in each of the Hib-MenCY 5/10/10, Hib-MenCY 5/5/5, and Menjugate groups reported a grade 3 local reaction. Overall, there was no clear dose-dependent relationship between previously administered Hib-MenCY-TT vaccine (all formulations) and frequency of local reactions ([(2.5µg/5 µg /5 µg n=46, 5 µg /10 µg /10 µg n=38, 5 µg /5 µg /5 µg n=34).

Irritability was most the most frequent systemic reaction, which occurred in 236 subjects [(2.5µg/5 µg/5 µg n=48, 5 µg /10 µg /10 µg n=48, 5 µg /5 µg /5 µg n=45), Menjugate (n=46), and ActHIB (n=49)]. Any systemic reaction characterized as grade 3 severity, except for irritability, occurred in n=1-3 Hib-MenCY-TT participants (all formulations). Overall, there was no clear dose-dependent relationship between the amount of PRP and meningococcal antigen in Hib-MenCY-TT vaccines and frequency of systemic reactions ([(2.5µg/5 µg /5 µg n=60, 5 µg /10 µg /10 µg n=59, 5 µg /5 µg /5 µg n=60).

Two SAEs in 2 subjects were reported during the course of study 002: one 11 month old subject with bronchiolitis 9 days after vaccination and one 13 month old with pneumonia 22 days. No deaths were reported. In addition, 14 subjects from study 792014/001 (primary immunization study) experienced SAEs during the period following the last study contact and preceding this study. Due to the nature and timing of the events, the 14 adverse events are unlikely to be related to vaccination.

Immunogenicity: Of 394 enrolled participants, 371 had evaluable results. Prior to the polysaccharide (PS) PRP vaccination, 100% of Hib-MenCY 2.5/5/5 and 97.1% of ActHIB subjects had anti-PRP antibody GMC $\geq$ 0.15 mcg/mL; 65.7% of Hib-MenCY 2.5/5/5 and 58.6% of ActHIB subjects had anti-PRP antibody GMC $\geq$ 1.0 mcg/mL. Following PS PRP vaccination, 100% of Hib-MenCY 2.5µg/5 µg /5 µg and 98.6% ActHIB subjects achieved anti-PRP antibody GMC $\geq$ 0.15 mcg/mL; 98.5% of Hib 2.5µg/5 µg /5 µg subjects and 80.6% of ActHIB subjects achieved anti-PRP antibody GMC $\geq$ 1.0 mcg/mL. The sera from a non-randomized subset of Hib-MenCY 2.5µg/5 µg /5 µg subjects were tested for SBA antibody with an assay using human complement. Meningococcal serogroup C antibody persistence, defined as a pre-4th dose MenC-hSBA titer $\geq$ 1:8, was seen in 27/35 [77.1% (59.9, 89.6)] of subjects. Meningococcal serogroup Y antibody persistence, defined as a pre-4th dose MenY-hSBA titer $\geq$ 1:8, was observed in 48/56 [85.7%, (73.8, 93.6)] of subjects.

Summary: Persistence of anti-PRP antibody, assessed by the percentage of participants achieving an antibody concentration $\geq$0.15 mcg/mL, was higher in Hib-MenCY-TT (any formulation) primed toddlers than for ActHIB primed participants, and, of the 3 formulations, highest (100%) in Hib-MenCY 2.5/5/5 group. An immune response to unconjugated PRP vaccine in toddlers 11-14 month old was indicative of a memory response. Following polysaccharide vaccination, more Hib-MenCY-TT 2.5/5/5-primed participants (98.5%) achieved an anti-PRP antibody concentration $\geq$1.0 mcg/mL compared to other Hib-MenCY-TT formulations, and compared to ActHIB primed participants.

Interpretation of meningococcal SBA antibody responses is limited since CBER currently does not consider rSBA antibody results to be a reliable indicator of inferred efficacy in children younger than 2 years old.

The safety profile was similar for among the three Hib-MenCY-TT formulations.

8.3.3 Study 003: 792014/003 (Hib-MenCY-TT-003)

A phase II, open (partially double-blind), randomised, controlled, multicentre, primary vaccination study to evaluate the immunogenicity, reactogenicity and safety of three different formulations of GSK Biologicals' combined Haemophilus influenzae type b-meningococcal serogroups C and Y- conjugate vaccine and one formulation of GSK Biologicals' Haemophilus influenzae type b-meningococcal serogroup C conjugate vaccine each given concomitantly with Infanrix™ penta, versus Meningitec™ given concomitantly with Infanrix™ hexa in infants according to a 2-3-4 month schedule.

Study Design: This study was an open (partially double-blind), randomized, dose-ranging, multicenter trial in Germany and Belgium. Enrollment included 388 infants 6-12 weeks old at time of first vaccination. Participants were vaccinated, intramuscularly, with three dosage levels of the Hib and meningococcal polysaccharide tetanus toxoid conjugate vaccine (Hib-MenCY 2.5µg/5 µg /5 µg, 5 µg /10 µg /10 µg, or 5 µg /5 µg /5 µg), Hib-MenC (5 µg /5 µg), or Menjugate. The MenCC vaccine available at the time was Menjugate (MenC-CRM 197), which

was given to control group participants rather than Meningitec (MenC-CRM 197). Infants received three vaccinations (n=77-78/group) at 2, 3, and 4 months of age.

Parent(s)/guardian(s) of the subjects reported solicited local (pain, redness and swelling) and general (drowsiness, fever, irritability, and loss of appetite) symptoms on diary cards for the 8-day post-vaccination period (Days 0 to 7). There was a 31-day (Days 0 to 30) follow-up period, after the 4th vaccine dose, of unsolicited non-serious adverse events (AEs); recording of serious adverse events (SAEs) during the entire study period.

Sera were collected at prior to first vaccination and one month after third vaccination (i.e., 5 months old) and tested for immunogenicity to Hib, meningococcal, tetanus, and pertussis antigens by rSBA-MenC and rSBA-MenY, anti-PSC IgG and anti-PSY IgG, anti-PRP IgG, anti-TT, anti-FHA, anti-PRN, and anti-PT. Only post-vaccination sera were tested for anti-D, anti-HBs, and anti-polio 1, 2, and 3.

Study Period: March 6, 2003 to December 16, 2003

Results:
Safety: For infants receiving Hib-MenCY-TT (2.5/5/5), overall, redness (44.9%) and swelling (39.7%) were reported more frequently than pain (26.9%). Pain was more frequent after the first dose, while redness and swelling were most frequent after the 2nd dose. Among the 3 Hib-MenCY-TT groups, overall, local symptoms were slightly less common in the 2.5/5/5 group.

Irritability was most frequent after the 1st dose and occurred in 228 subjects [(2.5µg/5 µg /5 µg n=44, 5 µg /10 µg /10 µg n=42, 5 µg /5 µg /5 µg n=51), Hib-MenC (5 µg /5 µg n=47), and Menjugate (n=44)]. Drowsiness was most common after the 1st dose and overall occurred in 218 subjects [(2.5µg/5 µg /5 µg n=39, 5 µg /10 µg /10 µg n=53, 5 µg /5 µg /5 µg n=43), Hib-MenC (5 µg /5 µg n=37), and Menjugate (n=46)]. Loss of appetite was most common after the 1st dose and occurred in 150 subjects [(2.5µg/5 µg /5 µg n=24, 5 µg /10 µg /10 µg n=34, 5 µg /5 µg /5 µg n=29), Hib-MenC (5 µg /5 µg n=33), and Menjugate (n=30)]. Fever occurred in the 2.5/5/5 group was most common after the 1st dose; overall, it occurred in 135 subjects [(2.5µg/5 µg /5 µg n=25, 5 µg /10 µg /10 µg n=28, 5 µg /5 µg /5 µg n=26), Hib-MenC (5 µg /5 µg n=28), and Menjugate (n=28)]. Rectal T >39 °C occurred in 13 subjects [(2.5µg/5 µg /5 µg n=2, 5 µg /10 µg /10 µg n=3, 5 µg /5 µg /5 µg n=3), Hib-MenC (5 µg /5 µg n=1), and Menjugate (n=4)]. Most fevers in the vaccine candidate group occurred within 1 day of vaccination. Seven SAEs were reported in seven subjects 5-27 days following vaccination. None of the SAEs occurred in the Hib-MenCY groups. No deaths were reported.

Immunogenicity: Of 388 enrolled participants, 353 had evaluable results.
After 3 vaccine doses, in all study groups, 100% of subjects achieved anti-PRP antibody $\geq$ 0.15 µg /mL. The percentage (95% CI) in each study group achieving $\geq$ 1.0 µg to PRP is as follows: Hib-MenCY 2.5/5/5 98.5 (92.0, 100.0), Hib-MenCY 5/10/10 98.5 (92.0, 100.0), Hib-MenCY 5/5/5/ 98.6 (92.3, 100.0), Hib-MenC 98.6 (92.7, 100.0), and Menjugate 80.3 (69.1, 88.8). The GMC (µg /mL) and (95% CI) are as follows: Hib-MenCY 2.5/5/5 9.0 (7.2, 11.2), Hib-MenCY 5/10/10 9.5 (7.7, 11.7), Hib-MenCY 5/5/5/ 8.1 (6.5, 10.0), Hib-MenC 10.4 (8.5, 12.8), and Menjugate 2.6 (2.0, 3.4). SBA-(b)(4) was utilized to determine bactericidal activity. CBER considers SBA results using ---(b)(4)---- complement to be an unreliable predictor of inferred efficacy in children younger than 2 years old.

Summary: No decrease in anti-PRP antibody response was observed following 3 doses of 2.5/5/5 Hib-MenCY-TT, which contains 1/5 the PRP amount compared to currently U.S. licensed

Hib conjugate vaccines (10ug PRP). Overall, there was no clear dose-dependent relationship between the doses of the Hib-MenCY-TT vaccines and adverse event frequency or severity. The choice of the selected dose and dosing regimen for Phase III infant studies was supported by the safety results.

8.3.4 Study 004: 100381/004 (Hib-MenCY-TT-004)

A Phase II open (partially-double blind), controlled, multicentre, booster vaccination study to assess the safety, reactogenicity and immunogenicity of a booster dose of each of the three formulations of GlaxoSmithKline (GSK) Biologicals' Hib-MenCY vaccine (co-administered with Infanrix™ penta) and GSK Biologicals' Hib-MenC vaccine (co-administered with Infanrix™ penta) compared to a booster dose of Menjugate™ (co-administered with Infanrix™ hexa) when given to toddlers primed in infancy in study 792014/003 (Hib-MenCY-TT-003).

Study Design: This study was an open, (partially double-blind), controlled, non-randomized extension of study 792014/003 conducted at the same German study sites. Randomization was maintained for the five study groups. Children received as the 4th dose the same formulation of Hib-MenCY-TT administered in the primary vaccination study (administered at 2-3-4 months). Enrollment included 222 infants 12-18 months old at time of 4th dose (n=43-47/group). Participants were vaccinated, intramuscularly, with three dosage levels of the Hib and meningococcal polysaccharide tetanus toxoid conjugate vaccine (Hib-MenCY 2.5µg/5 µg /5 µg, 5 µg /10 µg /10 µg, or 5 µg /5 µg /5 µg), Hib-MenC (5 µg /5 µg), or Menjugate. Sera were collected prior to and approximately one month after the 4th vaccination for measurement of antibody titres/concentrations against the Hib-MenCY and Hib-MenC vaccine antigens.

Parent(s)/guardian(s) of the subjects reported solicited local (pain, redness and swelling) and general (drowsiness, fever, irritability, and loss of appetite) symptoms on diary cards for the 8-day post-vaccination period (Days 0 to 7). There was a 31-day (Days 0 to 30) follow-up period, after the 4th vaccine dose, of unsolicited non-serious adverse events (AEs); recording of serious adverse events (SAEs) during the entire study period.

Study Period: January 28, 2004 – October 4, 2004

Results:
Safety: The most frequently reported solicited local adverse event after the 4th dose was redness, occurring in 92 subjects [Hib-MenCY (2.5µg/5 µg /5 µg n=20, 5 µg /10 µg /10 µg n=18, or 5 µg /5 µg /5 µg n=22), Hib-MenC (5 µg /5 µg n= 16), or Menjugate (n=16)]. Among the 3 formulations of Hib-MenCY, a clear dose-dependent relationship was not observed; however, a smaller percentage of subjects in the 2.5µg/5 µg /5 µg had local reactions. Drowsiness was reported in 85 subjects [Hib-MenCY (2.5µg/5 µg /5 µg n=14, 5 µg /10 µg /10 µg n=18, or 5 µg /5 µg /5 µg n=18), Hib-MenC (5 µg /5 µg n= 17), or Menjugate (n=18)]. Irritability was reported in 84 subjects [Hib-MenCY (2.5µg/5 µg /5 µg n=16, 5 µg /10 µg /10 µg n=18, or 5 µg /5 µg /5 µg n=19), Hib-MenC (5 µg /5 µg n= 14), or Menjugate (n=17)]. Loss of appetite was reported in 63 subjects [Hib-MenCY (2.5µg/5 µg /5 µg n=11, 5 µg /10 µg /10 µg n=16, or 5 µg /5 µg /5 µg n=12), Hib-MenC (5 µg /5 µg n= 10), or Menjugate (n=14)]. Any fever occurred in 73 subjects after the 4th dose [Hib-MenCY (2.5µg/5 µg /5 µg n=13, 5 µg /10 µg /10 µg n=10, or 5 µg /5 µg /5 µg n=16), Hib-MenC (5 µg /5 µg n= 18), or Menjugate (n=16)], and rectal-equivalent T>39C occurred in 16 subjects [Hib-MenCY (2.5µg/5 µg /5 µg n=5, 5 µg /10 µg /10 µg n=3, or 5 µg /5 µg /5 µg n=3), Hib-MenC (5 µg /5 µg n= 3), or Menjugate (n=2)]. In the 3 candidate vaccine recipients with fevers of T>39.5°C, fever began 1-5 days post-vaccination. There were three serious adverse events, 1 in the Hib-MenCY 2.5/5/5 group (14 month old hospitalized with

gastroenteritis 31 days after vaccination) 1 in the Hib-MenCY 5/10/10 group (18 month old hospitalized with upper airway infection, fever, and seizure 22 days after vaccination), and 1 in the Hib-MenC group (13 month old hospitalized with bilateral otitis media, fever, and seizure 20 days after vaccination). No deaths were reported.

Immunogenicity: Of 222 enrolled participants, 204 had evaluable results.
hSBA: A non-randomized subset of Hib-MenCY 2.5/5/5 participants was selected for SBA testing using human complement. MenC antibody persistence (pre-4th dose hSBA titer $\geq$1:8) was reported in 41/43 [95.3% (84.2, 99.4)] of subjects. The hSBA-MenC GMT pre-4th dose was 70.0 (46.1, 106.3). MenY antibody persistence (pre-4th dose hSBA titer $\geq$1:8) was observed in 48/56 [85.7%, (73.8, 93.6)] of subjects. The hSBA-MenY GMT pre-4th dose was 30.3 (21.0, 43.6).

Summary: The choice of selected dose and dosing regimen was supported by the safety results. hSBA testing was performed, in non-randomized Hib-MenCY 2.5/5/5 subset, to support criteria for meningococcal C and Y primary endpoints in a phase 3 study.

9 Overview of Immunogenicity (Effectiveness) Across Trials

9.1 Study Design and Methods

Six studies evaluating doses 1 -3 were submitted in support of this BLA, five studies included evaluation of dose 4, and two studies included evaluation of antibody persistence; these studies were performed in Australia, Belgium, Germany, Mexico, and the United. Study Hib-MenCY-TT-009/-010 was the pivotal phase III safety, immunogenicity, and lot to lot consistency study performed in support of the BLA. Study Hib-MenCY-TT-005/-006 contributes pivotal information on concomitant vaccine administration in U.S. subjects, study Hib-MenCY-TT-007/-008 contributes pivotal information on concomitant measles, mumps, rubella, and varicella vaccination, and study Hib-MenCY-TT-013 contributes information on 1 year antibody persistence. Six studies (Hib-MenCY-TT-001, -003, -005, -007, -009, and -011) evaluated the first 3 doses of Hib-MenCY-TT administered at either 2, 4, and 6 months of age or at 2, 3, and 4 months of age (study -003). In these studies, 7522 infants were included in study groups which received the licensure formulation of Hib-MenCY-TT. Five of these six studies evaluated immunogenicity (Hib-MenCY-TT-001, -003, -005, -007, and -009). In these studies, 4244 subjects were included in study groups which received the licensure formulation of Hib-MenCY-TT, and 4166 subjects were vaccinated according to a U.S. immunization schedule (2, 4, and 6 months of age). Five of the six completed studies (Hib-MenCY-TT-004, -006, -008, -010, and -012) evaluated Hib-MenCY-TT as a 4th dose at approximately 12 – 15 months of age. In these studies, 7025 subjects were included in study groups which received a dose of the licensure formulation. In four of these studies, a total of 3630 subjects received a 4th consecutive dose of Hib-MenCY-TT. Studies Hib-MenCY-TT-001/-002, -003/-004, -007/-008, and -013 were open-label studies. Studies Hib-MenCY-TT-005/-006, --009/-010, and -011/-012 were single-blinded. However, Hib-MenCY-TT-005 was not blinded with respect to the control group of children receiving Menomune, as this control group involved a different age group and only received one vaccination. Most subjects received Hib-MenCY-TT concomitantly at a separate site with DTaP-HBV-IPV and PCV7 vaccines as intramuscular injections at doses 1 – 3. Subjects in studies Hib-MenCY-TT-008 and -010 were co-administered MMR, V, and PCV7 at dose 4. Haemophilus b Conjugate Vaccines used as comparators included two currently U.S. licensed vaccines, ActHIB and PedvaxHIB. Notably, ActHIB is not licensed for ages 12 – 15 months in the U.S, although it was used in study Hib-MenCY-TT-006. As there was no U.S.-licensed meningococcal conjugate vaccine for the 6 week – 15 month age group, none of the studies included an age-matched comparator group that received a U.S.-licensed meningococcal conjugate vaccine.

Pre-vaccination blood samples were collected just prior to vaccination in studies Hib-MenCY-TT-001, -003, and -005. Post-dose 3 samples were taken from all subjects in studies Hib-MenCY-TT-001, -003, -005, and -009 and from a randomized subset of 50% of the subjects in study -007. In study Hib-MenCY-TT-007, a blood sample was taken to evaluate the immunogenicity of the Hib-MenCY-TT and Hib vaccines after the first two doses in a randomized subset of 50% of subjects; this blood draw occurred at the time of administration of the third vaccine dose (i.e., two months post-dose 2). Pre-dose 4 blood samples for the analysis of persistence after doses 1 – 3 were taken in all subjects enrolled in 4th dose studies, including study Hib-MenCY-TT-002 (but not study Hib-MenCY-TT-012, which only evaluated safety endpoints). Post-dose 4 blood samples were targeted at approximately one month in studies Hib-MenCY-TT-004 and -006 and at approximately 6 weeks in studies Hib-MenCY-TT-008 and -010. In study Hib-MenCY-TT-013, blood samples for antibody persistence were drawn approximately 1 year after the fourth dose vaccination in study Hib-MenCY-TT-006. The pre-defined interval between administration of the 3rd dose and the post-vaccination blood sample was 30 – 42 days in studies Hib-MenCY-TT-001 and -003 and 31 – 48 days in studies Hib-MenCY-TT-005, -007, and -009. Inclusion in the ATP immunogenicity cohort in studies Hib-MenCY-TT-005, -007, and -009 required a blood sample from days 21 – 48 post-dose 3.

In the pivotal studies, anti-PRP antibodies were measured using ELISA performed by GSK, either in Rixenstart, Belgium (studies Hib-MenCY-TT-005/-006, -007/-008, and -013) or in -----(b)(4)----- (studies Hib-MenCY-TT-009/-010). Anti-PRP in non-pivotal studies Hib-MenCY-TT-001/-002, and -003/-004 was measured by ELISA in the laboratory of ----------(b)(4)----------. CBER's assay reviewer determined that the anti-PRP assays used in the clinical studies of Hib-MenCY-TT were acceptable.

Studies Hib-MenCY-TT-001/-002 and -003/-004 were dose-finding studies; therefore, only a subset of subjects in each of those studies received the same composition of Hib-MenCY-TT intended for licensure in the U.S., as described in Section 1.2.3.

9.2 Immunogenicity Endpoints and Findings

In the studies that evaluated the immune response to Hib-MenCY-TT, 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. Since many subjects are expected to have an anti-PRP level $\geq$0.15 mcg/ml prior to 4th vaccination as a result of persistent immunity following primary immunization, the most informative parameters for evaluation of 4th vaccination with Hib-MenCY-TT are GMCs and anti-PRP levels $\geq$1.0 mcg/ml. Studies Hib-MenCY-TT-008 and -010 compared Hib-MenCY-TT to a vaccine licensed in the U.S. for the 4th dose. Primary endpoints were defined as anti-PRP antibody concentrations $\geq$1.0 mcg/ml in studies Hib-MenCY-TT-005/-006, -007, -009/-010. In terms of the long-term persistence of antibodies to PRP, the primary endpoint in study Hib-MenCY-TT-013 was anti-PRP antibody concentration $\geq$0.15 mcg/ml.

A co-primary objective in studies Hib-MenCY-TT-005, -007, and -009 was to demonstrate non-inferiority of the Hib-MenCY-TT vaccine to ActHIB in terms of PRP immune response. Non-inferiority criteria were met in all 3 studies, meaning that the lower limit of the two-sided standardized asymptotic 95% CI on the difference in the percentage of subjects with anti-PRP concentration $\geq$ 1.0 mcg/mL post-dose 3 was above -10%. A co-primary objective in studies Hib-MenCY-TT-006 and -010 was to demonstrate non-inferiority of the Hib-MenCY-TT vaccine to a Hib control vaccine in terms of immune response to PRP following the 4th dose. The pre-defined criterion was as stated above for post-dose 3 responses. Non-inferiority criteria were

satisfied. In study Hib-MenCY-TT-006, ActHIB was used as the 4th Hib dose, although it is not licensed for this use in the studied age group in the U.S. PedvaxHIB was used in study Hib-MenCY-TT-010, and pre-specified acceptance criteria were met. Analysis of between group differences in anti-PRP response was exploratory in study Hib-MenCY-TT-008.

Immune responses to meningococcal components were evaluated by hSBA assays in studies Hib-MenCY-TT-009/-010. The persistence of functional antibodies to MenC and MenY was evaluated by hSBA in study Hib-MenCY-TT-013. In both cases, the appropriate endpoints are hSBA-MenC and hSBA-MenY antibody titers $\geq$ 1:8. In study Hib-MenCY-TT-013, GSK specified, but CBER did not concur with, an endpoint of $\geq$ 1:4; thus, the clinical review presents results using the endpoint of $\geq$ 1:8.

Immune response to MenC after the fourth vaccination was a co-primary objective in study Hib-MenCY-TT-010. The lower limit of the 95% CI for the percentage of subjects with post-dose 4 hSBA-MenC titers $\geq$ 1:8 was $\geq$ 96.5%, above the pre-specified criteria of $\geq$ 90%. The GMT ratio was 12.0, with a lower limit of the 95% CI of 10.4. Immune reponse to MenY after the fourth vaccination was a co-primary objective in study Hib-MenCY-TT-010. The lower limit of the 95% CI for the percentage of subjects with post-dose 4 hSBA-MenY titers $\geq$ 1:8 was 97.0%, above the pre-specified criteria of $\geq$ 90%.

Immune response to MenY after the third vaccination was a powered secondary objective in study Hib-MenCY-TT-009. The criterion was that the lower limit of the 95% CI for the percentage of subjects with hSBA-MenC titers $\geq$ 1:8 was $\geq$ 90%. The point estimate was 98.8%, with a lower limit of the 95% CI of 97.4%. Post-hoc testing of a subset of subjects in studies Hib-MenCY-TT-005 and testing in a subset of subjects in -007 demonstrated lower limits of the 95% CI of 90.6% and 95.7%, respectively. A powered secondary objective in study Hib-MenCY-TT-009 was to demonstrate that the percentage of subjects with hSBA-MenY titers $\geq$ 1:8 was $\geq$ 85%. In this study, the point estimate was 95.8%, and the lower limit of the 95% CI around the estimate was 93.7%. Post-hoc testing of a sample of subjects in study Hib-MenCY-TT-005 demonstrated a point estimate of 89.4%, with the lower limit of the 95% CI of 83.1%.

Regarding immune interference with DTaP-HBV-IPV administration, study Hib-MenCY-TT-009/-010 had a powered secondary objective of demonstration of non-inferiority of anti-D and anti-T antibody concentrations $\geq$ 0.1 IU/mL, with the criterion of a lower limit of the 95% CI for the group difference (Hib-MenCY-TT 3 pooled lots group – Hib group) of $\geq$ -10%. For both antigens, the lower limit of the 95% CI was -1.04%. Study Hib-MenCY-TT-005/-006 had a co-primary objective to demonstrate the non-inferiority of the anti-PT, anti-FHA, and anti-PRN adjusted GMC ratios (Hib-MenCY-TT group/Hib group) with the criterion of a lower limit of the 95% CI for the adjusted GMC ratios of $\geq$ 0.67. The lower limits were 0.74, 0.73, and 0.70 for anti-PT, anti-FHA, and anti-PRN, respectively. The same statistical criteria for non-inferiority were applied in study Hib-MenCY-TT-009/-010, in which the evaluation was a powered secondary objective. In this study, the lower limits were 0.77, 0.72, and 0.77 for anti-PT, anti-FHA, and anti-PRN, respectively, meeting the study's criteria for non-interference. Study Hib-MenCY-TT-009/-010 had a powered secondary objective of demonstration of non-inferiority of response to the poliovirus component of DTaP-HBV-IPV; the criterion was a lower limit of the 95% CI for the group difference in proportion of subjects achieving anti-poliovirus titers $\geq$ 1:8 of $\geq$ -10%. The lower limits were -1.33% for all three poliovirus serotypes. No evidence of immune interference was observed, as criteria were met for evaluation of immune responses to vaccines admininstered concomitantly with Hib-MenCY-TT. No studies included a pre-specified hypothesis for evaluation of Hepatitis B response. Study Hib-MenCY-TT-005 included an exploratory analysis of the between group differences (Hib-MenCY-TT – Hib) regarding anti-

HBs antibody conentrations ≥ 10 mIU/mL and GMCs and suggested that there were no statistical differences between groups.

With respect to immune interference with PCV7, study Hib-MenCY-TT-005/-006 had a co-primary hypothesis of demonstration of non-inferiority of PCV7 when co-administered with Hib-MenCY-TT versus ActHIB. The criterion for non-inferiority was a lower limit of the 95% CI for the adjusted GMC ratio (Hib-MenCY-TT/Hib) for the post-dose 3 anti-pneumococcal antibodies of ≥ 0.5 for each pneumococcal serotype contained in PCV7. The lower limits were 0.64, 0.54, 0.72, 0.76, 0.68, 0.80, and 0.67 for serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, respectively. Based on criteria of a 2-fold GMC ratio (lower limit of 95% CI for the GMC ratio HibMenCY/ActHIB > 0.5), no evidence of immune interference was observed following the 4th dose of PCV7 administered concomitantly with Hib-MenCY-TT as compared with the 4th dose of PCV7 concomitantly administered with the Hib control vaccine at 12-15 months of age. However, the 4th dose of ActHIB control vaccine was administered on a schedule that is not licensed for use in the U.S. (i.e., at 12 – 15 months). Therefore, these data are insufficient to conclude that there is no immune interference in immune responses to the PCV7 serotypes when the 4th dose of PCV7 is administered concomitantly with Hib-MenCY-TT.

Studies Hib-MenCY-TT-007/-008 and Hib-MenCY-TT-009/-010 each had a co-primary endpoint to demonstrate non-inferiority of responses to MMR and V when co-administered with Hib-MenCY-TT compared with PedvaxHIB. The co-primary endpoint was to be evaluated on pooled data from Hib-MenCY-TT-008 and -010 if criteria for evaluation of MMR and V responses were met in each study separately. Based on pooling of the data from these two studies, for measles, mumps, and rubella, the non-inferiority criteria were set as the lower limit of the 95% CI of the group differences of -5%; these lower limits were -2.56%, -2.16%, and -0.57% for measles, mumps, and rubella. For varicella, the non-inferiority limit was -10%; in this dataset, the lower limit was -0.78%. The Hib-MenCY-TT-008 analysis plan was revised to reflect discussions with CBER, however, the protocols for Hib-MenCY-TT-008 and -010 included different primary endpoints for the non-inferiority evaluation. Therefore, although the analyses are presented for the pooled data, the analyses are also presented separately within the respective section of the clinical review. Non-inferiority criteria were met for Hib-MenCY-TT-010. Additionally, the percentages of subjects in the two studies individually meeting seroconversion criteria support that there is no immune interference when Hib-MenCY-TT is administered concomitantly with MMR and V vaccines.

9.4 Immunogenicity Conclusions

The available data demonstrate that anti-PRP post-dose 3 and post-dose 4 immune responses and hSBA post-dose 4 immune responses to Hib-MenCY-TT were robust. Across the studies, 1397 subjects who received licensure formulation Hib-MenCY-TT according to the standard U.S. infant immunization schedule were included in the post-dose 3 ATP immunogenicity analyses. For the post-dose 4 ATP immunogenicity analyses, there were 1127 subjects who received a fourth dose of Hib-MenCY-TT at 12 – 15 months.

The available ATP immunogenicity data on Hib-MenCY-TT were obtained from studies of generally healthy children who were predominantly Caucasian (77.1% - 100%). There are no data on the effectiveness of Hib-MenCY-TT in children who may be at increased risk for invasive disease due to *H. influenzae* type b or meningococcal disease, including 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 antibody responses to conjugate vaccines. American Indian/Alaska Native children comprised 0.4% of the ATP immunogenicity cohort in study Hib-MenCY-TT-009 and 0.3% in study Hib-MenCY-TT-010 and were not represented in studies Hib-MenCY-TT-005/-006 and -007/-008.

The available immunogenicity data, obtained in generally healthy children, demonstrate a robust immune response against PRP and meningococcal serogroups C and Y elicited by 4 doses of Hib-MenCY-TT administered concomitantly with DTaP-HBV-IPV and PCV7 at doses 1, 2, and 3 and with MMRII, V, and PCV7 at dose 4.

10 Overview of Safety Across Trials

10.1 Overall Safety Database

Six studies were submitted in support of the safety of Hib-MenCY-TT in the BLA (shown as studies evaluating doses 1 – 3 and extensions evaluating dose 4 in Table 2). Across the six completed studies evaluating doses 1 – 3, a total of 7521 infants received Hib-MenCY-TT as part of the administration of the first 3 doses. A total of 21,943 doses of Hib-MenCY-TT were administered. In five of these studies, a total of 7023 subjects received Hib-MenCY-TT dose 4. Of these 7023, 6686 subjects received a fourth consecutive Hib-MenCY-TT dose at approximately 12 to 15 months of age. In two of the five completed fourth dose phase studies, 337 subjects total received a first dose of Hib-MenCY-TT at approximately 12 to 15 months of age after receiving 3 doses of Hib vaccine (and in some cases, Meningitec, an Australian-licensed meningococcal serogroup C conjugate vaccine) at ages 2, 4, and 6 months. No Hib-MenCY-TT was administered in two completed extension studies. One study evaluated antibody persistence one year post-fourth dose immunization. An additional study includes 1290 children vaccinated with 3 doses of Hib-MenCY-TT at 2, 4, and 6 months of age. A subset of these subjects received a fourth dose of Hib-MenCY-TT at 12 to 15 months of age. While this study is part of a separate clinical development program for GSK's investigational meningococcal serogroups A, C, W-135, and Y conjugate vaccine, blinded data on number of SAEs in the study were submitted to the Hib-MenCY-TT BLA to support the safety profile. The comparator group received a U.S.-licensed Haemophilus b conjugate vaccine. When the study was planned, there was no U.S.-licensed meningococcal conjugate vaccine for this age group. The ISS analysis considered studies that included ActHIB or PedvaxHIB as the control group, and only subjects who received the fourth consecutive dose of the Hib-MenCY-TT vaccine were considered for analysis of the fourth dose. Across the 6 completed studies of doses 1 - 3, the mean age at receipt of Hib-MenCY-TT ranged from 37 to 111 days. Approximately half of subjects were male and most subjects were of White/Caucasian origin 50.4%), while 40.8% were Hispanic. Across the 5 completed fourth dose phase studies, the mean age at receipt of Hib-MenCY-TT ranged from 11 to 17 months. Approximately half of subjects were male and most subjects were of White/Caucasian origin (49.5%), while 42.4% were Hispanic.

10.2 Safety Assessment Methods

In all studies, subjects were observed for at least 30 minutes post-vaccination to detect and treat any immediate reactions. Reactogenicity following vaccination was monitored actively. Solicited and unsolicited AEs were monitored by the subject's parent/guardian using diary cards/memory aids provided by the applicant in all vaccination studies except Hib-MenCY-TT-011/-012. The diary cards captured occurrence of specific local and general adverse events on the day of vaccination and at least on the subsequent 3 days. Solicited local AEs included pain, redness, and swelling at the injection site. Solicited general adverse events included fever, loss of appetite, irritability/fussiness, and drowsiness. Additionally, increase in mid-limb circumference was solicited in studies Hib-MenCY-TT-006 and -010. Solicited general AEs specific to co-

administered MMR and varicella vaccines were solicited in studies Hib-MenCY-TT-008 and -010 (U.S. Safety and Immunogenicity Cohort) days 0 – 42 post-vaccination. These MMR and varicella-specific solicited general AEs were fever, rash/exanthema, parotid/salivary gland swelling, and suspected signs of meningitis/febrile seizures. Diary cards were used to follow fever, while parents/guardians were asked to bring their children to the study site for rash/exanthema and parotid/salivary gland swelling. Parents/guardians were asked to notify the investigator immediately and have neurological examination according to local medical practice, with lumbar puncture performed at the discretion of the treating physician. Pre-specified symptom intensity scales were applied in each study. Investigators inquired about the occurrence of AEs and SAEs at every study visit.

The parents/guardians were instructed to inform the investigator immediately of the occurrence of any sign or symptom perceived as serious at any time throughout the study periods.

In all studies except Hib-MenCY-TT-011/-012, unsolicited adverse events were monitored during the 31-day (Day 0 to Day 30) post-vaccination period after each dose.

In studies Hib-MenCY-TT-001, -003, and -004, all SAEs were to be reported from Day 0 after dose 1 until 1 month following administration of the last dose of study vaccine. In studies Hib-MenCY-TT-005, -007, -009, and -011, all SAEs were to be reported from Day 0 after dose 1 of study vaccine through the day preceding administration of dose 4 (end of the primary phase ESFU period), and for subjects who did not receive dose 4 until the end of the ESFU period lasting 6 months after the last vaccination. In studies Hib-MenCY-TT-006, -008, -010, and -012, all SAEs were to be reported from the day of administration of dose 4 of study vaccine until the end of the fourth dose ESFU period. In study Hib-MenCY-TT-002, all SAEs occurring within the 31-day follow-up period after administration of the polysaccharide challenge doses were to be reported. In study Hib-MenCY-TT-013, only SAEs considered by the investigator to be related to study procedure or vaccine previously administered in Hib-MenCY-TT-005/-006 or related to GSK medication were to be reported at 1 year post-fourth dose administration. In study MenACWY-TT-057, all SAEs from Day 0 after dose 1 up to the day of the first visit of the fourth dose phase and from day 0 of the fourth dose phase through 6 months post-4^{th} dose are to be reported. A serious adverse event was defined as: life-threatening, required hospitalization or prolongation of hospitalization, an event that resulted in disability or incapacity, any untoward medical occurrence that resulted in death, an important medical event that may have jeopardized the subject or may have required intervention to prevent one of the other outcomes listed above.

In studies Hib-MenCY-TT-005/-006, -007/-008, -009/-010, and -011/ -012 were followed for the occurrence of new onset of chronic disease (NOCD), rash, and AEs resulting in ER visits during the entire study period. Additionally, AEs resulting in physician office visits were recorded in studies Hib-MenCY-TT-005/-006, -007/-008, and -009/ -010. In studies Hib-MenCY-TT-005, -007, -009, and -011, reporting of these specific AEs included day 0 after dose 1 through the day preceding administration of dose 4 (end of the primary phase ESFU period), and for subjects who did not receive dose 4 until the end of the ESFU period lasting 6 months after the last vaccination. In studies Hib-MenCY-TT-006, -008, -010, and -012, reporting of these specific AEs included day 0 after dose 4 through 6 months after dose 4 (end of the fourth dose ESFU period).

For study MenACWY-057, only blinded data on serious adverse events were included in the BLA.

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

In the six studies of doses 1 - 3, among a total of 7521 subjects who received Hib-MenCY-TT, there were 11 deaths reported, while there were 7 deaths reported among the 2779 Hib recipients. Death was reported in an additional subject who had received a non-licensure formulation of Hib-MenCY-TT. In the five studies of dose 4, among the 6687 Hib-MenCY-TT recipients, there were 2 reported deaths, while there were no deaths reported among the 2267 Hib recipients. None of the deaths were thought by the investigator to be related to vaccination. Given the nature of these children's deaths and timing in relationship to vaccination, the clinical reviewer concurred with this assessment.

According to information provided by the applicant in the PVP, the overall background rate of SIDS in the United States is 54/100,000 live births, or 0.54/1000. The proportion of Hib-MenCY-TT subjects experiencing SIDS was 6/7521, or 0.80/1000 subjects. This number does not include the 2/1290 Hib-MenCY-TT subjects from study MenACWY-TT-057 who died of SIDS; together, this proportion would be 8/8811, or 0.90/1000. The proportion of Hib subjects experiencing SIDS was 2/2779, or 0.72/1000. If the 258 planned Hib recipients from study MenACWY-TT-057 are added to this denominator, the proportion of Hib subjects experiencing SIDS was 2/3037, or 0.66/1000. For 2/8 Hib-MenCY-TT and 2/2 Hib recipients who died of SIDS, the event occurred within 30 days of vaccination. According to the applicant's observed vs. expected analysis, the number of subjects in either treatment group dying of SIDS within 30 days of vaccination does not exceed the expected number.

Subjects who died had received concomitant immunizations.

Deaths across doses 1 – 4 in the pivotal safety studies (i.e., Hib-MenCY-TT-009/-010 and -011/-012):

Regarding reports of Sudden Infant Death Syndrome (SIDS):

- A 4 month-old U.S. female in study Hib-MenCY-TT-009 was found dead lying on her back in the crib 43 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. The autopsy was reported as SIDS.
- A 2 month-old Mexican male in study Hib-MenCY-TT-011 experienced SIDS 22 days post-dose 1 of Hib, DTaP-HBV-IPV, and PCV7. The autopsy revealed a small amount of blood in the stomach and was reported as SIDS.
- A 2 month-old Mexican female in study Hib-MenCY-TT-011 experienced SIDS 10 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. The autopsy was reported as SIDS.
- A 3 month-old U.S. male in study Hib-MenCY-TT-011 died of SIDS 38 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. Autopsy was reported as SIDS with mild pulmonary congestion, edema, and petechial hemorrhages of the right lobe of the liver.
- A 3 month-old Mexican female in study Hib-MenCY-TT-011 experienced SIDS 25 days post-dose 1 of Hib, DTaP-HBV-IPV, and PCV7. She was brought to the hospital, where the doctor diagnosed SIDS. Autopsy was not performed.
- A 3 month-old Mexican female in study Hib-MenCY-TT-011 developed SIDS 37 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was brought to the

hospital, where doctors confirmed her death. An autopsy was performed, but the death certificate and autopsy report were not available at the time of the report.

Other deaths in the pivotal studies but not included above:

- A 5 month-old Mexican male in study Hib-MenCY-TT-011 developed "bronchopneumonia" and pharyngitis 16 days post-2nd dose of Hib, DTaP-HBV-IPV, and PCV7. He died 7 days later.
- A 4 month-old Mexican male in study Hib-MenCY-TT-011 with history of total anomalous pulmonary venous return with surgical correction, moderate malnutrition, pulmonary hypertension, and ventricular hypertrophy developed pneumonia 13 days post-2nd dose of Hib, DTaP-HBV-IPV, and PCV7. He presented with cough, tachypnea, respiratory distress, and fever (40°C). On day 5 of the illness, he was hospitalized. Approximately 8 days later, he had improved and was discharged. Fever recurred the day after discharge, and he was treated with amikacin, secnidazole, dipyrone, amoxicillin, gentamicin, and ampicillin. He then developed malaise, refusal to eat, and "complaining". Three days later, (approximately 30 days following onset of the pneumonia), the mother noted he had worsened and had respiratory distress and tachypnea. He was brought to the hospital, but en route, the mother noted he was cyanotic and not breathing. Autopsy was not performed. The death certificate reportedly listed congestive heart failure, left pleural effusion, congenital "cardiopathy" surgery, and severe malnutrition. The principal investigator attributed the child's death to pneumonia, congestive heart failure, surgical correction of total anomalous pulmonary venous return, and moderate malnutrition.
- An 8 month-old Mexican female in study Hib-MenCY-TT-009 developed bronchial aspiration approximately 89 days post-3rd dose of Hib, DTaP-HBV-IPV, and PCV7 and 1.5 months and 12 days post-1st and 2nd doses of Fluzone. The child was transported to the hospital, and en route, the baby developed purple hands and lips, then looked pale with shallow breathing. On arrival, the baby was pale and not breathing. The doctors told the mother the baby was dead and that she had aspirated milk. A verbal autopsy was performed, and the cause of death was determined on that basis to be bilateral bronchopneumonia and chronic bronchiolitis (although the child was reported as previously healthy). It is possible that aspiration caused respiratory distress that precipitated death.
- A 10 month-old Mexican male in study Hib-MenCY-TT-011 with history of undernutrition and chronic lung disease developed pneumonia 77 days post-3rd dose of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with respiratory distress and refusing to eat and was evaluated by the nutrition department. At home, he continued with respiratory distress and developed malaise and fever. He was brought to the hospital 4 days after symptom onset, where he was nebulized without improvement. He then became cyanotic. He was hospitalized for pneumonia and intubated that day. The day after hospitalization, sepsis, gastrointestinal bleeding, and anemia were diagnosed, as well. Stool culture showed *Pseudomonas aeruginosa*, and chest x-rays showed upper right infiltrate and hyperinflation of the lungs. The child died on day 9 of the illness. The death certificate is reported to have stated the cause of death as sepsis, gastrointestinal bleeding, anemia, pneumonia, and chronic lung disease.
- A 13 month-old U.S. female in study Hib-MenCY-TT-010 died 29 days post-4th dose of Hib-MenCY-TT and PCV7 and post-1st dose of MMR and V due to trauma suffered during a motor vehicle accident. She was pronounced dead at the scene of the accident.

Given the nature of these children's deaths and timing in relationship to vaccination, the clinical reviewer concurred with the assessment that the deaths were not related to vaccination.

Among the approximately 1290 Hib-MenCY-TT recipients in study MenACWY-TT-057, 4 deaths were reported. Two subjects died of SIDS, one subject died of leukemia, and one subject died of Hemolytic Uremic Syndrome and septic shock. The investigator considered one of the deaths due to SIDS as causally related to vaccine. However, as the death occurred 89 days after vaccination, and the child received concomitant vaccines, the clinical reviewer's opinion is that it is difficult to attribute the death to Hib-MenCY-TT. There were no deaths reported among the approximately 258 Hib subjects in the study.

10.3.2 Serious Adverse Events

Review of the safety data on serious adverse events from the submitted studies raised no important safety concerns.

Details of SAEs across doses 1 – 4 in the pivotal studies were provided above. Across studies Hib-MenCY-TT-001, -005, -007, -009, and -011, at least one SAE occurring within the 31-day post-vaccination period was reported by 1.8% of subjects in the Hib-MenCY-TT group and 2.1% of subjects in the Hib group. SAEs reported within this period with a frequency of > 0.1% in either group included bronchiolitis, gastroenteritis, and bronchopneumonia. Nervous system disorder SAEs were reported in 4 subjects in each group: in the Hib-MenCY-TT group, 1 case each of epilepsy, intracranial hemorrhage, hypotonic-hyporesponsive episode, and nystagmus; in the Hib group, 1 case of febrile seizure, 2 cases of infantile spasms, and 1 case of nystagmus. There were 2 cases of pyelonephritis, both in the Hib-MenCY-TT group, while urinary tract infections were reported in 10 Hib-MenCY-TT subjects (0.1%) and 1 Hib recipient (0.0%). Across studies Hib-MenCY-TT-005, -007, -009, and -011, at least one SAE occurring from Day 0 after dose 1 through the day preceding administration of dose 4 was reported by 4.8% of Hib-MenCY-TT participants and 5.0% of Hib recipients. SAEs reported during this period with greater than 0.5% frequency in either group included: bronchiolitis (0.9% Hib-MenCY-TT subjects, 0.7% Hib subjects) and gastroenteritis (0.8% in both groups). Nervous system disorder SAEs were reported in 20 Hib-MenCY-TT recipients (0.27%) and 10 Hib participants (0.37%). These included: arachnoid cyst [no Hib-MenCY-TT subjects, 1 Hib subject (0.0%)], cerebellar ataxia [1 Hib-MenCY-TT subject (0.0%) and no Hib subjects], convulsion [3 Hib-MenCY-TT subjects (0.0%), no Hib subjects], depressed level of consciousness [no Hib-MenCY-TT subjects, 1 Hib subject (0.0%)], dyskinesia [no Hib-MenCY-TT subjects, 1 Hib subject (0.0%), epilepsy [3 Hib-MenCY-TT subjects (0.0%) and no Hib subjects], febrile seizures [8 Hib-MenCY-TT subjects (0.1%) and 3 Hib subjects (0.1%)], intracranial hemorrhage [1 Hib-MenCY-TT subject (0.1%) and no Hib subjects], hypotonia [1 Hib-MenCY-TT subject (0.1%) and no Hib subjects], hypotonic-hyporesponsive episode [1 Hib-MenCY-TT subject (0.1%) and no Hib subjects], infantile spasms [1 Hib-MenCY-TT subject (0.0%) and 2 Hib subjects (0.1%)], and nystagmus [1 subject in each group (0.1%)]. There were no reported cases of Guillain-Barre syndrome.

Across studies Hib-MenCY-TT-006, -008, -010, and -012, at least one SAE occurring within the 31-day post-vaccination period after dose 4 was reported by 0.5% of subjects in each treatment group. All events were reported with frequency $\leq$ 0.1%. One Hib-MenCY-TT recipient had a febrile seizure. No other nervous system disorder SAEs were reported during this time period. One Hib-MenCY-TT recipient had idiopathic thrombocytopenic purpura (ITP) 14 days post-vaccination. The event resolved 53 days later. The investigator considered the event to be unrelated to Hib-MenCY-TT, V, and PCV7 but considered the event to be associated with either a virus or the MMR vaccine. Urinary tract infection as an SAE was reported in one Hib

participant. From day 0 after dose 4 through the end of the ESFU period, at least one SAE was reported in 2.5% of Hib-MenCY-TT subjects and in 2.0% of the Hib participants. All SAEs were reported with a frequency of ≤ 0.2% except gastroenteritis, which was reported in 0.7% of Hib-MenCY-TT subjects and 0.5% of Hib subjects. Nervous system disorder SAEs were reported in 13 Hib-MenCY-TT recipients (0.20%) and 4 Hib recipients (0.18%). The reported events were: ataxia [1 case (0.0%) in each group], seizure [2 Hib-MenCY-TT participants (0.0%) and 1 Hib subject (0.0%)], febrile seizure [10 Hib-MenCY-TT subjects (0.2%) and 2 Hib subjects (0.1%)]. There were no reports of Guillain-Barre syndrome. One Hib-MenCY-TT recipient developed ITP 58 days post-vaccination. The event was unresolved at the time of reporting. One Hib-MenCY-TT participant had Henoch-Schonlein purpura (HSP) reported as an SAE 171 days after dose 4. The event resolved after 12 days. In the latter 2 cases, the investigator considered the events as unrelated to vaccination.

All submitted SAE data from study MenACWY-TT-057 were blinded as to treatment group, except for those resulting in death, which are mentioned above.

Pooled studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011:

Table 42: Percentages of subjects with SAEs, NOCD, rash, ER visits occurring after any of the first 3 doses from day 0 through day 30 after dose 3 and from day 0 through the ESFU, Primary Total Vaccinated Cohort

AE category	Time period	HibMenCY N = 6414				Hib N = 2157				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI			95% CI	
		n	%	LL	UL	N	%	LL	UL	RR	LL	UL
≥ 1 AE	0 - 30	975	15.2	14.3	16.1	334	15.5	14.0	17.1	0.98	0.90	1.08
	0 - ESFU	1409	22.0	21.0	23.0	487	22.6	20.8	24.4	0.98	0.91	1.05
SAE	0 - 30	173	2.7	2.3	3.1	57	2.6	2.0	3.4	1.02	0.82	1.27
	0 - ESFU	283	4.4	3.9	4.9	98	4.5	3.7	5.5	0.97	0.82	1.15
NOCD	0 - 30	143	2.2	1.9	2.6	49	2.3	1.7	3.0	0.99	0.78	1.25
	0 - ESFU	229	3.6	3.1	4.1	77	3.6	2.8	4.4	1.00	0.83	1.21
Rash	0 - 30	621	9.7	9.0	10.4	209	9.7	8.5	11.0	1.00	0.89	1.12
	0 - ESFU	856	13.3	12.5	14.2	288	13.4	11.9	14.9	1.00	0.91	1.10
ER visit	0 - 30	259	4.0	3.6	4.5	91	4.2	3.4	5.2	0.96	0.81	1.15
	0 - ESFU	266	4.6	4.1	5.2	102	5.3	4.3	6.4	1.00	0.87	1.14

Source: Modified from Tables 26 and 27, Hib-MenCY-TT-011 CSR

From day 0 through day 30, 22.0% and 22.6% of subjects in the Hib-MenCY-TT and Hib groups, respectively, reported at least one symptom within one of the specified categories. At least one SAE was reported for 1.8% and 1.9% of the subjects in the Hib-MenCY-TT and Hib groups, respectively. Two SAEs were assessed by the investigator to be related to vaccinations: 2 subjects in Hib-MenCY-TT-009 were hospitalized for pyrexia on the day of the first dose of Hib-MenCY-TT, PCV7, and DTaP-HBV-IPV which lasted for 3 days; both subjects recovered following maximum temperatures of 103.3°F rectal and 103.0°F axillary.

From day 0 through the ESFU, the percentage of subjects with an SAE, NOCD, rash, or ER visit was similar between groups. The following AEs were statistically higher in the Hib-MenCY-TT group, although the incidence was ≤ 0.9%: bronchiolitis (SAE), urinary tract infection (SAE), dry skin (rash), food allergy (NOCD), viral gastroenteritis (ER visit), head injury (ER visit). The following AEs were statistically higher in the Hib group, although the incidence was ≤ 0.6%: vomiting (SAE), influenza (SAE), bronchopneumonia (SAE), developmental delay (NOCD), bronchial hyperactivity (NOCD), abnormal feces (ER visit), acute sinusitis (ER visit), croup (ER visit), pharyngitis (ER visit), arthropod bite (ER visit), and hair-thread tourniquet syndrome (ER visit). Differences between incidences in the Hib-MenCY-TT and Hib groups did not vary significantly according to co-vaccination of DTaP-HBV-IPV, PCV7, influenza, and rotavirus vaccines, based on results of logistic regressions.

In the Pooled Primary Total Vaccinated cohort, during the ESFU, 283 Hib-MenCY-TT subjects (4.4%) reported a combined total of 386 SAEs, and 98 Hib subjects (4.5%) reported a combined total of 132 SAEs. Infectious processes accounted for 252/386 SAEs in the Hib-MenCY-TT group and 87/132 SAEs in the Hib group and included abscess, bronchiolitis, bronchitis, pneumonia, cellulitis, croup, gastroenteritis, Group B streptococcal sepsis, HIV infection, influenza, viral meningitis, nasopharyngitis, otitis media, pharyngitis, pyelonephritis, pertussis, septic shock, sinusitis, tonsillitis, tracheitis, typhoid fever, upper respiratory tract infection, varicella, viral infection, and urinary tract infection. There was a case imbalance in urinary tract infections in these studies, with 12 MedDRA-coded urinary tract infections reported as SAEs in the Hib-MenCY-TT subjects (0.2%) and 1 reported in the Hib subjects (0%); this imbalance was not found in the overall safety database. CBER requested additional information about these cases, including identification of cases with positive urine cultures and cases of sterile pyuria and screening for presence of symptoms of Kawasaki disease. Review of this information did not raise concern for Kawasaki disease. In this same cohort, during the period from day 0 after dose 1 through day 30 after dose 3, 113 Hib-MenCY-TT subjects (1.8%) reported 146 SAEs, and 41 Hib subjects (1.9%) reported 54 SAEs. Infectious processes accounted for 97/146 and 39/54 SAEs in the Hib-MenCY-TT and Hib groups, respectively.

In the Pooled Primary Total Vaccinated cohort, during the ESFU, 229 Hib-MenCY-TT subjects (3.6%) reported 287 NOCDs, and 77 Hib subjects (3.6%) reported 86 NOCDs. The most common NOCD was eczema in both groups (1.6% in Hib-MenCY-TT and 1.4% in Hib). Bronchial hyperreactivity was reported in 0.2% of Hib-MenCY-TT recipients and 0.5% of Hib participants. Asthma was reported in 0.4% of participants in both groups. All other NOCDs were reported in ≤ 0.3% of subjects. No analysis of NOCDs during the 31 days post-vaccination was performed on the pooled total vaccinated cohort for studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011.

During the ESFU, in the Pooled Primary Total Vaccinated cohort, 856 Hib-MenCY-TT subjects (13.3%) reported 983 episodes of rash, while 288 Hib subjects (13.4%) reported 328 rash events. The majority of events were coded as “rash” (306/983 events in the Hib-MenCY-TT group and 92/328 events in the Hib group). The next most frequent rashes reported were diaper dermatitis and eczema, reported in 2.2% and 3.3% of Hib-MenCY-TT participants and in 2.4% and 3.4% of Hib recipients. All other rashes were reported in ≤ 1.3% of subjects. Urticaria was reported in 49 Hib-MenCY-TT recipients (0.8%), and 18 Hib participants (0.8%). Petechiae were reported once in each group. Purpura was reported in 2 subjects in the Hib-MenCY-TT group, both from study Hib-MenCY-TT-009, one of whom had Henoch-Schonlein Purpura (HSP). The child with purpura presented with cough and congestion and was noted to have 20 – 30 non-palpable purpura on physical exam 26 days after dose 2; the rash resolved after 9 days and was grade 1 in intensity. By report, the subject’s platelet count was normal. The subject with HSP developed it

67 days after dose 3, with resolution after 41 days. No history of preceding illness was provided. No analysis of rash during the 31 days post-vaccination was performed on the pooled total vaccinated cohort for studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011.

In the Pooled Primary Total Vaccinated cohort, during the ESFU, 415 Hib-MenCY-TT subjects (6.5%) reported 663 AEs resulting in ER visits, while 141 Hib subjects (6.5%) reported 212. The most frequently reported AEs resulting in an ER visit were otitis media (0.9% in Hib-MenCY-TT and 0.7% in Hib), bronchiolitis (0.7% in each group), upper respiratory tract infections (0.8% in Hib-MenCY-TT and 0.6% in Hib), pyrexia (0.8% and 0.7% in Hib-MenCY-TT and Hib, respectively), gastroenteritis (0.6% in Hib-MenCY-TT and 0.8% in Hib), viral infection not otherwise specified (0.4% in Hib-MenCY-TT and 0.5% in Hib), and pneumonia (0.3% per group). All other AEs resulting in ER visits occurred in $\leq$ 0.2% of subjects in both groups. No analysis of AEs resulting in ER visits during the 31 days post-vaccination was performed on the pooled total vaccinated cohort for studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011.

Sixteen fatal SAEs were reported over doses 1 – 3 in Hib-MenCY-TT-009 and -011, 10 in the Hib-MenCY-TT group and 6 in the Hib group. The investigator did not determine any of these deaths to be vaccine-related. Six of the sixteen total deaths were attributed to sudden infant death syndrome, 4 in the Hib-MenCY-TT group and 2 in the Hib group. Five of the sixteen total deaths were attributed to pneumonia or bronchopneumonia, 2 in the Hib-MenCY-TT group and 3 in the Hib group; one of these deaths in the Hib group was co-attributed to congestive heart failure. All deaths occurred 10 – 89 days after vaccination, and 11 of the 16 deaths occurred within the 30 day study interval after each vaccine dose.

Pooled studies Hib-MenCY-TT-010 and Hib-MenCY-TT-012:

Table 43: Percentage of subjects in studies Hib-MenCY-TT-010 and Hib-MenCY-TT-012 with at least one symptom, SAE, NOCD, rash, or ER visit post-dose 4 from Day 0 through Day 30 and from Day 0 through the ESFU, Fourth dose Total Vaccinated Cohort

AE category	Time period	HibMenCY N = 5779				Hib N = 1933				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI			95% CI	
		n	%	LL	UL	N	%	LL	UL	RR	LL	UL
≥ 1 AE	0 - 30	419	7.3	6.6	7.9	146	7.6	6.4	8.8	0.96	0.84	1.10
	0 - ESFU	846	14.6	13.7	15.6	299	15.5	13.9	17.2	0.95	0.87	1.05
SAE	0 - 30	24	0.4	0.3	0.6	9	0.5	0.2	0.9	0.89	0.51	1.63
	0 - ESFU	119	2.1	1.7	2.5	36	1.9	1.3	2.6	1.11	0.85	1.46
NOCD	0 - 30	44	0.8	0.6	1.0	17	0.9	0.5	1.4	0.87	0.58	1.33
	0 - ESFU	135	2.3	2.0	2.8	51	2.6	2.0	3.5	0.89	0.71	1.13
Rash	0 - 30	309	5.3	4.8	6.0	98	5.1	4.1	6.1	1.05	0.90	1.25
	0 - ESFU	492	8.5	7.8	9.3	176	9.1	7.9	10.5	0.94	0.83	1.06
ER visit	0 - 30	77	1.3	1.1	1.7	38	2.0	1.4	2.7	0.68	0.51	0.91
	0 - ESFU	266	4.6	4.1	5.2	102	5.3	4.3	6.4	0.88	0.75	1.04

Source: Modified from Synopsis Tables 3 and 4, Hib-MenCY-TT-012 CSR

During the period from day 0 through the end of the ESFU, there were no statistically significant differences between groups in terms of the total number of adverse events reported overall, percentage of SAEs, NOCD, rash, and AEs leading to ER visits. Rash was the most frequently reported AE category, occurring in 8.5% and 9.1% of subjects in the Hib-MenCY-TT and Hib groups, respectively during the ESFU. During the 31 days post-4th dose, the only AE category in which there was a statistical imbalance was in the category of AEs resulting in ER visits, which occurred in a greater percentage of Hib-MenCY participants (1.3%) compared with Hib recipients (2.0%), with a relative risk of 0.68 ($p = 0.0092$). Results of analyses using the Pooled Fourth Dose ATP Cohort for Safety were similar. Overall, more AEs were reported among subjects in the U.S. and Australia compared to Mexico. However, the differences between the Hib-MenCY-TT and Hib groups did not vary across countries.

In the Pooled Fourth Dose Total Vaccinated cohort for Hib-MenCY-TT-010 and -012, during the ESFU, 119 Hib-MenCY-TT subjects (2.1%) reported a combined total of 150 SAEs, and 36 Hib subjects (1.9%) reported a combined total of 46 SAEs. Infectious processes accounted for 86/150 SAEs in the Hib-MenCY-TT group and 29/46 SAEs in the Hib group and included abscess, bronchiolitis, pneumonia, gastroenteritis, cellulitis, croup infection, erysipelas, folliculitis, influenza, osteomyelitis, otitis media, tracheitis, urinary tract infection, and upper respiratory tract infection. Among the SAEs were 1 occurrence of Henoch-Schonlein purpura and 2 occurrences of urticaria, all in the Hib-MenCY-TT group. The occurrence of Henoch-Schonlein and 1 of the occurrences of urticaria were discussed previously, reported among the Hib-MenCY-TT-012 unpooled subjects. During the 31 days post-4th dose, 24 Hib-MenCY-TT subjects (0.4%) reported 30 SAEs, and 8 Hib subjects (0.4%) reported 12 SAEs. Infectious processes accounted for the majority of SAEs (14/24 in Hib-MenCY-TT subjects and 7/12 in Hib subjects) and included viral infection, pneumonia, gastroenteritis, cellulitis, bronchiolitis, otitis media, reactive airway disease, and abscess.

In the Pooled Fourth Dose Total Vaccinated cohort, during the ESFU, 135 Hib-MenCY-TT subjects (2.3%) reported 166 NOCDs, and 51 Hib subjects (2.6%) reported 56 NOCDs. The most common NOCD in both treatment groups was asthma, reported in 0.5% and 0.6% of Hib-MenCY-TT and Hib recipients, respectively. Ezcema was reported in 0.4% and 0.3% of Hib-MenCY-TT and Hib subjects, respectively, and food allergy occurred in 0.3% of Hib participants. All other NOCDs were reported in $\leq$ 0.2% of subjects. During the 31 days post-4th dose, 40 Hib-MenCY-TT subjects (0.8%) reported 44 NOCDs, and 16 Hib subjects (0.9%) reported 18 NOCDs. Eczema was the most commonly reported NOCD during this period, reported in 8 Hib-MenCY-TT recipients and 3 Hib participants, or 0.2% in both groups. Pyelonephritis was reported as a NOCD in 1 subject, in the Hib-MenCY-TT group. Similar results were found in analyses based on the Fourth Dose ATP for safety cohort.

During the ESFU, in the Pooled Fourth Dose Total Vaccinated cohort, 492 Hib-MenCY-TT subjects (8.5%) reported 535 episodes of rash, while 176 Hib subjects (9.1%) reported 198 rash events. The majority of events were coded as "rash" (243/535 events in the Hib-MenCY-TT group and 102/198 events in the Hib group). Urticaria was reported in 49 Hib-MenCY-TT recipients (0.8%), and 19 Hib participants (1.0%). Henoch-Schonlein purpura was reported in one Hib-MenCY-TT recipient, discussed in the above section on analyses on unpooled Hib-MenCY-TT-012 data. Purpura was reported twice in the Hib-Men-CY-TT group. Four episodes of petechiae occurred in Hib-MenCY-TT participants. Erythema multiforme was reported in one Hib-MenCY-TT subject. In the 31-day post-4th dose period, 269 Hib-MenCY-TT subjects (5.2%) reported 284 episodes of rash, and 87 Hib subjects (5.0%) reported 92 episodes of rash. Again, "rash" was the most common diagnosis. Similar results were found in analyses based on the Fourth Dose ATP for safety cohort.

In the Pooled Fourth Dose Total Vaccinated cohort, during the ESFU, 266 Hib-MenCY-TT subjects (4.6%) reported 84 AEs resulting in ER visits, while 102 Hib subjects (5.3%) reported 25. In both groups, otitis media and pyrexia were the most frequently reported AE requiring a visit to the ER (0.6% and 0.4% in the Hib-MenCY-TT group and 0.8% and 0.3% in the Hib group), followed by bronchiolitis, gastroenteritis, upper respiratory tract infection, and febrile convulsion (all reported in 0.3% Hib-MenCY-TT participants and 0.2% - 0.4% of Hib recipients, respectively). All other AEs resulting in ER visits occurred in $\leq$ 0.1% of subjects in both groups. During the 31 day post-4th vaccination period, 77 Hib-MenCY-TT subjects (1.3%) reported 111 AEs resulting in ER visits, while 38 Hib subjects (2.0%) reported 49 AEs leading to ER visits. Otitis media was the most commonly reported AE resulting in an ER visit, occurring in 0.2% and 0.4% of Hib-MenCY-TT and Hib participants, respectively. All other AEs occurred in $\leq$ 0.2% of subjects.

One death was reported in the Pooled Fourth Dose Total Vaccinated Cohort, a child in study Hib-MenCY-TT-010 who died from multiple injuries in an automobile accident 29 days post-vaccination with Hib-MenCY-TT.

Pooled safety analyses across four doses for studies Hib-MenCY-TT-009, Hib-MenCY-TT-010, Hib-MenCY-TT-011, and Hib-MenCY-TT-012:

In response to CBER's request, the applicant provided safety analyses across the observation period of the four doses.

The Pooled Total Vaccinated Cohort from studies Hib-MenCY-TT-009 – Hib-MenCY-TT-012 included 8571 subjects (6414 in the Hib-MenCY-TT group and 2157 in the Hib group); 301 subjects from the non-compliant center were excluded. The Pooled Total Vaccinated Cohort with ESFU included 7986 subjects (5985 Hib-MenCY-TT recipients and 2001 Hib participants).

Table 44: Percentage of subjects in studies Hib-MenCY-TT-009, Hib-MenCY-TT-010, Hib-MenCY-TT-011, and Hib-MenCY-TT-012 with at least one symptom, SAE, NOCD, rash, or ER visit post-dose 4 from Day 0 through Day 30 and from Day 0 through the ESFU, Fourth dose Total Vaccinated Cohort

AE category	Time period	HibMenCY N = 6414				Hib N = 2157				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI			95% CI	
		n	%	LL	UL	n	%	LL	UL	RR	LL	UL
SAE	0 - 30	135	2.1	1.8	2.5	49	2.3	1.7	3.0	0.93	0.66	1.31
	0 - ESFU	388	6.0	5.5	6.7	130	6.0	5.1	7.1	1.00	0.82	1.23
NOCD	0 - ESFU	341	5.3	4.8	5.9	120	5.6	4.6	6.6	0.96	0.78	1.19
Rash	0 - ESFU	1209	18.8	17.9	19.8	416	19.3	17.6	21.0	0.98	0.88	1.10
ER visit	0 - ESFU	613	9.6	8.8	10.3	215	10.0	8.7	11.3	0.96	0.82	1.13

Source: Supplements 12 – 16, 9-10-11-12-report body.pdf, pages 68, 72, 79, 83, 85

Included in the SAEs were 1 report of erythema multiforme, 1 report of Henoch-Schonlein Purpura (HSP), 1 report of idiopathic thrombocytopenic purpura (ITP), and 2 reports of urticaria, all in Hib-MenCY-TT recipients. There were no such cases among Hib participants. There was one report of viral meningitis in a Hib recipient. There were no reported cases of bacterial meningitis among the SAEs. "Convulsion" was reported in 5 Hib-MenCY-TT subjects and 2 Hib subjects (0.1% each), while "febrile convulsion" was reported in 14 Hib-MenCY-TT recipients and 5 Hib participants (0.2% each). Epilepsy was reported in 1 Hib-MenCY-TT participant.

Intracranial hemorrhage, hemorrhagic infarction, and hypotonia were each reported in 1 Hib-MenCY-TT subject (the first two events occurred in 1 subject). SAEs reported in > 0.5% of subjects in either group were bronchiolitis (1.0% of Hib-MenCY-TT subjects and 0.7% of Hib recipients), bronchopneumonia (0.3% of Hib-MenCY-TT recipients and 0.6% of Hib participants), and gastroenteritis (1.3% of Hib-MenCY-TT and Hib subjects). The above-mentioned report of HSP occurred in an 18 month-old Mexican male in study Hib-MenCY-TT-012 6 months post-4th dose of Hib-MenCY-TT, MMRII, V, and PCV7. He presented with fever (38°C), sore throat, and petechial rash on the head and arms. He was hospitalized and received dipyrone, dexamethasone, penicillin, naproxen, prednisolone, and amoxicillin/clavulanic acid. The event resolved day 12. The child with ITP reported as a SAE was a 13 month-old U.S. male in study Hib-MenCY-TT-010 who developed ITP 14 days post-4th doses of Hib-MenCY-TT and PCV7, 1st doses of MMRII and V. He was hospitalized the day he presented and found to have a platelet count of 2300mm^3. On further review, the platelet count was reported as 16000mm^3. He received immunoglobulin and was discharged the next day. The ITP resolved on day 53. One reported case of urticaria occurred in a 15 month-old female in study Hib-MenCY-TT-012 approximately 3 months post-4th dose of Hib-MenCY-TT, MMRII, V, and PCV7 and approximately 2 months post-dose 1 of Fluzone and 1 month post-dose 2 of Fluzone. She had a history of food and drug allergies and became ill after ingesting fish, presenting with generalized erythematous papules and swelling in both hands. The event resolved day 4. The other reported case of urticaria occurred in a 15 month-old Mexican female in study Hib-MenCY-TT-010 who developed symptoms 95 days post-4th doses of Hib-MenCY-TT and PCV7 and post-1st doses of MMR and V, and approximately 9 and 8 months post-1st and 2nd doses of Fluzone. She presented with erythematous papules on both hands and legs with itching; these increased over a few days and rhinorrhea, cough, and fever began. A physician referred her to the ER, where she was found to have erythematous plaques surrounded by urticarial flare in the face, trunk, extremities, and buttocks, with periorbital swelling. The also found her to have sore throat and tonsillar swelling, so they diagnosed urticaria and hospitalized her. The event resolved on day 18. The child with erythema multiforme was a 9 month-old Mexican female who presented with polymorphous erythema and "spots and welts disseminate from both arms to thorax and abdomen" 95 days post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was treated with topical colloidal plasma expander solution and another unspecified medication without improvement, and she was hospitalized. Target lesions were noted. She received hydrocortisone and loratadine. She was improving by day 3.

There were 14 reports of urinary tract infection (UTI) or *Escherichia* urinary tract infection among Hib-MenCY-TT subjects (0.2%) and 1 report among Hib recipients (0.0%). Pyelonephritis was reported in 4 Hib-MenCY-TT participants (0.1%) and 1 Hib subject (0.0%). Initially, many SAE narratives did not include information regarding urine culture results. Based on review of additional information provided by the applicant, it seems unlikely that these children had Kawasaki disease presenting as sterile pyuria. Additional details regarding these reports of UTI and pyelonephritis follow and are based on SAE narratives provided in the BLA and on further information requested from the applicant:

- A 2-month old U.S. female in study Hib-MenCY-TT-009 developed UTI 4 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She had fever to 40.1°C 2 days and increased irritability 3 days post-vaccination, then presented to the ER with vomiting and diarrhea 4 days post-vaccination. She was hospitalized, treated with ceftriaxone and gentamicin, and was reported to have recovered on day 6 (10 days post-vaccination). A catheterized urine specimen demonstrated 30 – 40 white blood cells (WBCs) per high power field (hpf) on urinalysis and > 100,000 colony forming units (CFUs)/mL of *E. coli* on urine culture. Vesicoureterogram was negative. Presence or absence of symptoms

suggestive of Kawasaki disease was not specified. However, given the positive urine culture, it is most likely that the pyuria was due to UTI.

- A 2-month old U.S. female in study Hib-MenCY-TT-009 developed UTI 2 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She presented with fever of 40 C and was hospitalized. She received ceftriaxone, cefixime, and amoxicillin. The event resolved the next day. Catheterized urine for urinalysis demonstrated 10 – 20 WBCs/hpf and urine culture positive for > 100,000 CFUs/mL of *E. coli*. Duration of fever was unavailable. Absence of lymphadenopathy was noted. Presence or absence of other symptoms suggestive of Kawasaki disease was not documented. Given the positive urine culture, UTI is the most reasonable explanation for pyuria.
- A 3-month old Australian female in study Hib-MenCY-TT-009 developed fever 21 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. Four days later (25 days post-vaccination), she was hospitalized and found to have 200 WBCs/hpf on urinalysis (clean catch). Blood and urine cultures were positive for *Escherichia coli*. She was treated with amoxicillin and gentamicin, then discharged on bactrim. Renal ultrasound and cystourethrogram were normal. Timing of resolution is unclear. Despite the fact that the method of collecting the urine specimen was clean catch, rather than catheterization, the positive blood culture for the same organism as found in the urine culture increases the likelihood that the *E. coli* in the urine culture was not a contaminant and that this child most likely had a UTI as the cause of pyuria.
- A 5-month old U.S. female in study Hib-MenCY-TT-009 developed fever (40C), cough, nasal congestion, fussiness, and decreased oral intake 22 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was hospitalized and diagnosed with right otitis media, intermittent wheezing, upper respiratory infection, and UTI. Fever lasted for 24 hours. Mild petechial rash was noted on the trunk. Absence of erythema of the lips and oropharynx, swelling, conjunctival symptoms, and enlarged lymph nodes was noted. Presence or absence of lip cracking was not specified. Catheterized urine specimen demonstrated 11 WBCs/hpf, and urine culture was positive for 10, 000 – 100,000 CFUs/mL of *Escherichia coli*. She was treated with ceftriaxone and cefdinir. The event resolved on day 3. Given the positive urine culture, short duration of fever, and noted absence of the majority of symptoms associated with Kawasaki disease, it is reasonable to assume that this child did not have Kawasaki disease and that her UTI and/or fever caused the pyuria.
- A 2-month old U.S. male in study Hib-MenCY-TT-009 developed UTI 28 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with cough, congestion, fever of 40.3°C, heart rate of 200 bpm, and respiratory rate of 45 and was hospitalized. Chest X-ray and cerebrospinal fluid were normal. Catheterized urine specimen demonstrated 0 – 2 WBCs/hpf, and urine culture was positive for > 100,000 CFUs/mL of *Escherichia coli*. He was treated with cefuroxime. Renal ultrasound showed grade 1 hydronephrosis. Voiding cystourethrogram was scheduled at the time of the report. The event resolved on day 49. Rash, peripheral edema, conjunctival symptoms, and lymphadenopathy were noted as absent. The presence or absence of erythema of the lips or oropharynx and lip cracking were not specified. Given the positive urine culture and absence of most symptoms of Kawasaki disease, it is reasonable to assume that this child had UTI and not Kawasaki disease.
- A 5 month-old U.S. male in study Hib-MenCY-TT-009 developed viral illness with rash and diagnosis of urinary tract infection 20 days post-dose 2 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7 and 20 days post-dose 1 of Rotateq. He was hospitalized, found to have 25 – 50 WBCs/hpf on urinalysis, with negative urine culture. He was treated with antibiotics until cultures were negative, and events resolved day 6. Rash was reported as erythema from head to toe, with concentration in the axillary and elbow areas. He was

noted to have an absence of lymphadenopathy. The presence or absence of other symptoms suggestive of Kawasaki disease and information on fever duration were not noted. Catheterized urine showed 25 – 50 WBCs/hpf on urinalysis and no growth on culture. Given that no other Kawasaki symptoms were described, it is reasonable to ascribe the pyuria to fever.

- A 6 month-old U.S. male in study Hib-MenCY-TT-009 with past medical history of urinary tract infection (mentioned below as the 2 month-old U.S. male with viral illness and UTI 8 days post-dose 1) developed UTI 60 days post-dose 2 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with nasal congestion and respiratory symptoms suggestive of reactive airway disease. He was hospitalized and treated with antibiotics. Urine culture was positive for *Escherichia coli*. Renal ultrasound was normal. Event resolved on day 13. Fever was noted, but duration of fever was not available. Facial rash, diagnosed as eczema, was noted. The presence or absence of other symptoms suggestive of Kawasaki disease was not noted. Catheterized urine yielded 0 – 2 WBCs/hpf on urinalysis and a urine culture positive for > 100,000 CFUs/mL of E. coli. This information supported the diagnosis of UTI.
- A 2 month-old U.S. male in study Hib-MenCY-TT-011 developed UTI 8 days post-dose 1 of Hib-MenCY-TT, Infanrix penta, and PCV7. He presented with fever of 39.06C, mild cough, nasal congestion for one day, was found to be irritable, and was admitted for sepsis work up and intravenous antibiotics. During hospitalization, he developed hematuria secondary to a blood clot in the bladder which followed bladder catheterization. He then became anemic. Blood and cerebrospinal fluid cultures were negative. Catheterized urine specimen showed no WBCs/hpf and > 100,000 CFUs/mL of enterococcus. Vesicoureterogram results were not given. Renal ultrasound results reported as resolved hematoma. Event resolved on day 23. Duration of fever was not available. Presence or absence of rash, erythema and/or swelling of the extremities, conjunctival symptoms, erythema and/or cracking of the lips, oral mucosa, and oral pharynx was not specified. Given the positive urine culture, UTI is the most reasonable diagnosis.
- A 12 month-old U.S. female in study Hib-MenCY-TT-009 developed UTI, pneumonia, respiratory syncytial virus (RSV) infection, and otitis media 6 months post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She presented with decreased energy, decreased sleep, and wheezing and was hospitalized. She was afebrile. Chest X-ray showed right middle lobe pneumonia. RSV was positive. An apparently catheterized specimen showed 2 – 5 WBCs/hpf; urine culture was positive for > 100,000 CFUs/mL of *Escherichia coli*. She received cefuroxime and cefdinir, in addition to other treatment. The UTI resolved on day 12. Absence of rash, erythema of the lips and oropharynx, lip cracking, swelling, conjunctival symptoms, and lymphadenopathy was noted. Given the absence of fever and other symptoms suggestive of Kawasaki disease, and the positive urine culture, UTI, rather than Kawasaki disease, is a reasonable cause of pyuria.
- A 7 month-old Mexican female in study Hib-MenCY-TT-011 developed UTI 29 days post-3rd dose of Hib-MenCY-TT, Infanrix penta, and PCV7. She presented with fever and malaise, was hospitalized, and received benzathine penicillin and Bactrim. Method of obtaining urine specimen was not specified. Urinalysis was reported as abnormal, and urine culture was not obtained. The event resolved on day 15. Duration of fever was unavailable. Presence or absence of rash, erythema of the lips and oropharynx, lip cracking, swelling, conjunctival symptoms, and lymphadenopathy was not specified. It is unclear whether "abnormal" urinalysis signifies pyuria, but this would be a reasonable assumption since the child was diagnosed with UTI.
- A 7 month-old Australian male in study Hib-MenCY-TT-009 developed UTI 35 days post-3rd dose of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with fever

and was hospitalized. Blood cultures were negative. Renal ultrasound was normal. He was treated with amoxicillin, ampicillin, gentamicin, and Augmentin. Urine apparently was a bagged specimen and reported as 3+ WBCs; catheterized urine was obtained for culture, which was positive for *E. coli*. The event resolved day 13. Presence or absence of symptoms consistent with Kawasaki disease was not specified. Despite this, given the positive urine culture on a catheterized specimen, UTI is most likely the cause of the pyuria.

- A 3 month-old U.S. male in study Hib-MenCY-TT-011 developed UTI 30 days post-1st dose of Hib-MenCY-TT, Infanrix penta, and PCV7. She presented with fever of 38.9C and was hospitalized. Urine catherization was ordered, but true route of obtaining urine specimen was unknown. Urinalysis showed 10 – 25 WBCs/hpf, and urine culture grew > 100,000 CFUs/mL of *E coli*. Renal ultrasound and voiding cystourethrogram were normal. She received cephalexin, and the event resolved on day 3. Duration of fever was unavailable. Absence of rash and ocular discharge was noted. Presence or absence of erythema, extremity swelling, conjunctival symptoms, erythema and/or cracking of the lips, oral mucosa, and oral pharynx was not specified. Given the short duration of symptoms suggested by resolution in 3 days and the positive urine culture, UTI is the most reasonable explanation for the pyuria.
- A 9 month-old U.S. female in study Hib-MenCY-TT-011 developed UTI and febrile convulsion 81 and 82 days, respectively, post-3rd dose of Hib-MenCY-TT, Infanrix penta, and PCV7. She was diagnosed with UTI 81 days post-vaccination but had not started antibiotics 82 days post-vaccination, when she had a febrile seizure. Temperature was 40.6C and of unknown duration. She was hospitalized and received ceftriaxone, Augmentin, and Septra. Catheterized urine specimen showed 685 WBCs/hpf, and urine culture grew *E. coli*. Colony count was unavailable. Renal ultrasound and voiding cystourethrogram were normal. The UTI resolved on day 14. Presence or absence of rash, erythema/swelling of the extemities, conjunctival symptoms, lymphadenopathy, and erythema of the lips or oropharynx or lip cracking was not specified. Given the positive urine culture, it is reasonable to attribute the pyuria to UTI.
- A 3-month old U.S. female in study Hib-MenCY-TT-009 developed pyelonephritis 19 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She presented with increased respiratory rate and fever, and was hospitalized. Urine culture was positive for *Escherichia coli*. She was treated with ampicillin, gentamicin, and sulfatrim. The subject was reported as recovered on day 29 of the illness. Renal ultrasound was normal.
- A 4-month old U.S. male in study Hib-MenCY-TT-011 developed pyelonephritis 45 days post-dose 1 of Hib-MenCY-TT, Infanrix penta, and PCV7. She presented with fever of 39.8C, rhinorrhea, nasal congestion, and increased sleeping and hospitalized. Blood culture was negative. Urinalysis was positive for bacteria and white blood cells. Urine culture was positive for gram negative bacilli. Renal ultrasound was normal. She was treated with cefotaxime and bactrim. The event resolved on day 3.
- A 3-month old U.S. female in study Hib-MenCY-TT-011 developed pyelonephritis 1 day post-dose 1 of Hib-MenCY-TT, "Infanrix penta", and PCV7. She presented with fever of 39.3 – 39.7C and was hospitalized. Urinalysis showed no bacteria but 1+ gram negative rods. Blood culture was negative. She was treated with cephalexin, and the event resolved day 4.
- A 12 month-old U.S. female in study Hib-MenCY-TT-011 developed pyelonephritis, streptococcal pharyngitis, and dehydration 5 months post-3rd dose of Hib-MenCY-TT, Infanrix penta, and PCV7. She presented to the ER with history of fever for 5 days, irritability, and decreased oral intake. She was hospitalized and received cefotaxime, cefdinir, and cefixime. Urinalysis indicated moderate WBCs, with > 20 WBCs/hpf.

Urine culture was positive for *E. coli*. Renal ultrasound indicated possible pyelonephritis. Voiding cystourethrogram was normal. The event resolved on day 20.

- A 7-month old U.S. male in study Hib-MenCY-TT-009 developed UTI and intussusception 17 days post-dose 3 of Hib, DTaP-HBV-IPV, and PCV7. He presented with fever of 38.9C, cough, congestion, runny nose, vomiting, diarrhea, decreased oral intake, and irritability. He was hospitalized, treated with cefotaxime, cefdinir, and gastrografin enema. Abdominal magnetic resonance imaging (MRI) had shown interrupted colon sign along with a halo sign in the right upper quadrant and mid-abdominal regions. Ultrasound revealed normal blood flow to the intussuscepted intestine. Catheterized urine culture grew > 100,000 CFUs/mL of *Escherichia coli*. The event resolved in 8 days. Fever duration was 24 hours. Rash, erythema of the lips and oropharynx, swelling, conjunctival symptoms, and lymphadenopathy were documented as absent. Presence or absence of lip cracking was not specified. Given the positive urine culture results, it is reasonable to assume this child had a UTI.

In additional, on review of the SAE narratives, several subjects were noted to have pyuria. Details regarding these subjects follow:

- A 2 month-old U.S. male developed viral illness 8 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with fever of 38.1C and was seen in the ER, where septic work-up was initiated. He was given paracetamol and told to return the next day. Four days later, the subject went to the ER and was "found to be febrile" with a documented temperature of 37.1C. Urine culture showed "traces of bacteria", while blood and cerebrospinal fluid cultures were negative, although the laboratory test list gives urinalysis results as "bacteria" and urine culture results as "negative". Renal ultrasound was normal. The child received antibiotics. The event resolved on day 13. Voiding cystourethrogram was normal.
- An 11-month old Mexican female developed febrile seizure 173 days post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7, approximately 4 months and 3 months post-doses 1 and 2, respectively, of Fluzone. She presented with seizure, cyanosis, and fever of 39.5C of unknown duration. She was hospitalized. Urine specimen was obtained by unknown method for urinalysis and demonstrated WBCs too numerous to count and 4+ bacteria. Urine culture was not performed. According to the SAE narrative, a concomitant diagnosis of UTI was given, although not included in the labeling of the SAE. Absence of erythema of the lips and oropharynx, lip cracking, and conjunctival symptoms was specified. Presence or absence of rash, erythema and/or swelling of the extremities and lymphadenopathy was not specified. Given the presence of 1+ epithelial cells in the urinalysis, it is difficult to call this "sterile pyuria"; additionally, there is no negative urine culture to confirm sterile pyuria. The specified absence of many of the symptoms associated with Kawasaki disease is reassuring.
- A 2 month-old U.S. female developed irritability 20 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was hospitalized for suspected sepsis; notably, her twin sister was hospitalized with group B streptococcus neonatal sepsis. Method of obtaining the urine specimen was not specified. Urinalysis showed occult blood and moderate WBCs. Blood and urine cultures were negative. She received ampicillin and cefotaxime and was discharged day 3, when the event was considered resolved. Despite the apparent presence of possible sterile pyuria (or presence of blood in urine, perhaps related to catheterization), Kawasaki disease is unlikely in this case as symptoms resolved by day 3. Presence or absence of other symptoms, including fever, was not mentioned.
- A 9 month–old Mexican female developed gastroenteritis and malnutrition 105 days post-dose 3 of Hib, DTaP-HBV-IPV, and PCV7. She presented with vomiting, diarrhea,

and fever, then had a febrile seizure. She was hospitalized and received dicloxacillin, cefotaxime, and Bactrim. Duration of fever was not available. Presence or absence of rash, erythema of the lips and oropharynx, lip cracking, swelling of the extremities, conjunctival symptoms, and lymphadenopathy was not specified. Urine specimen was obtained by unknown method and showed 28 – 40 WBCs/hpf, 3+ bacteria, and 2+ epithelial cells. The SAE narrative specifies that Bactrim was started for abnormal urinalysis. It is not specified whether a urine culture was performed. The gastroenteritis resolved day 3, and the malnutrition was apparently unresolved 6 months later. The presence of epithelial cells in the urinalysis suggests that the urine specimen was not obtained by catheterization. Given their presence and the lack of a urine culture, it is difficult to view this child as having sterile pyuria; contaminated urine specimen may be likely.

- A 4-month old U.S. male developed viral syndrome and fever to 38.56C 30 days post-dose 1 of Hib, DTaP-HBV-IPV, and PCV7. He had a 2-day history of irrability. He was hospitalized to rule out UTI. Blood culture was negative. Catheterized urine specimen showed 10 – 20 WBCs/hpf; urine culture was negative after 24 hours. Renal ultrasound was normal. He received intravenous antibiotics, and the event resolved on day 4. Absence of erythema of the oropharynx and lymphadenopathy was noted. Presence or absence of rash, erythema of the lips, lip cracking, and conjunctival symptoms was not specified. Total duration of fever was < 3 days. Given the duration of fever, Kawasaki disease is unlikely, and it is reasonable to attribute the pyuria to fever.

Neurological SAEs of interest:

The 3 month old Mexican female in study Hib-MenCY-TT-011 with hemorrhagic infarction, intracranial hemorrhage, peripheral edema, and hypovolemic shock was found without movement, hyporeactive, hypoactive, cold, and refusing to eat 14 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was given paracetamol. She had hypothermia and was found to have absent respiratory effort, bradycardia (60 beats per minute), temperature of 34.5C, and pallor at hospitalization. She was intubated. Her fontanelle was dilated and tense, pupils were 4mm bilaterally without light response, the liver was 1 cm below the right costal margin, and there was a 4 X 3 cm area of edema on the lateral aspect of the left thigh. Chest X-ray showed a mild right infiltrate. Computed tomography (CT scan) showed severe cerebral edema and right hemorrhagic infarct. Blood culture was negative; cerebrospinal fluid was not obtained. She was diagnosed with left upper thigh edema, intracranial hemorrhage, septic shock, pneumonia, and secondary ileus. She was treated with ranitidine, midazolam, dopamine, dobutamine, cefotaxime, amikacin, furosemide, phenytoin, and blood transfusion. On day 8, she was pronounced dead. An autopsy was not performed. Initial white blood count and pH were apparently 28200/mm3 and 7.24, respectively. Activated partial thromboplastin time, factor VIII level, and fibrinogen appear to have been drawn post-transfusion, according to dates. The child had been born by cesarean and received vitamin K at birth. There was no family history of hematologic disease. Sepsis and/or congenital coagulopathy are possible etiologies.

A 12 month-old U.S. male in study Hib-MenCY-TT-009 developed an SAE of cerebellar ataxia 186 days post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He had been evaluated for fever as an outpatient during the previous week and treated with ophthalmic antibiotics; he then presented with new onset “crying spells” followed by “staring spells” of 10 – 20 minutes, “falling down when walking”, and fever of 40.3C. Mild conjunctivitis of the left eye was noted in the ER. Absence of rash and lymphadenopathy was noted. Routine EEG was within normal limits awake and asleep; 12-lead ECG showed normal sinus rhythm; chest x-ray was normal; non-contrast head CT was normal; cerebrospinal fluid culture was negative for bacterial growth and Lyme antigen; nasopharyngeal swab for viral culture was positive for adenovirus. Final

diagnosis was acute cerebellar ataxia, most likely of viral origin, which resolved after 3 days. Given the length of time between vaccination and the event, it is reasonable to assess this event as unrelated to vaccination.

An 18 month-old Mexican male in study Hib-MenCY-TT-012 developed ataxia 6 months post-4th dose of Hib, MMRII, V, and PCV7. He presented with drowsiness and ataxic gait, head contusion (attributed to the ataxic gait) and was brought to the hospital 4 days later, where he as found to have "sore throat, ataxia, staggering and 'reeling' gait". His strength, tone, and reflexes were normal. He was hospitalized and evaluated by a neurologist, who found pupils to be slowly reactive to light. Clonazepam levels were sent but results not provided. The child improved and was discharged day 5.

A 16 month-old Mexican male with past medical history of fractured temporal bone, head injury, and subdural hematoma, developed ataxia 4 months post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7 and 5.5 months and 3.5 months post-vaccination with Fluzone doses 1 and 2. He presented with vomiting, ataxia, "reeling gait", difficulty walking "and laterally of the right side". Four days later, he was taken to the hospital, where he was diagnosed with otitis media and pharyngitis. The child was subsequently evaluated by an otorhinolaryngologist, and neurologist. A head CT was reported as normal. At a neurology appointment 59 days after onset, the neurologist found no ataxia. Subsequent course not provided, but the event apparently resolved day 59.

A 2 month-old Mexican female with family history of seizures in study Hib-MenCY-TT-011 developed nystagmus 1 day post-dose 1 of Hib, Infanrix penta, and PCV7. She presented with abnormal eye movements for 3 – 4 minutes on 3 occasions. She had no fever or other symptoms, and her clinical and neurological exams were reported as normal. She was hospitalized and treated with phenobarbitone. Apparently, the event resolved that day.

A 2 month-old Mexican male in study Hib-MenCY-TT-011 developed nystamus 8 days post-dose 1 of Hib-MenCY-TT, Infanrix penta, and PCV7. The baby presented with abnormal eye movements 6 – 8 days post-vaccination, was less reactive to mother's stimulation, and had increased sleeping. Apparently, clinical and neurological exams were normal. The narrative mentions laboratory evaluations were normal but does not list them, other than the lab results section, which includes ammonia, electrolytes, renal function, and complete blood count. The child was observed in the ER for 17 hours and then discharged. The event resolved the day after onset.

Regarding convulsions/seizures:

- A 4 month-old Mexican male in study Hib-MenCY-TT-009 with family history of seizures and birth history significant for nuchal cord and Apgars of 7/9 developed seizures 39 days post-dose 1 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. He presented with eye rolling, cyanosis, sucking, and generalized tonic posturing. On hospital arrival he was noted to have fever (38C). Three additional seizures occurred. CT scan showed frontal cortex atrophy, thought to be secondary to asphyxia. Lumbar puncture, EEG, and ultrasound were not performed. He was diagnosed as having seizures and treated with phenytoin, diazepam, and phenobarbitone. He was discharged on phenytoin on day 3 and presented the next day with seizure and was hospitalized overnight. The SAE narrative lists "hypoxia" on his birth date, but source of that information is unclear.
- A 5 month-old U.S. male in study Hib-MenCY-TT-009 developed seizure-like activity 54 days post-dose 2 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. The child's

mother was holding him when he had several “jerking episodes” lasting approximately 1 second. The subject cried after each episode. He also had hiccups, possibly at the same time. He had no recent illness, no fevers, no head trauma or vomiting. The subject was attentive after the episode. He was hospitalized for monitoring, during which period no further seizure activity was noted. An EEG was normal. The event resolved the same day. The investigator felt it was unclear but doubtful that the subject had experienced true seizure activity.

- A 5 month-old Mexican male in study Hib-MenCY-TT-011 developed seizures 47 days post-dose 2 of Hib-MenCY-TT, Infanrix penta, and PCV7. He presented with generalized tonic movements (four times) with lip and ocular deviations lasting approximately 30 seconds. Six days later, he had hypotonia, tonic movements in the left arm, sialorrhea, and unconsciousness for 1 minute. He was afebrile. He was hospitalized. An EEG was normal, and the child was discharged on valproic acid, with the event considered ongoing at the time of the report.
- A 4 month-old Mexican female in study Hib-MenCY-TT-011 developed febrile seizure 57 days post-dose 1 of Hib-MenCY-TT, Infanrix penta, and PCV7. She was hospitalized for 16 days, at which point the event was considered resolved. Further details were unavailable.
- A 6 month-old U.S. female in study Hib-MenCY-TT-011 developed 3 seizures 65 days post-dose 2 of Hib-MenCY-TT, Infanrix penta, and PCV7. The child reportedly had no other symptoms. Each seizure lasted 35 – 40 seconds. The mother did not go to the ER for evaluation but contacted the investigator 4 days later. The event was considered to be life-threatening, but it appears that no medical evaluation occurred. The event is termed “febrile convulsion”; the child’s temperature was approximately 37.8C.
- An 11 month-old Mexican female in study Hib-MenCY-TT-009 developed febrile seizure 6 months post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7, approximately 5 months post-dose 1 of Fluzone and approximately 4 months post-dose 2 of Fluzone. She presented with fever of 39.5C and generalized tonic seizures, and cyanosis. She was hospitalized and received Bactim and ceftibuten. No EEG, head CT, or lumbar puncture was performed. Urinalysis obtained by unknown method demonstrated pyuria. No urine culture was performed, but UTI was added to her diagnosis of febrile seizure. The event resolved 2 months later.
- A 9 month-old Mexican female in study Hib-MenCY-TT-011 developed fever of 38.5C, liquid stools, and seizures of 3 minutes duration 115 days post-dose 3 of Hib-MenCY-TT, Infanrix penta, and PCV7. She was hospitalized, and the event resolved the same day.
- An 11 month-old Australian male in study Hib-MenCY-TT-009 with family and personal history of febrile seizures presented with atypical febrile seizure 6 months post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. Upper respiratory tract infection apparently accompanied the fever. He presented with unresponsiveness, fluttering eyes, drooling, and stiffening. He was still unresponsive and twitching on admission and was treated with clonazepam. Approximately 30 minutes later, he had increasing rigidity and received midazolam. Approximately 30 minutes later, he again seized and received midazolam. Outpatient EEG was normal. The seizure event apparently resolved that day.
- A 7 month-old Mexican female developed seizures 41 days post-dose 3 of Hib-MenCY-TT, Infanrix penta, and PCV7. She presented with gastroenteritis and abnormal movements in the right leg, ocular deviation, and then generalized tonic movements. The child was hospitalized. Head CT was performed, but results were not given. Outpatient EEG showed probably partial seizures, and the child was being treated with valproic acid at the time of report.

- A 13 month-old Mexican male in study Hib-MenCY-TT-012 developed febrile seizure 6 months post-dose 3 of Hib-MenCY-TT, Infanrix penta, and PCV7. He presented with fever (38C) and tonic-clonic movements in both upper extremities, with ocular deviation. He was treated with ampicillin for pharyngitis and received ambulatory treatment only. The event apparently resolved that day.
- A 12 month-old Mexican male in study Hib-MenCY-TT-012 developed febrile seizure 3 days post-4th dose of Hib-MenCY-TT, MMRII, V, and PCV7. He presented with fever of 40C and productive cough, then had ocular deviation and generalized tonic-clonic movements with < 1 minute duration. He was evaluated at the hospital and found to have ocular secretions and "sore throat". He was not hospitalized and was treated with penicillin and chloramphenicol for conjunctivitis and pharyngitis. Apparently, the seizure event resolved that day.
- A 14 month-old U.S. female in study Hib-MenCY-TT-012 developed seizure 79 days post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7. He presented with concurrent history of pneumonia and respiratory syncytial virus (RSV), seizure activity of approximately 30 seconds, followed by possible loss of consciousness for approximately 30 seconds. He was irritable and crying in the ER, received ceftriaxone, and was discharged that day. Blood cultures were negative. The pneumonia and RSV were reported as ongoing at the time of the report, while seizures apparently had resolved.
- A 17 month-old Mexican female in study Hib-MenCY-TT-012 developed seizure 5 months post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7 and approximately 2.5 and 1.5 months post-vaccination with doses 1 and 2 of Fluzone. She presented with vomiting, loose stools and fever (39C), then had approximately 2 minutes of generalized tonic clonic movements, for which she was brought to a doctor. She received amikacin, saccharomyces boulardii, and nifuroxazide. Date of resolution was unclear, but the child was not hospitalized.
- A 16 month-old Mexican female in study Hib-MenCY-TT-012 with a family history of febrile seizures developed seizure 4 months post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7 and 2.5and 1.5 months post-vaccination with doses 1 and 2 of Fluzone. One and a half months earlier, she presented with atonic seizures, perioral cyanosis, chewing movements, and sialorrhea of < 1 minute duration. She also had an upper respiratory tract infection, was evaluated as an ouptient, and discharged home without medication. She then had generalized tonic clonic seizures with fever (39C) and was hospitalized overnight approximately 17 days prior to the event described in the SAE narrative. Four months post-vaccination, she had a febrile seizure presenting with atonic seizures and fever (39C), was diagnosed with pharyngitis, and was treated with Bactrim, azithromycin, and phenytoin. She had a normal head CT and EEG. Apparently, she was referred to a neurosurgeon for consultation.
- A 16 month-old U.S. female in study Hib-MenCY-TT-012 developed seizure 4 months post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7. She presented with fever, pain when walking, and a seizure reportedly lasting 1 hour 30 minutes with associated perioral cyanosis. Upon arrival at the hospital, she was noted to be post-ictal, then had another brief generalized seizure lasting < 1 minute. She was hospitalized for observation. The event ended the same day; outpatient EEG was scheduled at the time of report.
- A 15 month-old Mexican male in study Hib-MenCY-TT-012 developed seizure 80 days post-dose 4 of Hib-MenCY-TT, MMRII, V, and PCV7 and approximately 1.5 months and 3 weeks post-vaccination with doses 1 and 2 of Fluzone. Two days prior to the event, he had presented with fever (39C) and cough, was evaluated at a hospital and discharged home. Fever persisted, and on the day of the SAE, the child developed generalized tonic clonic movements and perioral cyanosis with a duration < 1 minute on

nine occasions. He was hospitalized, found to have a "sore throat", had a normal EEG and lumbar puncture, and was discharged on an unspecified day.

- A 2 month-old Mexican female in study Hib-MenCY-TT-011 developed gastroenteritis and febrile seizure 6 days post-dose 1 of Hib, Infanrix penta, and PCV7. She presented with fever (41.5C), crying, hypertonia, ocular deviation, liquid stools, and dehydration, with initial sodium of 150. She was hospitalized and treated with ampicillin and amikacin. Urine and cerebrospinal fluid cultures were negative.
- An 11 month-old U.S. male in study Hib-MenCY-TT-009 with a family history of seizures and with a recent history of upper respiratory infection had fever and 3 episodes of seizure 4 months post-dose 3 of Hib, DTaP-HBV-IPV, and PCV7. Chest x-ray, lumbar puncture, influenza test were performed, and pneumonia was diagnosed. EEG was abnormal, with 3 bursts of sharp dow activity in the bifrontal temporal distribution. Magnetic resonance imaging (MRI) was normal. She was treated with Augmentin and Diastat and discharged on day 3. The child had a follow up appointment with a neurologist and was not started on antiepileptics for the diagnosis of complex febrile seizure.
- A 9 month-old U.S. female in study Hib-MenCY-TT-009 developed influenza 61 days post-dose 3 of Hib, DTaP-HBV-IPV, and PCV7. The child had a history of viral meningitis, described above. She was treated with oseltamivir, experienced vomiting, and was started on ondansetron. On day 7 of the influenza illness, her fever "spiked", and she had a febrile seizure lasting 2 – 3 minutes. She was found to be apneic and severely hypoxic in the ER, was intubated, had an interosseous line placed for rapid fluid recussitation, a right femoral central venous line and right radial artery line placed, and received phenobarbitone, vancomycin, and cefotaxime. Sodium was 127, and her liver function tests were reported as minimally elevated. EEG, CT, MRI, and lumbar puncture were reportedly normal, while chest x-ray showed left pneumonia. Date of resolution was not provided, although the child was discharged day 13.
- A 17 month-old Mexican female in study Hib-MenCY-TT-012 developed seizure 5 months post-dose 4 of Hib, MMRII, V, and PCV7 and 3 days post-vaccination with Fluzone. She presented with 1 day history of fever (39C), generalized tonic-clonic movements, ocular deviation, and vomiting. She was evaluated in the ER the next day and was observed for a few hours. At some point, otitis media was apparently diagnosed. Date of resolution unclear.
- A 16 month-old Mexican female in study Hib-MenCY-TT-012 developed seizure 4 months post-dose 4 of Hib, MMRII, V, and PCV7. She presented with fever (42C), cough, generalized tonic clonic movements, and ocular deviation. She was evaluated, apparently outpatient, returned home, and seized again. The next day, the mother brought the child to the doctor again, where he prescribed unspecified treatment. The child was not hospitalized. Date of resolution not given.

The 4 month-old U.S. male in study Hib-MenCY-TT-009 who developed viral meningitis had onset of fever (>40C) 58 days post-1st dose of Hib, DTaP-HBV-IPV, and PCV7. Cerebrospinal fluid bacterial culture was negative, glucose was 46 mg/dL, protein was 45 mg/dL, and viral culture was positive for enterovirus. The event resolved day 6.

Included in the SAEs were 1 report of erythema multiforme, 1 report of Henoch-Schonlein Purpura (HSP), 1 report of idiopathic thrombocytopenic purpura (ITP), and 2 reports of urticaria, all in Hib-MenCY-TT recipients. There were no such cases among Hib participants. There was one report of viral meningitis in a Hib recipient. There were no reported cases of bacterial meningitis among the SAEs. "Convulsion" was reported in 5 Hib-MenCY-TT subjects and 2 Hib subjects (0.1% each), while "febrile convulsion" was reported in 14 Hib-MenCY-TT recipients

and 5 Hib participants (0.2% each). Epilepsy was reported in 1 Hib-MenCY-TT participant. Intracranial hemorrhage, hemorrhagic infarction, and hypotonia were each reported in 1 Hib-MenCY-TT subject (the first two events occurred in 1 subject). SAEs reported in > 0.5% of subjects in either group were bronchiolitis (1.0% of Hib-MenCY-TT subjects and 0.7% of Hib recipients), bronchopneumonia (0.3% of Hib-MenCY-TT recipients and 0.6% of Hib participants), and gastroenteritis (1.3% of Hib-MenCY-TT and Hib subjects). The above-mentioned report of HSP occurred in an 18 month-old Mexican male in study Hib-MenCY-TT-012 6 months post-4th dose of Hib-MenCY-TT, MMRII, V, and PCV7. He presented with fever (38C), sore throat, and petechial rash on the head and arms. He was hospitalized and received dipyrone, dexamethasone, penicillin, naproxen, prednisolone, and amoxicillin/clavulanic acid. The event resolved day 12. The child with ITP reported as a SAE was a 13 month-old U.S. male in study Hib-MenCY-TT-010 who developed ITP 14 days post-4th doses of Hib-MenCY-TT and PCV7, 1st doses of MMR and V. He was hospitalized the day he presented and found to have a platelet count of 2300mm^3. On further review, the platelet count was reported as 16000mm^3. He received immunoglobulin and was discharged the next day. The ITP resolved on day 53. One reported case of urticaria occurred in a 15 month-old female in study Hib-MenCY-TT-012 approximately 3 months post-4th dose of Hib-MenCY-TT, MMR, V, and PCV7 and approximately 2 months post-dose 1 of Fluzone and 1 month post-dose 2 of Fluzone. She had a history of food and drug allergies and became ill after ingesting fish, presenting with generalized erythematous papules and swelling in both hands. The event resolved day 4. The other reported case of urticaria occurred in a 15 month-old Mexican female in study Hib-MenCY-TT-010 who developed symptoms 95 days post-4th doses of Hib-MenCY-TT and PCV7 and post-1st doses of MMRII and V, and approximately 9 and 8 months post-1st and 2nd doses of Fluzone. She presented with erythematous papules on both hands and legs with itching; these increased over a few days and rhinorrhea, cough, and fever began. A physician referred her to the ER, where she was found to have erythematous plaques surrounded by urticarial flare in the face, trunk, extremities, and buttocks, with periorbital swelling. The also found her to have sore throat and tonsillar swelling, so they diagnosed urticaria and hospitalized her. The event resolved on day 18. The child with erythema multiforme was a 9 month-old Mexican female who presented with polymorphous erythema and “spots and welts disseminate from both arms to thorax and abdomen” 95 days post-dose 3 of Hib-MenCY-TT, DTaP-HBV-IPV, and PCV7. She was treated with topical colloidal plasma expander solution and another unspecified medication without improvement, and she was hospitalized. Target lesions were noted. She received hydrocortisone and loratadine. She was improving by day 3.

10.3.3 Dropouts

Information on study completion for the Hib-MenCY-TT groups is provided in the below table. In studies Hib-MenCY-TT-005/006, -007/008, -009/010, and -011/012 that included an ESFU phase, information on withdrawal from the ESFU phase due to AE/SAE was not collected. In study Hib-MenCY-TT-013, the total vaccinated cohort for Hib-MenCY-TT subjects was 138.

Table 45: Study completion: reasons for drop-out, Hib-MenCY-TT groups

Study	Number of subjects vaccinated	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
Hib-MenCY-TT-001	82	80	0	0	0	1	1	0	0
Hib-MenCY-TT-002	80	80	0	0	0	0	0	0	0
Hib-MenCY-TT-003	78	76	0	1	0	0	0	1	0
Hib-MenCY-TT-004	47	45	0	0	0	0	0	2	0
Hib-MenCY-TT-005	287	262	2	0	0	12	1	7	3
Hib-MenCY-TT-006	236	232	0	0	0	0	0	3	1
Hib-MenCY-TT-007	661	647	3	1	1	2	3	3	1
Hib-MenCY-TT-008	625	623	0	0	0	0	1	0	1
Hib-MenCY-TT-009	3136	2888	7	3	27	93	26	60	32
Hib-MenCY-TT-010	2769	2682	1	0	0	10	1	53	22
Hib-MenCY-TT-011	3278	3114	9	0	14	50	27	55	9
Hib-MenCY-TT-012	3010	2985	0	0	0	0	0	19	6

Source: Modified from Summary of Clinical Efficacy Tables 39, 40

*The total number of subjects vaccinated does not include data from subjects enrolled at one location in the U.S. and participating in studies Hib-MenCY-TT-009/-010 and -011/ -012

10.4 Other Safety Findings

10.4.1 Solicited Local Reactions and General Adverse Events

Across studies, Hib-MenCY-TT was generally no more reactogenic than Hib on the basis of the incidence overall per subject of solicited local and general AEs reported within the 4-day post-vaccination period. Pain was the most frequently reported local AE after doses 1 – 3, occurring in 73.8% of Hib-MenCY-TT recipients and 73.5% of Hib recipients in studies Hib-MenCY-TT-001, -005, -007, and -009. Redness was the most frequently reported local AE after dose 4, reported in 47.8% and 54.9% of Hib-MenCY-TT and Hib recipients, respectively, in studies Hib-MenCY-TT-006, -008, and -010. Irritability was the most frequently reported solicited general AE after doses 1 – 3, reported in 88.7% and 90.0% of Hib-MenCY-TT and Hib subjects, respectively in studies Hib-MenCY-TT-001, -005, -007, and -009. Irritability was also the most frequently reported general AE after dose 4, reported in 57.9% and 61.9% of Hib-MenCY-TT and Hib participants, respectively, in studies Hib-MenCY-TT-006, -008, and -010.

With respect to MMR- and varicella-specific solicited general AEs reported within the 43 day post-vaccination period, there were no reports of meningitis/febrile seizures. The proportions of subjects reporting parotid/salivary gland swelling were 0.3% and 0.0% in the Hib-MenCY-TT and Hib groups, respectively. Fever occurred in just less than half the subjects in both groups, while fever > 39.0C was reported in 16.4% and 15.5% of Hib-MenCY-TT and Hib subjects, respectively. Fever > 40.0C was reported in 1.7% and 1.9% of subjects in these groups. Measles/rubella/varicella-like rash was reported in 25.0% of Hib-MenCY-TT subjects and 22.6% of Hib subjects. Rashes with more than 200 lesions were reported in 3.3% and 2.7% of Hib-MenCY-TT and Hib recipients, respectively.

Across studies Hib-MenCY-TT-001, -005, -007, and -009, unsolicited AEs were reported in 61.9% and 62.5% of Hib-MenCY-TT and Hib subjects, respectively. One Hib-MenCY-TT subject reported pyelonephritis as an unsolicited AE (0.0%). Sixteen Hib-MenCY-TT participants (0.4%) and 7 Hib recipients (0.7%) reported urinary tract infections as unsolicited AEs. An additional 2 Hib-MenCY-TT subjects reported *Escherichia* urinary tract infections. Erythema multiforme was reported in 1 Hib-MenCY-TT recipient. Petechiae were reported in 2 Hib-MenCY-TT subjects (0.0%) and 2 Hib subjects (0.1%). Purpura was reported in 1 Hib-MenCY-TT participant. Urticaria was reported in 9 Hib-MenCY-TT participants (0.2%) and 3 Hib subjects (0.2%). Papular urticaria was reported in 2 Hib-MenCY-TT subjects and 1 Hib subject. Across studies Hib-MenCY-TT-006, -008, and -010, unsolicited AEs were reported in 42.5% and 41.4% of Hib-MenCY-TT and Hib subjects, respectively. ITP was reported in 1 Hib-MenCY-TT recipient. Urinary tract infections were reported as unsolicited AEs in 6 Hib-MenCY-TT and 4 Hib subjects. Petechiae were reported in 2 Hib-MenCY-TT participants. Urticaria was reported in 10 Hib-MenCY-TT subjects (0.3%) and 6 Hib subjects (0.5%). Eczema was reported in 40 (1.1%) Hib-MenCY-TT subjects and 4 (0.3%) Hib subjects.

10.4.2 New onset chronic disease, rash, emergency room visits across doses 1 – 4 in the pivotal studies

The NOCDs included 1 report each of “coronary artery disease”, dystonia, idiopathic thrombocytopenic purpura, and petechiae in a Hib-MenCY-TT subject and 1 report of juvenile arthritis in a Hib participant. Two Hib-MenCY-TT subjects reported urticaria.

Among the Hib-MenCY-TT subjects reporting rash, there were 7 reports of ecchymosis, 3 of erythema multiforme, 2 of Henoch-Schonlein Purpura, 5 of petechiae, 3 of purpura, 92 of urticaria, and 4 of papular urticaria. Among Hib subjects reporting rash, there were 1 of petechiae, 35 of urticaria, and 2 of papular urticaria. Details regarding the reports of purpura

were provided by the applicant as follows. One Hib-MenCY-TT subject in study Hib-MenCY-TT-009 developed purpura 26 days post-dose 2. Concurrent symptoms included cough and congestion. Physical exam included 20 – 30 non-blanching, non-palpable purpura of 2 -3 mm in diameter. The subject was diagnosed with otitis media. A basic metabolic panel and complete blood count were reportedly normal. The purpuric rash resolved after 9 days and was graded as mild. Another Hib-MenCY-TT participant, in study Hib-MenCY-TT-010, developed purpura 103 days post-dose 4. Physical exam reported petechial and purpuric lesions from head to toe in this afebrile child. A complete blood count revealed a white blood cell count of 9.1, a hemoglobin of 11.5, and a platelet count of 276,000. No specific therapy was given, and the grade 1 purpura resolved after 7 days. A Hib-MenCY-TT recipient in study Hib-MenCY-TT-012 developed "petechial purpura" 117 days after dose 4. The subject presented with cough, wheezing, diarrhea, and facial rash. Physical exam noted purpuric/petechial rash on the face and legs. A complete blood count was essentially normal. The child was diagnosed with a viral-associated syndrome and was prescribed albuterol for wheezing, saline drops and bulb suction for nasal congestion, and multivitamins with iron. The grade 1 petechial purpura resolved after 7 days. One Hib-MenCY-TT recipient in study Hib-MenCY-TT-009 developed Henoch-Schonlein Purpura 67 days after dose 3. The child was seen in the ER but not admitted, and is not counted among the SAEs. The child presented with red and violaceous macular lesions that started on the face and spread to all four extremities. No gastrointestinal, joint, or renal symptoms were present at the time of evaluation. A urinalysis was reportedly normal, but the complete blood count was notable for an elevated white blood cell count of ~ 23,000. The child was discharged to home from the ER, and the grade 1 HSP resolved after 41 days.

The reported AEs resulting in ER visits included 1 report of idiopathic thrombocytopenic purpura in a Hib-MenCY-TT recipient, 3 reports of sudden infant death syndrome (SIDS) – 2 in Hib-MenCY-TT subjects and 1 in a Hib subject, 1 report of pyelonephritis in a Hib-MenCY-TT subject, and 19 reports of urinary tract infections – 14 in Hib-MenCY-TT subjects (0.2%) and 5 in Hib subjects (0.2%). There were 2 reports of convulsions and 1 of epilepsy in Hib-MenCY-TT subjects, and 30 reports of febrile convulsions – 22 in Hib-MenCY-TT participants and 8 in Hib subjects. There was 1 report each of erythema muliforme, Henoch-Schonlein Purpura, idiopathic thrombocytopenic purpura, and petechiae among Hib-MenCY-TT subjects. There were 9 Hib-MenCY-TT and 5 Hib recipients with urticaria. The most frequently reported AEs resulting in an ER visit included otitis media (1.5% in the Hib-MenCY-TT group and 1.3% in the Hib group), pyrexia (1.2% Hib-MenCY-TT subjects and 1.0% Hib subjects), and upper respiratory tract infection (1.1% Hib-MenCY-TT recipients and 1.0% Hib participants).

10.4.3 Post-Marketing Experience

There is no post-marketing experience with Hib-MenCY-TT, as it is not licensed anywhere at this time. However, based on post-marketing experience with Hiberix, licensed in Germany in 1996, GSK proposed that the following events be included in the Postmarketing Experience section of the US Prescribing Information for Hib-MenCY-TT: rash, convulsion (with or without fever), hypotonic-hyporesponsive episode, syncope or vasovagal responses to injection, somnolence, apena, urticaria, allergic reactions (including anaphylactic and anaphylactoid reactions), angioedema, extensive swelling of the vaccinated limb, and injection site induration. Based on post-marketing experience with Menitorix (*Haemophilus influenzae* type b polysaccharide conjugated to tetanus toxoid and *Neisseria meningitidis* serogroup C polysaccharide conjugated to tetanus toxoid), licensed in the UK, ----------(b)(4)----------.

10.5 Safety Conclusions

Safety data from the clinical studies in which Hib-MenCY-TT was administered raise no particular concerns about the safety of vaccination with Hib-MenCY-TT. These studies support the safety of Hib-MenCY-TT in children 6 weeks through 18 months of age.

11 Additional Clinical Issues

11.1 Directions for Use

In clinical studies of Hib-MenCY-TT, the lyophilized vaccine and the saline diluent were supplied in separate vials. In all of the clinical studies, Hib-MenCY-TT was administered intramuscularly. The thigh was the protocol-specified site for Hib-MenCY-TT administration.

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

1) Cleanse both vial stoppers. Withdraw 0.6 mL of saline from diluent vial.
2) Transfer saline diluent into the lyophilized vaccine vial.
3) Shake the vial well.
4) After reconstitution, withdraw 0.5 mL of reconstituted vaccine and administer intramuscularly.

The proposed storage and handling instructions specify that:

- Hib-MenCY-TT is available in single-dose vials of lyophilized vaccine, accompanied by vials containing 0.85 mL of saline diluent (packaged without syringes or needles)
- Lyophilized vaccine vials: Store refrigerated between 2° and 8°C (36° and 46°F). Protect vials from light
- Diluent: Store refrigerated or at controlled room temperature between 2° and 25°C (36° and 77°F). Do not freeze. Discard if the diluent has been frozen.
- After reconstitution, administer Hib-MenCY-TT immediately. Do not freeze. Discard if the vaccine has been frozen.

Please refer to the CBER product review of the Hib-MenCY-TT BLA for CBER's assessment of stability data and the acceptability of the proposed directions for storage and handling of Hib-MenCY-TT.

11.2 Dose Regimen

As reviewed in Sections 8, 9, and 10, the available data support vaccination with Hib-MenCY-TT a four dose series of 0.5 ml in children 6 weeks through 18 months of age. In the BLA, GSK did not request an indication for use in any other age groups.

11.3 Special Populations: Pediatrics

Children in the U.S. are recommended to receive vaccines to prevent invasive disease due to *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroup A, C, Y and W-135. The recommended schedules, outlined below, are based on the epidemiology of the diseases.

Infants are recommended to receive the first dose of the Hib vaccination series at 2 months of age (minimum 6 weeks of age) and to complete the vaccination series by 15 months of age. Routine catch-up vaccination in children with delayed Hib vaccination is recommended through age 4 years (before the 5th birthday). Currently, there are 5 US licensed Hib conjugate vaccines (either monovalent or in combination with other recommended vaccines), including 4 that are approved

for use in infants as young as 6 weeks of age and 4 that are approved for use in children as old as 59 months (before the 5th birthday).

Currently, there are two quadrivalent (A, C, Y and W-135) meningococcal conjugate vaccine licensed in the US- one is approved for use in children 9 months of age and older and one is approved for use in children 2 years of age and older. The two peaks of meningococcal disease occur in infancy and adolescence. The majority of meningococcal disease in children < 1 year of age is caused by serogroup B, for which there is no licensed vaccine. The proportion of disease in the U.S. caused by serogroups C and Y is much higher in adolescents. In other words, while infants younger than 1 year of age are at greater risk for meningococcal disease, the amount of vaccine preventable disease in infants is low, and morbidity and mortality is lower in infants compared with other age groups[141]. Therefore, the ACIP recommends *N. meningitidis* vaccination with quadrivalent meningococcal vaccine for all children at age 11 or 12 years, or at age 13 – 18 years if not vaccinated previously; previously unvaccinated first year college students living in dormitories; children ages 2 – 10 years with terminal complement deficiency, anatomic or functional asplenia, and certain other groups at high risk; persons who received the quadrivalent polysaccharide vaccine (MPSV) 5 or more years previously and remain at increased risk for meningococcal disease.

Partial Waiver Justification:

Pediatric age group(s) to be waived:

0- < 6 weeks of age,
19 months – < 5 years of age,
5 years - < 17 years of age

Reason(s) for waiving pediatric assessment requirements:

Children 0-<6 weeks of age:
The product fails to represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age **and** is unlikely to be used in a substantial number of children 0-<6 weeks of age.

Four doses of MenHibrix are required to complete the immunization series. Available data on two Haemophilus b Conjugate Vaccines suggest that neonatal immunization does not provide evidence of substantially earlier or enhanced protection compared with vaccination beginning at 6 weeks of age. 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, DT (Diphtheria and Tetanus Toxoids Adsorbed) Daptacel (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), and an acellular pertussis vaccine.[15]

Children 19 months – <5 years of age:
In children 19 months - < 5 years of age MenHibrix fails to represent a meaningful therapeutic benefit over vaccination with existing vaccines (Haemophilus b Conjugate Vaccine and quadrivalent meningococcal vaccine) **and** is unlikely to be used in this age group.

A booster dose of Haemophilus b Conjugate Vaccine administered in the second year of life completes the ACIP recommended immunization series for Haemophilus b Conjugate Vaccine. Completing the Hib vaccination series with MenHibix in children in this age group whose vaccination is delayed does not offer a benefit over completing the series with licensed Haemophilus b Conjugate Vaccine. There is no universal recommendation for administration of meningococcal vaccine in this age group; however, if vaccination with a meningococcal conjugate vaccine is necessary quadrivalent vaccine is available for use in children >9 m of age.

Children 5-< 17 years of age:
In the pediatric population 5- <17 years of age, MenHibrix fails to represent a meaningful therapeutic benefit over vaccination with existing vaccines **and** is unlikely to be used in this age group.

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, and catch-up vaccination is not recommended generally for children 5 years of age and older.

The ACIP recommends *N. meningitidis* vaccination at age 11 or 12 or at age 13 – 18 years if not vaccinated previously; previously unvaccinated first year college students living in dormitories; children ages 2 – 10 years with terminal complement deficiency, anatomic or functional asplenia, and certain other groups at high risk; persons who received MPSV 5 or more years previously and remain at increased risk for meningococcal disease. Quadrivalent meningococcal vaccine is available for children 9 months to 18 years of age. Thus, administration of the bi-valent meningococcal product in lieu of the quadrivalent offers no meaningful therapeutic benefit and is unlikely to be used.

Based on clinical studies of immunization with Hib-MenCY-TT in children 6 weeks through 18 months of age, an indication for use in children 6 weeks through 18 months of age was presented to the Pediatric Review Committee (PeRC), and the PeRC concurred. Thus, children who have received the first 3 doses in the Hib-MenCY-TT series but have their 12 or 15 month pediatric visit slightly later could receive the 4th dose of Hib-MenCY-TT through 18 months of age.

In summary, a waiver to conduct studies of MenHibrix in children 0 to <6 weeks of age is justified because the product fails to represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is unlikely to be used in a substantial number of children 0 – <6 weeks of age. A waiver to conduct studies of MenHibrix in children 19 months to less than 17 years of age is justified because in these age groups, use of Hib-MenCY-TT is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules, and Hib-MenCY-TT is not likely to be used in a substantial number of patients.

12 Conclusions—Overall

The available safety and immunogenicity data from clinical studies support the approval of Hib-MenCY-TT for the prevention of invasive disease due to *H. influenzae* type b and *N.meningitidis* serogroups C and Y in the proposed age range of 6 weeks through 23 months of age. No evidence of immune interference was observed with concomitant administration of routine childhood immunizations, i.e. DTaP, PCV7, Hepatitis B, MMR, and varicella vaccines. Insufficient data are available to assess the safety and immunogenicity of Hib-MenCY-TT when administered with rotavirus, hepatitis A, and influenza vaccines.

13 Recommendations

13.1 Approval Recommendation

I recommend approval of Hib-MenCY-TT for immunization for the prevention of invasive disease due to *H. influenzae* type b and *Neisseria meningitidis* serogroups C and Y in children 6 weeks through 23 months of age.

13.2 Recommendations on Postmarketing Actions

As recommended by CBER, GSK has committed to conduct a Phase IV trial in the U.S. In the proposed trial, Hib-MenCY-TT will be administered concomitantly with other vaccines that are recommended for U.S. children, specifically Havrix and Rotarix. The planned trial is intended to provide confirmatory evidence of the safety of immunization with Hib-MenCY-TT. GSK expects to initiate the study by October 31, 2013 and to submit the final study report by December 15, 2016.

13.2.1 Clinical Trial Postmarketing Requirement (if applicable)

Review of the clinical data in the BLA did not identify a serious risk related to the use of MenHibrix, a signal of a serious risk related to the use of Menhibrix, or the potential for a serious risk that would require any post-approval studies of MenHibrix under section 901 Title IX of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

13.2.2 Pharmacovigilance Plan

Please refer to the review by the Office of Biostatistics and Epidemiology/Division of Epidemiology for the Hib-MenCY-TT BLA for their assessment and recommendations regarding GSK's pharmacovigilance plan for Hib-MenCY-TT and post-marketing safety surveillance, including use of the Vaccines Adverse Events Reporting System.

13.3 Recommendations Regarding PREA

The PeRC concurred with the recommendation to waive a requirement for studies of Hib-MenCY-TT in pediatric populations 0-<6 weeks of age and 19 months to < 17 years of age. The requirement for pediatric studies in the age group 6 weeks through 18 months of age is fulfilled with this approval.

14 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. Description of the study design of additional studies was incorporated, and the data on solicited adverse events were presented for U.S. subjects from study Hib-MenCY-TT-009/-010, rather than on all subjects in that study, as the review found notable differences between the reported incidences of solicited adverse events in U.S. subjects as compared with Australian and Mexican subjects.

15 References

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