



DEPARTMENT OF HEALTH & HUMAN SERVICES
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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 INDs:**

- IND –(b)(4)-: GSK’s Haemophilus b and Neisseria meningitides Serogroups C and Y – Conjugate (Tetanus Toxoid Conjugate) Vaccine
- IND –(b)(4)-: GSK’s Neisseria meningitides 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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HFM-475

1.1.4 Submission Received by FDA: August 12, 2009**1.2 Product****1.2.1 Proper Name:** Meningococcal Groups C and Y and Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)**1.2.2 Proposed Proprietary Name:** MenHibrix**1.2.3 Product Formulation:** MenHibrix is a lyophilized vaccine of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b, *Neisseria meningitidis* serogroup C capsular polysaccharide (PSC), and *Neisseria meningitidis* serogroup Y capsular polysaccharide (PSY), each covalently bound to tetanus toxoid. Each 0.5 mL dose of MenHibrix contains 2.5 mcg of purified PRP, 5 mcg PSC, and 5 mcg PSY covalently bound to 6.25 mcg of tetanus toxoid (PRP), 5 mcg of tetanus toxoid for PSC, and 5 mcg tetanus toxoid for PSY. Each MenHibrix dose also contains 96.8 mcg of Tris (trometamol)-HCl, 12.6 mg of sucrose, and ≤ 0.72 mcg of residual formaldehyde.**1.3 Applicant:** GlaxoSmithKline 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.**1.6 Dosage Forms and Route of Administration:** MenHibrix is a solution for intramuscular injection (0.5 mL dose) supplied as vials of lyophilized vaccine to be reconstituted with the accompanying saline diluent in ----b(4)-----.

2 Executive Summary

The proposed MenHibrix indication is for active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis* serogroups C and Y. Use of MenHibrix is proposed as a 4-dose primary series in children 6 weeks to 15 months of age. MenHibrix safety, immunogenicity and lot consistency were supported by data from a pivotal immunogenicity study, a large safety trial, six supporting studies and one year antibody persistence data. The studies were conducted in Germany and Belgium, Australia, Mexico, and the United States. The pivotal immunogenicity study was designated as separate studies for infant (Hib-MenCY-TT-009) and toddler dose (Hib-MenCY-TT-010) evaluations. The same terminology was used for large safety trial infant (Hib-MenCY-TT-011) and toddler (Hib-MenCY-TT-012) evaluations.

Effectiveness of MenHibrix was inferred from an evaluation of serum antibody levels for each of the vaccine components, compared to a U.S. licensed Hib vaccine control group. All pre-specified Hib endpoints in the pivotal immunogenicity study were met. The anti-PRP levels of 0.15 mcg/mL and 1.0 mcg/mL chosen as study endpoints are consistent with antibody levels needed for Hib disease prevention. These antibody levels to the Hib capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP) were shown to be protective based on effectiveness data from a Hib polysaccharide vaccine trial¹ and passive antibody studies². Studies by Goldschneider et al. support use of serum bactericidal antibody (SBA) as an immunological surrogate for meningococcal disease prevention. A meningococcal bactericidal titer $\geq 1:8$ after the 3rd MenHibrix dose and SBA GMT ratio following the 4th dose were co-primary endpoints for the serogroup C (MenC) and Y (MenY) components. Meningococcal antibody titers were measured by human complement-based SBA (hSBA) assay.

Pivotal immunogenicity study (Hib-MenCY-TT-009/010):

- (1) The primary endpoints for manufacturing lot consistency were met for the MenC, but not MenY, component. CBER CMC review of the hSBA-MenY assay information noted unexplained decreases in antibody titer over a specified time period. Reduced hSBA-MenY GMTs were observed following repeated testing of Phase 2 study Hib-MenCY-TT-005 sera; to a lesser extent, the findings occurred with tested pivotal immunogenicity study samples. The applicant will be requested to provide, in response to anticipated CBER Complete Response (CR) letter comments, information to support hSBA-MenY assay performance reliability and consistency. Clinical review of meningococcal immunogenicity data was subsequently deferred pending the outcome of CBER's review addendum of hSBA MenY assay information.
- (2) The primary endpoints for the Hib vaccine component were met.
- (3) Of note, due to study site non-compliance, treatment assignment could not be confirmed for 6% (261/4441) of the total enrolled infant cohort and 8.5% (93/1084) of the safety and immunogenicity cohort (cohort 1). Of the Total Vaccination cohort 1 (i.e., excludes participants from the site described above), ~30% (306/991) were excluded from the Primary ATP immunogenicity cohort. Subjects in the 4th dose ATP Immunogenicity Cohort are not a subset of the subjects in the Primary ATP Immunogenicity Cohort, i.e., some subjects in the 4th dose ATP Immunogenicity Cohort are not included in the Primary ATP Immunogenicity Cohort.
- (4) More infants appear to have completed the interim safety follow-up (after the 3rd dose and prior to the 4th dose) than the safety evaluation through 1 month post-dose 3.

In total, 7521 infants received one to three MenHibrix doses, and 7023 toddlers received a 4th MenHibrix vaccination. An additional 1290 subjects received at least one dose of MenHibrix in ongoing study 057. In accordance with prior agreement with FDA, the sponsor submitted blinded data on occurrence of SAEs and deaths in study 057 to support the safety assessment of MenHibrix. The overall study population included approximately 50% Caucasian, 40% Hispanic, 5% African American/Black, 1% Asian and 4% individuals of other racial backgrounds. Solicited local reactions and systemic adverse events were monitored during Days 0-3 post-vaccination. Serious and non-serious unsolicited adverse events were monitored during Days 0-30 post-vaccination. Specific adverse events of interest (SAEs, new onset chronic disease, rash, AEs resulting in an emergency room visit, AEs resulting in physician office visits) were followed for 6 months following the last immunization in certain studies. *Review of the safety data contained in the initial BLA amendment did not identify any major safety concerns.*

MenHibrix safety and immunogenicity were assessed when co-administered with Infanrix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, DTaP]; Pediarix [Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, DTaP-HBV-IPV]; Prevnar [7-valent pneumococcal CRM₁₉₇ conjugate vaccine, PCV7]; MMR_{II}; and, varicella (Varivax) vaccine. *All pre-specified endpoints for concomitantly administered vaccine antigens were met. There was no evidence of immune interference with the studied vaccines.*

The applicant requested a waiver to conduct studies of MenHibrix in children 0 to <6 weeks of age and in children 5 to 17 years of age because in these age groups, use of MenHibrix is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules, and MenHibrix is not likely to be used in a substantial number of patients.

In addition, for children 5 to 17 years of age, studies with MenHibrix would be impossible or highly impracticable. *Final decisions regarding PREA requirements are deferred pending presentation to the PERC committee.*

Final conclusions and recommendations are pending review of the sponsor's response to CBER issued complete response comments.

3 Significant Findings from Other Review Disciplines

Please see individual review memos for CMC, statistical, and toxicology disciplines.

4 Clinical and Regulatory Background

4.1.1 Epidemiology

Meningitis and bacteremia are important manifestations of invasive disease due to *Haemophilus influenzae* type b (Hib) and to *Neisseria meningitidis* (*N. meningitidis*). Other important clinical presentations include pneumonia and occult bacteremia.

In 2007, the incidence of invasive Hib disease in the United States was 0.08/100,000³ among children younger than five years; in infants younger than one year, the incidence that year was 0.20/100,000⁵, while the incidence in children 2 – 4 years was 0.07/100,000³. The incidence of meningococcal C disease in the United States among children ages < 1 year and 1 – 2 years, respectively, was 0.76/100,000⁴ and 0.19/100,000 in 2007⁴. Meningococcal Y disease rates were 0.76/100,000 for children ages < 1 year⁴ and 0.00/100,000 for children ages 1 – 2 years⁴. In 1999-2008, Active Bacterial Core Surveillance showed that 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 old⁵.

The mortality rate due to invasive Hib disease overall is 3 – 6%, and 20% of survivors experience long-term sequelae, including permanent hearing loss⁶. For meningococcal disease the overall mortality rate is 3.8% - 14%^{5,7,8,9}, and is up to 21.2% of children in specific age groups⁹. The overall mortality rate for meningococemia was 20% in 2007⁴. Despite broad antibiotic susceptibility, 11 – 19 % of survivors of meningococcal disease experience long-term sequelae⁷. Such sequelae include neurosensory hearing loss, skin necrosis, seizures, and amputation⁹. Notably, ciprofloxacin resistance emerged in 2007 in the United States in *N. meningitidis* serogroup B^{9,10}.

4.1.2 Immune correlates

The role of anti-Hib polysaccharide serum concentration in protection against Hib disease was reviewed by Kayhty¹¹. In 1933, Hib disease occurrence was noted to be higher in younger children, who had lower levels of serum bactericidal titers¹². A similar finding was shown for specific anticapsular antibodies¹³. Later studies investigated the protective concentration of anti-Hib polysaccharide antibodies, and this concentration was established in the 1980s in studies of passive immunoprophylaxis in a high-risk population. The anti-Hib polysaccharide antibody levels in the immunoglobulin recipients were measured, and the protective concentration was estimated to be 0.05 – 0.15 mcg/mL^{14, 15}.

The role of bactericidal antibody in protection against meningococcal disease is predicated on 1960s studies of military recruits. Recruits who developed invasive meningococcal serogroup C disease lacked detectable serum bactericidal antibody^{16,17}. In these studies, presence or absence of functional antibody was determined using a serum bactericidal assay (SBA) with an intrinsic human complement source. A positive result indicated the presence of complement mediated anti-meningococcal group C antibody and was a qualitative measurement at an estimated dilution of 1:4. Further, it had also been observed that the age of highest incidence of meningococcal disease correlated with age of lowest prevalence of bactericidal antibody: age 6 – 12 months. Additionally, people with C3, C5 – C9 complement deficiencies are at increased risk of meningococcal disease⁸. Since *in vitro* measurement of bactericidal antibody using intrinsic complement was predictive of functional antibody *in vivo*, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) considered serum bactericidal antibody to be a reliable indicator of vaccine effectiveness (VRBPAC, September 15, 1999). Clinical effectiveness of monovalent meningococcal C polysaccharide vaccines was confirmed in large-scale field trials in 1969 – 1970¹⁸.

4.1.3 Rationale for selected formulation

MenHibrix contains the capsular polysaccharides of *N. meningitidis* serogroups C and Y, and the PRP component of *H. influenzae* type b, each conjugated to tetanus toxoid. Generally, benefits of an effective polysaccharide-protein conjugate vaccine include induced T cell-dependent antibody response, affinity antibody maturation, immunologic memory and consequent enhanced antibody response. According to the sponsor's assessment, early dose-finding studies suggested the combined selected doses of vaccine components were safe and immunogenic. The immunogenicity data included in this license application are intended to support demonstration of short-term and long-

term protection against *H. influenzae* type b compared to *ActHIB*® and *PedvaxHIB*® and of short-term protection against *N. meningitidis* serogroups C and Y. Studies regarding longer-term protection against the vaccine components are ongoing, specifically antibody persistence studies at 1, 3, and 5 years following 4-dose immunization series.

4.2 Regulatory Background Information

4.2.1 Chronology of Regulatory Review

5/14/04: IND submitted
 8/14/08: Manufacturing pre-BLA meeting
 6/19/09: Clinical pre-BLA meeting
 8/12/09: Biologics License Application received

4.2.2 Basis for Licensure

Based on pre-specified criteria agreed upon by the FDA, the licensure of MenHibrix would be based on the following aspects:

- Demonstration of effectiveness: Non-inferiority comparison of immune responses to the Hib component, compared to a control group receiving a U.S. licensed monovalent Hib vaccine. For meningococcal components, MenHibrix participants needed to achieve a pre-specified seroresponse rate after the 4th dose.
- Demonstration of safety compared to U.S. licensed monovalent Hib vaccine
- Demonstration of lot consistency

4.2.2.1 Use of Immunologic Correlates for Licensure of *H. influenzae* type b and Meningococcal Vaccines

Demonstration of effectiveness, inferred from immunogenicity data, was an approach used as a basis for licensing *ActHIB*®¹⁸, *Menomune*®, and *Menactra*®. In September, 1991, the FDA Vaccines and Related Biological Products Advisory Committee concluded that immunological criteria could be the basis for demonstrating clinical effectiveness of a new *H. influenzae* type b conjugate vaccine¹⁹. Use of immunologic correlates as an approach for approval of new meningococcal conjugate vaccines for age groups older than those in the proposed MenHibrix indication was discussed and found acceptable by the vaccine advisory committee in September 1999. This is the first time these meningococcal immunologic correlates have been applied by the FDA in children younger than 2 years of age.

5 Clinical Data Sources, Review Strategy and Data Integrity

5.1 Material Reviewed

5.1.1 BLA Sections Reviewed

The following sections of the BLA were reviewed:

m 1.3.4 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 Effectiveness Information – Summary of Clinical Effectiveness
 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)

Amendment 2 (January 8, 2010): (response to CBER request of October 21, 2009)

5.2 Overview of Clinical Studies

Safety and immunogenicity data from thirteen clinical studies were included in the BLA, which included a pivotal immunogenicity study, a large safety trial, six supporting studies and one year antibody persistence data. The pivotal immunogenicity study was designated as separate studies for infant (Hib-MenCY-TT-009) and toddler dose (Hib-MenCY-TT-010) evaluations. The same terminology was used for the other studies that included infant and toddler evaluations.

Table 1: Overview of clinical studies (source: reviewer-generated with sponsor-provided information from BLA)

Study [No.] Country	Description	Vaccination schedule	Concomitant Vaccines	Number of subjects
				Total Cohort receiving license formulation
Hib-MenCY-TT-009 [103813] United States Australia Mexico	P3 lot consistency, immunogenicity, and safety MenHibrix doses 1-3 Com vx: diphtheria, tetanus, poliovirus, PT, FHA, PRN, hepatitis B	2, 4, 6 months	MenHibrix + Pediarix Pevnar	3136
Hib-MenCY-TT-010 [105067] United States Australia Mexico	P3 immunogenicity and safety of 4 th MenHibrix dose Com vx: MMR and V	12 – 15 months	Cohort 1: MenHibrix + MMRII + Varivax Cohorts 2, 3: MenHibrix Co-admin of Pevnar, MMRII, and Varivax permitted	2769
Hib-MenCY-TT-007 [102370] Australia	P2 immunogenicity and safety MenHibrix doses 1-3 Relevance to U.S. licensure: concomitant MMR and V evaluation	2, 4, 6 months	Pediarix + Pevnar + MenHibrix	661
Hib-MenCY-TT-008 [102371] Australia	P2 immunogenicity and safety 4 th MenHibrix dose Relevance to U.S. licensure: concomitant MMR and V evaluation	12 – 15 months	MenHibrix + MMRII + Varivax	<i>625 who received MenHibrix + Pediarix + Pevnar for doses 1 – 3</i> <i>206 who received Meningitec + ActHIB + Pediarix + Pevnar in study -007</i>
Hib-MenCY-TT-005 [101858] United States	P2 immunogenicity and safety MenHibrix doses 1-3 Com vx: PT, FHA, PRN, and PCV7, diphtheria, tetanus, and poliovirus hepatitis B	2, 4, 6 months	MenHibrix + Pediarix + Pevnar	287
Hib-MenCY-TT-006 [102015] United States	P2 immunogenicity and safety 4 th MenHibrix dose Evaluation of non-inferiority to Hib control (post-dose 4), non-inferiority of co-administration with PCV7 (post-dose 4)	12 – 15 months	MenHibrix + Pevnar	<i>236* who received MenHibrix + Pevnar + Pediarix doses 1 – 3</i> <i>132 who received ActHIB + Pevnar + Pediarix for doses 1 - 3</i>

Study [No.] Country	Description	Vaccination schedule	Concomitant Vaccines	Number of subjects
				Total Cohort receiving license formulation
Hib-MenCY-TT-011 [105987] United States, Mexico	P3 safety MenHibrix doses 1-3 Evaluation of safety with respect to SAEs, NOCD, rash, AEs resulting in ER or physician office visits through 6 months post-dose 3	2, 4, 6 months	MenHibrix + Pediarix Co-admin of Prevnar strongly encouraged (if available) Co-admin of influenza vaccine, RotaTeq, and Synagis permitted according to local recommendations and availability	3278
Hib-MenCY-TT-012 [105988] United States, Mexico	P3 safety 4 th MenHibrix dose Evaluation of safety with respect to SAEs, NOCD, rash, AEs resulting in ER or physician office visits through 6 months post-dose 4	12 – 15 months	MenHibrix Co-admin of Prevnar, MMRII, and Varivax strongly encouraged Co-admin of influenza vaccine, hepatitis A vaccine permitted	3010
Hib-MenCY-TT-013 [107824] United States	P2 one year antibody persistence study	Not applicable	Not applicable	138 who received <i>MenHibrix doses 1 – 3</i> 62 who received <i>ActHIB doses 1 - 3</i>
057** United States	Ongoing P3 immunogenicity and safety study Relevance to U.S. licensure: SAE evaluation	2, 4, 6 months	MenHibrix + Pediarix Co-admin of Prevnar strongly encouraged Co-admin of influenza and rotavirus vaccines permitted	1290
Hib-MenCY-TT-001 [792014/001] Australia	P2 dose ranging study	2, 4, 6 months	Infanrix penta + Prevnar + MenHibrix	82
Hib-MenCY-TT-002 [792014/002] Australia	P2 study of immune memory	12 months	10 µg plain PRP and 1/5 of a dose of polysaccharide ACWY (Mencevax®)	80
Hib-MenCY-TT-003 [792014/003] Belgium Germany	P2 dose ranging study	2, 3, 4 months	MenHibrix + Infanrix hexa	78
Hib-MenCY-TT-004 [100381/004] Germany	P2 dose ranging study and 4 th dose evaluation	12 – 18 months	MenHibrix + Infanrix hexa	47

** SAE data submitted to the MenHibrix BLA was not categorized by treatment assignment since the study is ongoing. In study Hib-MenCY-TT-006, the 236 subjects in the total vaccinated cohort of the MenHibrix group includes 235 subjects from the MenHibrix group who received a fourth dose of MenHibrix vaccine at approximately 12 to 15 months of age after 3 doses of MenHibrix vaccine at 2, 4, and 6 months and one subject who was assigned incorrectly to the MenHibrix group in the fourth dose phase after having received 3 doses of ActHIB in study Hib-MenCY-TT-005

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

Infanrix hexa = Diphtheria and Tetanus Toxoids and Acellular Pertussis, Hepatitis B, Inactivated Poliovirus Vaccine and Hemophilus influenzae type b Vaccine Combined, GSK

Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined, GSK (licensed in U.S. as a 3-dose primary series in children 6 weeks to 7 years of age)

ActHIB = Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur

PedvaxHIB = Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate), Merck & Co, Inc.

Source: m 2.7.3 sum-clin-eff-prev-hibnmency.pdf, m 2.7.4 summary-clin-safety.pdf, m 5.3.5.1 clinical study reports

The table provides the study numbers, countries in which the studies were conducted, study description, vaccination schedule, concomitant vaccines administered, and the number of subjects receiving the license formulation.

6 Clinical Studies

Pivotal Clinical Studies:

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 manufacturing 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 is the timeframe that includes data collected from the day of 1st vaccination to 6 months after the third dose. The fourth 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.

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*® 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} and *Varivax*®
- 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 *Pediarix*® at 2, 4, and 6 months of age and with *MMR*®_{II} and *Varivax*® at 12 to 15 months of age
- To evaluate the specific effect of a 4th dose of Hib-MenCY-TT co-administered with *MMR*®_{II} and *Varivax*® 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*®, each co-administered with *Pediarix*®, 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*_{II} when co-administered with a 4th dose of Hib-MenCY-TT compared to *MMR*_{II} co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with *Varivax*[®].
- To demonstrate non-inferiority of immune response to *Varivax*[®], measured by -----(b)(4)-----, co-administered with a 4th dose of Hib-MenCY-TT compared to *Varivax*[®] co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with *MMR*_{II}

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 *Pediarix*[®]
- *To evaluate the MenY immune response as measured by hSBA to 3 doses of Hib-MenCY-TT (3 pooled lots), co-administered with *Pediarix*[®]
- *To demonstrate non-inferiority of immune responses to 3 doses of *Pediarix*[®] when co-administered with Hib-MenCY-TT compared to when co-administered with *ActHIB*[®]
- 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 $\geq 1:4$ and $\geq 1:8$
- To evaluate immunogenicity following 3-dose primary series of Hib-MenCY-TT compared to that of *ActHIB*[®], each co-administered with *Pediarix*[®], 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 *ActHIB*[®] and to evaluate percentage of subjects with hSBA-MenC and hSBA-MenY antibody titers $\geq 1:4$ following 3-dose primary series of Hib-MenCY-TT and *ActHIB*[®]
- To evaluate immunogenicity following 3-dose primary series of *Pediarix*[®] co-administered with Hib-MenCY-TT compared to that of *Pediarix*[®] co-administered with *ActHIB*[®] 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-PSC and anti-PSY GMCs, as measured by ELISA, in the Hib-MenCY-TT (pooled lots) and the *ActHIB*[®] 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 $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$ 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 *Pediarix*[®]
- To evaluate safety and reactogenicity of a 3-dose primary series of Hib-MenCY-TT compared to *ActHIB*[®], each co-administered with *Pediarix*[®]
- To summarize safety of a 3-dose primary vaccination course of Hib-MenCY-TT compared to *ActHIB*[®], stratified by receipt of *Prevnar*[®], 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 *ActHIB*[®], each co-administered with *Pediarix*[®], in terms of anti-PRP GMCs and antibody concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL, hSBA-MenC and hSBA-MenY GMTs, antibody titers $\geq 1:4$
- Exploratory evaluation of persistence of hSBA-MenY antibody titers $\geq 1:8$
- 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 *ActHIB*[®] 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*_{II} and *Varivax*®, 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*_{II} and *Varivax*®, to *N. meningitidis* serogroups C and Y in terms of hSBA-MenC/Y antibody titers $\geq 1:4$
- 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*® 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*_{II} when co-administered with a 4th dose of Hib-MenCY-TT compared to *MMR*_{II} co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with *Varivax*®
- To demonstrate the non-inferiority of *Varivax*® co-administered with a 4th dose of Hib-MenCY-TT compared to *Varivax*® co-administered with a 4th dose of monovalent Hib vaccine, each co-administered with *MMR*_{II} 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*_{II} and *Varivax*® when co-administered with a 4th dose of Hib-MenCY-TT compared with immunogenicity of *MMR*_{II} and *Varivax*® 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 $\geq 1:40$, 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 $\geq 51\text{ED}_{50}$ in initially seronegative subjects ($< 24\text{ED}_{50}$)

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 $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$, compared to *PedvaxHIB*®, 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 *PedvaxHIB*®
- To summarize the safety of a 4th dose of Hib-MenCY-TT compared to that of *PedvaxHIB*®, stratified by receipt of *Pprevnar*®, influenza vaccine, hepatitis A vaccine, and *MMR*_{II} and *Varivax*®

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 *Pediarix*® at doses 1-3 and with *MMR*_{II} and *Varivax*® vaccines at dose 4.

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.

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 ≥ 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*®, *Prevnar*®, 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 $<38.0^{\circ}\text{C}$, axillary/oral temperature $<37.5^{\circ}\text{C}$, tympanic temperature on oral setting $<37.5^{\circ}\text{C}$, or tympanic temperature on rectal setting $<38.0^{\circ}\text{C}$).
- 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*®_{II} and *Varivax*® 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 $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$), axillary/oral temperature $\geq 37.5^{\circ}\text{C}$ ($\geq 99.5^{\circ}\text{F}$), tympanic temperature on oral setting $\geq 37.5^{\circ}\text{C}$ ($\geq 99.5^{\circ}\text{F}$), or tympanic temperature on rectal setting $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$).

Vaccine administration

Participants received, intramuscularly, Hib-MenCY-TT or a monovalent Hib vaccine. For the primary vaccination phase, *ActHIB*® was administered. *PedvaxHIB*® was used for the fourth Hib vaccination.

Prevnar® (4th dose), *MMR_{II}*®, and *Varivax*® vaccines were provided as study vaccines for the U.S. safety and immunogenicity cohort (cohort 1). *MMR_{II}*®, and *Varivax*® 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, *Prevnar*® 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. Influenza, rotavirus, hepatitis A vaccines were permitted to be administered according to local recommendations.

MenHibrix is lyophilized and reconstituted with supplied saline diluent. Each 0.5 mL intramuscular dose of MenHibrix contains 2.5 mcg purified 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) covalently bound to 6.25 mcg of tetanus toxoid (PRP), 5 mcg of tetanus toxoid for PSC, and 5 mcg tetanus toxoid for PSY.

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 ≥ 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 ≥ 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_{II}*® (42 days post-4th dose): Anti-measles concentration ≥ 150 mIU/mL in initially seronegative subjects (< 150 mIU/mL), anti-mumps neutralization titer ≥ 28 ED₅₀ in subjects with initial anti-mumps antibody < 28 ED₅₀, anti-rubella concentrations ≥ 10 IU/mL in initially seronegative subjects (< 4 IU/mL)
7. Co-administration with *Varivax*® (42 days post-4th dose): Anti-varicella (-(b)(4)-) 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 ≥ 0.15 mcg/mL and ≥ 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 ≥ 0.1 IU/mL and GMCs
- Anti-T antibody concentration ≥ 0.1 IU/mL and GMCs
- Anti-HBs GMCs and antibody concentrations ≥ 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 ≥ 5 EL.U/mL and GMCs
- Anti-poliovirus types 1, 2, and 3 antibody neutralization titers ≥ 8 ED₅₀ and GMTs
- Anti-PSC and anti-PSY concentrations ≥ 0.3 mcg/mL and ≥ 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 ≥ 0.15 mcg/mL and ≥ 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 ≥ 0.3 mcg/mL and ≥ 2.0 mcg/mL and GMCs

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

- Fever $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$ in the 4-day follow-up period after any dose (pooled Hib-MenCY-TT vaccine lots vs. ActHIB®)
- 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 ActHIB®
- 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 ≥ 0.15 mcg/mL and ≥ 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 ≥ 0.3 mcg/mL and ≥ 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 ≥ 0.15 mcg/mL and ≥ 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 ≥ 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 ≥ 0.15 mcg/mL and ≥ 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 ≥ 0.3 mcg/mL and ≥ 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 ≥ 200 mIU/mL in initially seronegative subjects (< 150 mIU/mL)
- Anti-mumps GMTs and concentration ≥ 28 ED₅₀ and ≥ 51 ED₅₀ in initially seronegative subjects (< 24 ED₅₀)
- Anti-rubella GMCs and concentration ≥ 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 $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$ 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 *PedvaxHIB*® 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 subject's parents decided not to include their child in the study, the randomization assignment for that subject was cancelled with vial reassignment in the randomization system.

Surveillance

Safety parameters:

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. Information on unsolicited adverse events was collected via daily recording during the 30 days post-immunization and via telephone contact days 31 – 48. Information on medically attended visits, NOCD, and rash were collected throughout the study via telephone contact or on visit days 182 - 194. 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*®_{II} and *Varivax*®. Serious adverse events¹ 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.

Effectiveness (immunogenicity):

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.

¹ A serious adverse event was defined as any untoward medical occurrence resulting in death, life-threatening experience, inpatient hospitalization, prolonged existing hospitalization, persistent of significant disability/incapacity, or a congenital anomaly/birth defect.

Assay methods and laboratories:

Table 2: Assay methods and laboratories (source: sponsor’s Table 6, Hib-MenCY-TT-009 clinical study report, page 109 and Table 8, Hib-MenCY-TT-010 clinical study report, page 141)

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

* 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)-----

† -----(b)(4)-----

§ ED₅₀ = Endpoint dilution 50

Two 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, US subjects (i.e., Cohort 1) were assayed for measles, mumps, rubella, varicella, and (where applicable) influenza H1N1, H3N2, and B. Anti-PSC and anti-PSY were tested in those subjects in Cohorts 1 and 3 that had sera available. As discussed with the sponsor during clinical development, the FDA does not consider rSBA, anti-PSC, or anti-PSY adequate and reliable to predict immune response in the studied population.

Statistical plan*Sample size calculations*

Number of enrolled (evaluable) participants:

<u>Study #</u>	<u>Hib-MenCY-TT</u>	<u>Monovalent Hib</u>
Hib-MenCY-TT 009 (Cohort 1: US safety and immuno)	810	270
Hib-MenCY-TT 009 (Cohort 2: Safety - US and non-US)	2340	780
Hib-MenCY-TT 009 (Cohort 3: non-US safety and immuno)	150	50
Hib-MenCY-TT 010 (Cohort 1: US safety and immuno)	618	198
Hib-MenCY-TT 010 (Cohort 2: Safety - US and non-US)	2015	678
Hib-MenCY-TT 010 (Cohort 3: non-US safety and immuno)	136	47

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 ≥ 1.0 mcg/mL after 4th vaccination** by demonstrating the lower limit of 95% CI for (pooled Hib-MenCY-TT – *ActHIB*®) in percentage of subjects with anti-PRP concentrations ≥ 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 ≥ 2 .
5. To demonstrate non-inferiority of **immunogenicity post-3rd dose with respect to anti-PRP concentration ≥ 1.0 mcg/mL** following 3 doses of Hib-MenCY-TT compared to *ActHIB*® by demonstrating the lower limit of the standardized asymptotic 95% CI for [pooled Hib-MenCY-TT – *ActHIB*®] in percentage of subjects with anti-PRP concentrations ≥ 1.0 mcg/mL is $\geq 10\%$.
6. To demonstrate **non-inferiority of *MMR*®_{II} 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 – *PedvaxHIB*®) in percentage of subjects with anti-measles concentration ≥ 150 mIU/mL, anti-mumps titer ≥ 28 ED₅₀, anti-rubella concentration ≥ 10 mIU/mL 42 days post-4th dose.
7. To demonstrate **non-inferiority of *Varivax*® 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 – *PedvaxHIB*®) 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 *Pediarix*® co-administered with Hib-MenCY-TT or *ActHIB*®** one month after 3rd dose by showing lower limits of 95% CIs as **either**: $\geq 10\%$ on the difference (pooled Hib-MenCY-TT – *ActHIB*®) in percentages of subjects with concentrations ≥ 0.1 IU/mL or titers ≥ 8 ED₅₀ for Diphtheria and tetanus antigens or poliovirus antigens, respectively **OR** ≥ 0.67 on the GMC ratios ($GMC_{\text{pooled Hib-MenCY-TT}}/GMC_{\text{ActHIB®}}$) 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 *Pediarix*® with the lower limit of the 95% CI of $\geq -2.4\%$ on (*ActHIB*® – 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_{II} 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 – *PedvaxHIB*®) in percentage of subjects with anti-measles concentration ≥ 200 mIU/mL, anti-mumps titer ≥ 28 ED₅₀ (in initially seronegative subjects with anti-measles < 150 mIU/mL and anti-mumps < 24 ED₅₀) 42 days post-4th dose.
- To demonstrate **non-inferiority of Varivax® 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 – *PedvaxHIB*®) 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 *PedvaxHIB*® within 4 days of 4th vaccination with the lower limit of the 95% CI of $\geq -1.6\%$ on (*PedvaxHIB*® – pooled HibMenCY-TT) in percentage of subjects with fever > 39.5°C/103.1°F

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, excluding subjects from the dropped U.S. site. The total vaccinated cohort for the 4th dose vaccination study period included all participants who received a 4th dose of study vaccine. 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 cohort for safety for the primary vaccination study period included all subjects eligible for inclusion in the Primary total vaccinated cohort, who 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 ATP cohort for the 4th dose vaccination included all evaluable participants who received 3 doses in the primary vaccination course and the fourth dose and who had not received a vaccine not specified in the protocol.

The Enlarged Fourth dose ATP cohort for immunogenicity was the same as the 4th dose ATP cohort for immunogenicity except that the interval between visits 5 and 6 was 35-77 days.

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 for the first 3 doses 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.

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_{II}*® and *Varivax*® was performed on data pooled from Hib-MenCY-TT-010 and the non-U.S. study Hib-MenCY-TT-008. The criteria for pooling were that the point estimates within each study were above the pre-specified non-inferiority limit for the evaluation of the group differences on the pooled dataset (i.e., point estimate for the group difference above -5% for measles, mumps, and rubella and above -10% for varicella in each individual study).

Safety Analyses

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

Analyses included number and percentage of participants with immune response 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 (submitted as amendments to IND):

The FDA concurred with the following protocol amendments:

Hib control group in Australia was offered a licensed meningococcal serogroup C vaccine after completion of the safety follow-up.

Protocol amended to allow sites to co-administer rotavirus vaccine with study vaccines or according to local recommendations.

Antibody concentrations for hepatitis B were to be measured by an in-house developed ELISA. Statistical methods were changed so that the data to demonstrate immunogenicity would be based on US subjects only (Cohort 1). Primary immunogenicity objectives and secondary objectives were revised to include hSBA-MenC and hSBA-MenY antibody persistence. *Pevnar*®, *MMR_{II}*®, and *Varivax*® were provided as study vaccines. Analyses were included based on country and co-administered vaccines.

Evaluation of the immunogenicity of the vaccine as a 4 dose series was made a primary endpoint, and post-dose 3 endpoints for hSBA-MenC and hSBA-MenY were revised as secondary endpoints.

Concomitant evaluation of *Pediarix*® antigens and fever study objective were revised as secondary endpoints.

GMT ratio post-/pre- fourth dose for hSBA-MenC and hSBA-MenY was added as a primary endpoint, additional measles, mumps, rubella, and varicella non-inferiority secondary endpoints were added, the interval for blood sampling for inclusion in the Fourth dose ATP Cohort for Immunogenicity for Cohort 1 was changed to 35 – 56 days post-fourth dose, and a complementary analysis was to be performed on the original interval of 35 – 77 days.

Other important changes:

Sensitivity analyses were performed to evaluate the potential impact of the exclusion of one study site on safety data as well as to address concerns regarding potential differences between the primary phase population and the fourth dose population.

Results:

Population

A total of 4441 subjects were enrolled in study Hib-MenCY-TT-009. One study site (Center 24660), which enrolled 261 subjects excluded from the Primary Total Vaccination Cohort, due to GCP violations and protocol non-compliance. The Total Vaccination Cohort included 4180 (Hib-MenCY-TT n=3136, Hib n=1044) subjects. Due to enrollment difficulties with Cohort 1, some U.S. study centers were converted from Cohort 2 to Cohort 1 after the enrollment of Cohort 2 was completed. In study Hib-MenCY-TT-009, 331 subjects (n= 248 Hib-MenCY-TT, n=83 Hib) withdrew from study participation; 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 (2898 Hib-MenCY-TT participants and 955 Hib subjects). The most frequent reasons for study withdrawal were consent withdrawal (n=133), lost to follow-up (n=74) and protocol violations (n=33). Seven HibMenCY-TT subjects withdrew from the study due to a SAE, and 4 for AEs (n=3 HibMenCY-TT, n=1 Hib). Three deaths occurred during the study.

A total of 3883 toddlers were enrolled in study Hib-MenCY-TT-010, 189 participated at study center 34932 (designated as Center 24660 in study Hib-MenCY-TT-009, and 3581 subjects completed the study (n=2682 Hib-MenCY-TT, n= 899 Hib). A total of 111 subjects were withdrawn from the study due a motor vehicle accident that resulted in death (n=1 Hib-MenCY-TT), voluntary reasons (n=10 Hib-MenCY-TT, n=1 Hib), moving away from the study area (one subject in each group). 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 phase of the study was 3531 (2640 in the Hib-MenCY-TT group and 891 in the Hib group).

Due to the elimination of data from centers 24660 and 34932, 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 ≥ 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 outcome.

Safety population:

The Primary Total Vaccinated cohort population for safety included 4180 participants (Hib-MenCY-TT n=3136, Hib n=1044) for study Hib-MenCY-TT-009. The Primary Total Vaccinated Cohort 1 included 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). 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 in study Hib-MenCY-TT-010 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). Safety analyses that excluded Center 24660 [designated as Center 34932 in Hib-MenCY-TT-010] were provided as separate analyses.

Immunogenicity population:

The Primary ATP Immunogenicity Cohort 1 included 695 subjects (Hib-MenCY-TT n=522, Hib n=173). *Primary immunogenicity analyses were based on the Primary ATP cohort for immunogenicity, Cohort 1, and the supplemental immunogenicity analyses were performed on the Primary Total Vaccinated cohort, 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. 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). 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. Additional analyses of 4th dose immune responses were performed on the 4th dose ATP Cohort 3 for Immunogenicity, 4th dose Total Vaccinated Cohort 3.*

Safety:

Overall safety profile:

During the primary vaccination phase, the incidence of any adverse event (solicited and unsolicited) was 96.4% [3022/3136] in the pooled Hib-MenCY-TT group and 95.2% [994/1044] in the Hib group. The confidence intervals (CI) overlapped. The incidence [95% CI] of any systemic 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 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. 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.

Safety analyses of concomitant influenza vaccination (n= 29 HibMenCY-TT, n=16 Hib) and of hepatitis A co-vaccination (N=80 for HibMenCY-TT and N= 26 for Hib) were performed for US subjects in study Hib-MenCY-TT-010 only, since few non-US subjects received either vaccination.

Immediate reactions:

None

Local reactions:

In the primary vaccination phase, the overall occurrence per subject of any (solicited and unsolicited) grade 3 local reactions was 18.4% [576/3136] and 25.7% [268/1044] among pooled Hib-MenCY-TT and Hib recipients, respectively. The 95% confidence intervals (CIs) did not overlap. Local reactions were reported in 87.8% [2752/3136]

and 87.0% [908/1044] of pooled Hib-MenCY-TT and *ActHIB*[®] participants, respectively. The respective 95% CIs were (86.6, 88.9) and (84.8, 89.0). The incidence [95% CI] of any local 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 both groups, a trend towards decreased injection site pain and increased redness/swelling occurred with subsequent doses. Similar trends were observed for each of the HibMenCY-TT lots.

Table 3: Local adverse reactions at any injection site (Days 0 – 3), overall per subject following any of the first 3 doses (source: modified from sponsor’s Table 52, Hib-MenCY-TT-009 clinical stu Clinical Review, June 3, 2010 - MenHibrixdy report, pages 198 – 200)

Hib-MenCY-TT-009: Local adverse reactions, any injection site (Days 0 – 3), Primary Total Vaccinated Cohort, occurring after any of the first 3 doses								
Reaction	Severity	Days	HibMenCY (pooled lots)			HIB		
			N=3088			N=1016		
			n	%	95% CI	n	%	95% CI
Redness	Any	0 - 3	2052	66.5	64.8, 68.1	691	68.0	65.0, 70.9
	Grade 2 or 3	0 - 3	502	16.3	15.0, 17.6	184	18.1	15.8, 20.6
	Grade 3	0 - 3	77	2.5	2.0, 3.1	36	3.5	2.5, 4.9
	Medical Attention	0 - 3	5	0.2	0.1, 0.4	0	0.0	0.0, 0.4
Swelling	Any	0 - 3	1707	55.3	53.5, 57.0	568	55.9	52.8, 59.0
	Grade 2 or 3	0 - 3	468	15.2	13.9, 16.5	144	14.2	12.1, 16.5
	Grade 3	0 - 3	91	2.9	2.4, 3.6	36	3.5	2.5, 4.9
	Medical Attention	0 - 3	6	0.2	0.1, 0.4	0	0.0	0.0, 0.4
Pain	Any	0 - 3	2419	78.3	76.8, 79.8	819	80.6	78.0, 83.0
	Grade 2 or 3	0 - 3	1346	43.6	41.8, 45.4	546	53.7	50.6, 56.8
	Grade 3	0 - 3	467	15.1	13.9, 16.4	232	22.8	20.3, 25.5
	Medical Attention	0 - 3	4	0.1	0.0, 0.3	1	0.1	0.0, 0.5

Hib-MenCY-TT = Hib-MenCY-TT + DTaP-HBV-IPV + PCV7
 ActHIB® = ActHIB® + DTaP-HBV-IPV + PCV7
 Grade 2 pain = cried/protected on touch
 Grade 3 pain = cried when limb was moved/spontaneously painful
 Med Attn = event that prompted the parent/guardian to seek medical advice
 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
 Any = all events, any intensity

Table 4: Local adverse reactions at any injection site (Days 0 – 3) by lot, overall per subject following any of the first 3 doses (source: modified from sponsor’s Table 55, Hib-MenCY-TT-009 clinical study report, pages 204 – 206)

Hib-MenCY-TT-009: Local adverse reactions, any injection site (Days 0 – 3), Primary Total Vaccinated Cohort, overall/subject occurring after any of the first 3 doses													
Reaction	Severity	HibMenCY Lot A			HibMenCY Lot B			HibMenCY Lot C			HIB		
		N =1023			N = 1036			N = 1029			N=1016		
		n	%	95% CI						95% CI	n	%	95% CI
Redness	Any	676	66.1	63.1, 69.0	699	67.5	64.5, 70.3	677	65.8	62.8, 68.7	691	68.0	65.0, 70.9
	Grade 2 or 3	164	16.0	13.8, 18.4	170	16.4	14.2, 18.8	168	16.3	14.1, 18.7	184	18.1	15.8, 20.6
	Grade 3	27	2.6	1.7, 3.8	20	1.9	1.2, 3.0	30	2.9	2.0, 4.1	36	3.5	2.5, 4.9
	Medical Attention	2	0.2	0.0, 0.7	1	0.1	0.0, 0.5	2	0.2	0.0, 0.7	0	0.0	0.0, 0.4
Swelling	Any	571	55.8	52.7, 58.9	571	55.1	52.0, 58.2	565	54.9	51.8, 58.0	568	55.9	52.8, 59.0
	Grade 2 or 3	153	15.0	12.8, 17.3	150	14.5	12.4, 16.8	165	16.0	13.8, 18.4	144	14.2	12.1, 16.5
	Grade 3	26	2.5	1.7, 3.7	27	2.6	1.7, 3.8	38	3.7	2.6, 5.0	36	3.5	2.5, 4.9
	Medical Attention	3	0.3	0.1, 0.9	1	0.1	0.0, 0.5	2	0.2	0.0, 0.7	0	0.0	0.0, 0.4
Pain	Any	802	78.4	75.7, 80.9	812	78.4	75.7, 80.8	805	78.2	75.6, 80.7	819	80.6	78.0, 83.0
	Grade 2 or 3	447	43.7	40.6, 46.8	435	42.0	39.0, 45.1	464	45.1	42.0, 48.2	546	53.7	50.6, 56.8
	Grade 3	157	15.3	13.2, 17.7	161	15.5	13.4, 17.9	149	14.5	12.4, 16.8	232	22.8	20.3, 25.5
	Medical Attention	2	0.2	0.0, 0.7	1	0.1	0.0, 0.5	1	0.1	0.0, 0.5	1	0.1	0.0, 0.5

Descriptive evaluation of differences between countries:

In study Hib-MenCY-TT-009, redness and swelling were reported more commonly in Australian subjects when compared with Mexican and U.S. subjects, while pain was least commonly reported in Australian subjects when compared to U.S. or Mexican subjects. Pain was most commonly reported in Mexican subjects. The 95% confidence intervals around the point estimates for percentages of subjects reporting pain were non-overlapping between countries, although they did overlap between HibMenCY-TT and Hib groups within each country.

During study Hib-MenCY-TT-010, observed rates of any adverse event reported 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) when 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. The 95% CIs around the point estimates for percentages of subjects reporting any Grade 3 AEs were predominantly 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 5: Local adverse reactions at any injection site (Days 0 – 3) following the 4th dose (source: modified from sponsor’s Table 58, Hib-MenCY-TT-010 clinical study report, pages 229 - 231)

Hib-MenCY-TT-010: Local adverse reactions, any injection site (Days 0 – 3), Primary Total Vaccinated Cohort, post-4 th dose								
Reaction	Severity	Days	HibMenCY (pooled lots)			HIB		
			N=2528 (2526 swelling, 2769 circ)			N=832 (833 redness)		
			n	%	95% CI	n	%	95% CI
Redness	Any	0 - 3	1213	48.0	46.0, 50.0	463	55.6	52.1, 59.0
	Grade 2 or 3	0 - 3	242	9.6	8.5, 10.8	110	13.2	11.0, 15.7
	Grade 3	0 - 3	64	2.5	2.0, 3.2	22	2.6	1.7, 4.0
	Medical Attention	0 - 3	0	0.0	0.0, 0.1	1	0.1	0.0, 0.7
Swelling	Any	0 - 3	936	37.1	35.2, 39.0	334	40.1	36.8, 43.6
	Grade 2 or 3	0 - 3	211	8.4	7.3, 9.5	87	10.5	8.5, 12.7
	Grade 3	0 - 3	52	2.1	1.5, 2.7	23	2.8	1.8, 4.1
	Medical Attention	0 - 3	0	0.0	0.0, 0.1	2	0.2	0.0, 0.9
Pain	Any	0 - 3	1319	52.2	50.2, 54.1	494	59.4	55.9, 62.7
	Grade 2 or 3	0 - 3	440	17.4	15.9, 18.9	218	26.2	23.2, 29.3
	Grade 3	0 - 3	60	2.4	1.8, 3.0	57	6.9	5.2, 8.8
	Medical Attention	0 - 3	0	0.0	0.0, 0.1	1	0.1	0.0, 0.7
Increase in arm circumference*	Any	0 - 3	1489	53.8	51.9, 55.6	503	54.5	51.2, 57.7
	Grade 2 or 3	0 - 3	260	9.4	8.3, 10.5	93	10.1	8.2, 12.2
	Grade 3	0 - 3	34	1.2	0.9, 1.7	7	0.8	0.3, 1.6
	Medical Attention	0 - 3	0	0.0	0.0, 0.1	1	0.1	0.0, 0.6

HibMenCY = HibMenCY-TT + MMR2 + Varivax + Prevnar in subjects who received 3 doses of HibMenCY-TT + Pediarix + Prevnar in study Hib-MenCY-TT-009

Hib = PedvaxHIB + MMR2 + Varivax + Prevnar in subjects who received 3 doses of ActHIB + Pediarix + Prevnar

N = number of subjects with administered dose

n/% = number/percentage of subjects with at least one local symptom whatever the number of injections

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

Grade 2 pain = cried/protected on touch

Grade 3 pain = cried when the limb was moved/spontaneously painful

Grade 2 redness/swelling = >10 mm to ≤ 30 mm

Grade 3 redness/swelling = > 30 mm

Grade 2 circumference = > 20 mm - ≤ 40 mm

Grade 3 circumference = > 40 mm

Medical Attention = event which prompted the parent(s)/guardian(s) to seek medical attention

* subjects with all missing safety parameters were not excluded; grade 1 intensity was imputed when all intensity values were absent

During the 4-day post-4th vaccination period, 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). Reported measurement values ranged from 50 – 70 mm in the HibMenCY-TT group and from 3 – 90 mm in the Hib group; for 12 reactions, no measurement was provided by the parent/guardian.

Systemic reactions:

In study Hib-MenCY-TT-009, 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. 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, with overlapping confidence intervals. 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].

Table 6: Solicited systemic adverse reactions, (Days 0 -3), Primary Total Vaccinated Cohort, overall/subject after any of the first 3 doses (source: modified from sponsor's Table 56, Hib-MenCY-TT-009 clinical study report, page 209 – 210)

Hib-MenCY-TT-009: Solicited systemic adverse reactions, (Days 0 -3), Primary Total Vaccinated Cohort, overall/subject after any of the first 3 doses											
Reaction	Severity	Hib-MenCY					Hib				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Drowsiness	All	3088	2418	78.3	76.8	79.7	1015	804	79.2	76.6	81.7
	Grade 2-3	3088	924	29.9	28.3	31.6	1015	344	33.9	31.0	36.9
	Grade 3	3088	201	6.5	5.7	7.4	1015	73	7.2	5.7	9.0
	Medical Advice	3088	15	0.5	0.3	0.8	1015	6	0.6	0.2	1.3
Fever (°C)	All	3089	1434	46.4	44.7	48.2	1015	463	45.6	42.5	48.7
	> 38.5	3089	532	17.2	15.9	18.6	1015	195	19.2	16.8	21.8
	> 39.0	3089	152	4.9	4.2	5.7	1015	53	5.2	3.9	6.8
	> 39.5	3089	46	1.5	1.1	2.0	1015	16	1.6	0.9	2.5
	> 40.0	3089	9	0.3	0.1	0.6	1015	3	0.3	0.1	0.9
Medical Advice	3089	37	1.2	0.8	1.6	1015	16	1.6	0.9	2.5	
Irritability	All	3088	2740	88.7	87.6	89.8	1015	926	91.2	89.3	92.9
	Grade 2 - 3	3088	1559	50.5	48.7	52.3	1015	579	57.0	53.9	60.1
	Grade 3	3088	335	10.8	9.8	12.0	1015	150	14.8	12.7	17.1
	Medical Advice	3088	32	1.0	0.7	1.5	1015	14	1.4	0.8	2.3
Loss of appetite	All	3088	1764	57.1	55.4	58.9	1015	609	60.0	56.9	63.0
	Grade 2 - 3	3088	499	16.2	14.9	17.5	1015	187	18.4	16.1	20.9
	Grade 3	3088	45	1.5	1.1	1.9	1015	17	1.7	1.0	2.7
	Medical Advice	3088	18	0.6	0.3	0.9	1015	5	0.5	0.2	1.1

In both groups, irritability was the most frequently solicited systemic reaction in the 4 day follow up period post-vaccination and occurred in 88.7% [2740/3088] of Hib-MenCY-TT participants and 91.2% [926/1015] Hib participants. Confidence intervals overlapped. Grade 3 irritability occurred in 10.8% and 14.8% of Hib-MenCY-TT and Hib subjects, respectively. Grade 3 fever (> 40.0°C) was reported in 0.3% of subjects. Most solicited fevers occurred on Days 0 – 1 after each dose. The observed incidence of fever was highest post-dose 2 in both treatment groups; observed incidence of the other systemic adverse events generally did not increase with subsequent doses, and trends over doses were similar across the individual HibMenCY-TT lots, with the exception of a slighter greater incidence of irritability post-dose 2 compared with post-dose 1 in Lots A and B.

Table 7: Solicited systemic adverse reactions, (Days 0 -3), Primary Total Vaccinated Cohort, overall/subject after any of the first 3 doses (source: modified from sponsor’s Table 58, Hib-MenCY-TT-009 clinical study report, page 213 – 214)

Hib-MenCY-TT-009: Systemic adverse reactions, (Days 0 – 3), Primary Total Vaccinated Cohort, overall/subject after any of the first 3 doses																
Reaction	Severity	HibMenCY Lot A			HibMenCY Lot B			HibMenCY Lot C			HibMenCY pooled lots			HIB		
		N =1022 (1023 for fever)			N = 1037			N = 1029			N = 3088 (3089 for fever)			N=1015		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Drowsiness	Any	790	77.3	74.6, 79.8	824	79.5	76.9, 81.9	804	78.1	75.5, 80.6	2418	78.3	76.8, 79.7	804	79.2	76.6, 81.7
	Grade 2 or 3	304	29.7	27.0, 32.7	318	30.7	27.9, 33.6	302	29.3	26.6, 32.2	924	29.9	28.3, 31.6	344	33.9	31.0, 36.9
	Grade 3	68	6.7	5.2, 8.4	62	6.0	4.6, 7.6	71	6.9	5.4, 8.6	201	6.5	5.7, 7.4	73	7.2	5.7, 9.0
	Medical Attention	7	0.7	0.3, 1.4	3	0.3	0.1, 0.8	5	0.5	0.2, 1.1	15	0.5	0.3, 0.8	6	0.6	0.2, 1.3
Fever	All	480	46.9	43.8, 50.0	486	46.9	43.8, 50.0	468	45.5	42.4, 48.6	1434	46.4	44.7, 48.2	463	45.6	42.5, 48.7
	> 38.5	184	18.0	15.7, 20.5	181	17.5	15.2, 19.9	167	16.2	14.0, 18.6	532	17.2	15.9, 18.6	195	19.2	16.8, 21.8
	> 39.0	58	5.7	4.3, 7.3	47	4.5	3.3, 6.0	47	4.6	3.4, 6.0	152	4.9	4.2, 5.7	53	5.2	3.9, 6.8
	> 39.5	20	2.0	1.2, 3.0	9	0.9	0.4, 1.6	17	1.7	1.0, 2.6	46	1.5	1.1, 2.0	16	1.6	0.9, 2.5
	> 40.0	2	0.2	0.0, 0.7	1	0.1	0.0, 0.5	6	0.6	0.2, 1.3	9	0.3	0.1, 0.6	3	0.3	0.1, 0.9
	Medical Attention	17	1.7	1.0, 2.6	10	1.0	0.5, 1.8	10	1.0	0.5, 1.8	37	1.2	0.8, 1.6	16	1.6	0.9, 2.5
Irritability	Any	881	86.2	83.9, 88.3	939	90.5	88.6, 92.3	920	89.4	87.4, 91.2	2740	88.7	87.6, 89.8	926	91.2	89.3, 92.9
	Grade 2 or 3	510	49.9	46.8, 53.0	529	51.0	47.9, 54.1	520	50.5	47.4, 53.6	1559	50.5	48.7, 52.3	579	57.0	53.9, 60.1
	Grade 3	116	11.4	9.5, 13.5	107	10.3	8.5, 12.3	112	10.9	9.0, 12.9	335	10.8	9.8, 12.0	150	14.8	12.7, 17.1
	Medical Attention	16	1.6	0.9, 2.5	8	0.8	0.3, 1.5	8	0.8	0.3, 1.5	32	1.0	0.7, 1.5	14	1.4	0.8, 2.3
Loss of appetite	Any	582	56.9	53.8, 60.0	593	57.2	54.1, 60.2	589	57.2	54.2, 60.3	1764	57.1	55.4, 58.9	609	60.0	56.9, 63.0
	Grade 2 or 3	167	16.3	14.1, 18.8	169	16.3	14.1, 18.7	163	15.8	13.7, 18.2	499	16.2	14.9, 17.5	187	18.4	16.1, 20.9
	Grade 3	15	1.5	0.8, 2.4	13	1.3	0.7, 2.1	17	1.7	1.0, 2.6	45	1.5	1.1, 1.9	17	1.7	1.0, 2.7
	Medical Attention	8	0.8	0.3, 1.5	4	0.4	0.1, 1.0	6	0.6	0.2, 1.3	18	0.6	0.3, 0.9	5	0.5	0.2, 1.1

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).

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 MenHibrix 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% MenHibrix participants and 20.0% Hib recipients), otitis media (13.8% of MenHibrix subjects and 13.4% of Hib subjects), and pyrexia (10.4% and 11.9% of MenHibrix and Hib subjects, respectively).

Table 8: Systemic adverse reactions after the 4th dose, Fourth dose Total Vaccinated cohort (source: sponsor's Table 59, Hib-MenCY-TT-010, page 237)

Hib-MenCY-TT-010: Systemic adverse reactions after the 4 th 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 2 or 3	2526	269	10.6	9.5	11.9	830	98	11.8	9.7	14.2
	Grade 3	2526	42	1.7	1.2	2.2	830	13	1.6	0.8	2.7
	Med Attn	2526	12	0.5	0.2	0.8	830	4	0.5	0.1	1.2
Fever (rectally)	Any (≥ 38.0°C)	2527	341	13.5	12.2	14.9	831	134	16.1	13.7	18.8
	> 38.5°C	2527	126	5.0	4.2	5.9	831	58	7.0	5.3	8.9
	> 39.0°C	2527	49	1.9	1.4	2.6	831	17	2.0	1.2	3.3
	> 39.5°C	2527	18	0.7	0.4	1.1	831	5	0.6	0.2	1.4
	> 40.0°C	2527	4	0.2	0.0	0.4	831	1	0.1	0.0	0.7
Med Attn	2527	17	0.7	0.4	1.1	831	7	0.8	0.3	1.7	
Irritability	Any	2526	1482	58.7	56.7	60.6	830	534	64.3	61.0	67.6
	Grade 2 or 3	2526	519	20.5	19.0	22.2	830	217	26.1	23.2	29.3
	Grade 3	2526	78	3.1	2.4	3.8	830	31	3.7	2.6	5.3
	Med Attn	2526	18	0.7	0.4	1.1	830	7	0.8	0.3	1.7
Loss of appetite	Any	2526	825	32.7	30.6	34.5	830	287	34.6	31.3	37.9
	Grade 2 or 3	2526	174	6.9	5.9	7.9	830	78	9.4	7.5	11.6
	Grade 3	2526	36	1.4	1.0	2.0	830	15	1.8	1.0	3.0
	Med Attn	2526	16	0.6	0.4	1.0	830	4	0.5	0.1	1.2

Hib-MenCY-TT = Hib-MenCY-TT + MMRII + Varivax + Prevnar in subjects who received 3 doses of Hib-MenCY-TT + Pediarix + Prevnar in study Hib-MenCY-TT-009

Hib = PedvaxHIB + MMRII + Varivax + Prevnar in subjects who received 3 doses of ActHIB + Pediarix + Prevnar 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

All = all events, any intensity

Grade 2-3: all events grade 2 or grade 3 intensity

Grade 2 = drowsiness that interfered with normal activity; temperature >39.0°C - ≤ 40.0°C; crying more than usual/interfered with normal activity; eating less than usual/interfered with normal activity

Grade 3 = drowsiness that prevented normal activity; temperature > 40.0°C; crying that could not be comforted/prevented normal activity; not eating at all

Med Attn = event that prompted the parent/guardian to seek medical advice

In Hib-MenCY-TT-010, 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 ($> 40^{\circ}\text{C}$) 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 $< 39.0^{\circ}\text{C}$.

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.

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 $> 40^{\circ}\text{C}$ 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 $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$:

A co-secondary objective was to demonstrate the non-inferiority of Hib-MenCY-TT compared to *PedvaxHIB*[®] in terms of the incidence of fever $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{F}$ within the 4-day follow-up period after co-vaccination with *MMR_{II}*[®] and *Varivax*[®]. The between group difference in $p_{\text{Hib}} - p_{\text{HibMenCY}}$ was -0.11% [-0.66, 0.72], which met 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 $p_{\text{Hib}} - p_{\text{HibMenCYLot A}}$ was -0.38% [-1.59, 0.80], while for Hib-MenCY-TT Lots B and C combined overall/subject, the between group difference in $p_{\text{Hib}} - p_{\text{HibMenCYLots B and C}}$ was 0.32% [-0.52, 1.37]

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:

Study Hib-MenCY-TT-009:

Table 9: Comparison of percentage of subjects with SAE, NOCD, rash, AE resulting in ER visit, and AE resulting in medical doctor visit from Day 0 after Dose 1 to Month 6 following the 3rd dose or until administration of the 4th dose, whichever came first (Primary Total Vaccinated Cohort) (source: sponsor's Table 60, Hib-MenCY-TT-009 clinical study report, page 224)

	Hib-MenCY N = 3136				Hib N = 1044				Relative Risk (Hib-MenCY/Hib)		
	n	%	95% CI		n	%	95% CI		RR	95% CI	
LL			UL	LL			UL	LL		UL	
Primary System Organ Class											
At least one symptom	1552	49.5	47.7	51.3	515	49.3	46.3	52.4	1.00	0.91	1.11
SAE	126	4.0	3.4	4.8	50	4.8	3.6	6.3	0.84	0.60	1.19
NOCD	163	5.2	4.4	6.0	52	5.0	3.7	6.5	1.04	0.76	1.45
Rash	470	15.0	13.8	16.3	154	14.8	12.7	17.0	1.02	0.85	1.23
Emergency Room Visits	217	6.9	6.1	7.9	72	6.9	5.4	8.6	1.00	0.77	1.33
Physician Office Visits	1336	42.6	40.9	44.4	433	41.5	38.5	44.5	1.03	0.92	1.15

Hib-MenCY = 3 Hib-MenCY lot groups pooled: Hib-MenCY-TT Lot A, Lot B, or Lot C + Pediarix (+ Prevnar if available)

Hib = ActHIB + Pediarix (+ Prevnar 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

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

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

95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)

Note that the RR across countries is estimated by taking into account the country effect

Table 10: 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 (source: sponsor's Supplement 192, Hib-MenCY-TT-009 clinical study report, page 523)

Hib-MenCY-TT-009: 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															
	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	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
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

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, 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, *Pediarix*®, and *Prevnar*®. 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, *Pediarix*®, and *Prevnar*®.
- A 6 month old male Mexican infant died of “unknown” cause of death on day 30 after the 3rd Lot B HibMenCY-TT dose, *Pediarix*®, and *Prevnar*® 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, *Pediarix*®, and *Prevnar*®, 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 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. The rate of overall office visits were similar 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 relative risk of 2 events was statistically significantly greater in the Hib group as compared to the pooled HibMenCY-TT group: anorexia occurred in 0 HibMenCY-TT recipients and in 4 (0.4%) Hib subjects. The respective 95% CIs were [0.0, 0.1] and [0.1, 1.0]. The p-value for the relative risk is 0.0078. However, the point estimates and relative risks of similar diagnoses showed different trends. For example, poor weight gain was reported in 12/3136 HibMenCY-TT subjects, or 0.4% [0.2, 0.7] and in 0/1044 Hib subjects, or 0% [0.0, 0.4]. Although the percent difference of 0.4% is the same, the relative risk of infinity has a p-value of 0.637. Similarly, although the relative risk of bronchial hyperreactivity was statistically significantly higher in the Hib group (by p-value for the relative risk, although the 95% CI for the point estimates of the percentage of subjects with this entity overlapped), there was no statistically significant difference in relative risk of asthma.

Table 11: 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 (source: modified from sponsor's Tables 66, 67, 68, Hib-MenCY-TT-009 clinical study report, page 253 – 254)

HibMenCY-TT-009: 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																		
	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

Observed rates of any adverse event reported during the 4-day post-vaccination period tended to be higher in Australia (ranging from 99.3% of HibMenCY-TT recipients to 100% of Hib subjects) and Mexico (98.0% of subjects in both the HibMenCY-TT and Hib groups) than in the United States (95.2% of HibMenCY-TT and 93.4% of Hib recipients).

The sponsor 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.

Analyses of solicited local and systemic adverse events during days 0 -3 post-vaccination according to co-vaccination status during HibMenCY-TT-009:

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 *Pediarix*® and *Prevnar*®. In the U.S., 98.5% of subjects were fully co-vaccinated with *Pediarix*® and *Prevnar*® 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 study Hib-MenCY-TT-009 who did not participate in study Hib-MenCY-TT-010

A total of 558 subjects (including 72 subjects from the dropped U.S. study center) from study Hib-MenCY-TT-009 did not participate in Hib-MenCY-TT-010. Comparison of the incidence of adverse events in the subjects who did not continue to study 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 4th dose study. Generally, the rates of adverse events during study Hib-MenCY-TT-009 tended to be higher in subjects who continued into study HibMenCY-TT-010.

Study Hib-MenCY-TT-010:

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

Table 12: 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)

Hib-MenCY-TT-010 Serious adverse events, new onset of chronic disease(s), rash, emergency room visits and physician office visits through 31 days post-4 th dose vaccination (Fourth dose Total Vaccinated Cohort)								
	HibMenCY N = 2769				Hib N = 923			
	n	%	95% CI		n	%	95% CI	
			LL	UL			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

Hib-MenCY-TT = Hib-MenCY-TT + MMRII + Varivax + Prevnar in subjects previously given 3 doses of Hib-MenCY-TT + *Prevnar*® + *Pediarix*®

Hib = PedvaxHIB + MMRII + Varivax + *Prevnar*® in subjects previously given 3 doses of *ActHIB*® + *Prevnar*® + *Pediarix*®

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 mm³, and resolved 53 days later. Fever was present 2 days prior to ITP onset.

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 $\geq 5\%$ 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.

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

Table 13: 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 (source: sponsor Table 63, Hib-MenCY-TT-010 clinical study report, page 250)

Hib-MenCY-TT-010 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-4 th 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

During the period between fourth vaccination through the end of the ESMU, 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 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 mm³ range (normal range: 140,000 – 400,000 mm³). 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.

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.

Table 14: Percentage of subjects with SAE, NOCD, Rash, AE resulting in ER visit, and AE resulting in MD visit through ESFU (Fourth dose Total Vaccinated Cohort) following the 4th dose (source:

MenCY-TT-010: Percentage of subjects with SAE, NOCD, Rash, AE resulting in ER visit, and AE resulting in MD visit through ESFU (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%
at least one symptom	185	41.5	36.9, 46.2	62	42.5	34.3, 50.9	45	7.9	5.8, 10.5	9	4.7	2.2, 8.7	630	35.9	33.6, 38.2	203	34.8	30.9, 38.7
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, 3.3
new onset chronic disease	16	3.6	2.1, 5.8	7	4.8	1.9, 9.6	0	0.0	0.0, 0.6	0	0.0	0.0, 1.9	69	3.9	3.1, 4.9	26	4.5	2.9, 6.3
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, 13.5
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, 9.4
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, 30.7

Integrated summary of adverse events (Hib-MenCY-TT-009 and -010): Four dose series from dose 1 through the end of the ESFU after dose 4

At least one SAE was reported in 5.2% of MenHibrix 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 MenHibrix recipients and 1.1% of Hib participants.

At least one NOCD was reported in 7.3% of MenHibrix 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% MenHibrix subjects and 2.2% Hib subjects), asthma (1.1% of MenHibrix recipients and 1.3% of Hib participants), and bronchial hyperreactivity (0.5% of MenHibrix and 1.1% of Hib subjects).

At least one rash event was reported in 21.1% of MenHibrix 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% MenHibrix recipients and 5.0% Hib subjects), diaper dermatitis (3.0% MenHibrix subjects and 3.1% Hib participants), urticaria (1.7% MenHibrix participants and 1.8% Hib subjects), dermatitis (0.8% of MenHibrix and 1.2% of Hib subjects, respectively), and atopic dermatitis (0.9% MenHibrix and 1.1% Hib recipients).

At least one AE prompting an ER visit was reported in 10.3% of MenHibrix 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 MenHibrix and 0.8% of Hib subjects), upper respiratory tract infections (1.2% of MenHibrix and 1.1% of Hib recipients), pyrexia (1.1% of MenHibrix and 1.0% of Hib participants), bronchiolitis (1.0% of MenHibrix and 0.8% of Hib subjects), and viral infection (0.9% and 1.1% of MenHibrix and Hib recipients, respectively).

Analysis of solicited local and systemic adverse events during days 0 -3 post-vaccination according to co-vaccination status during HibMenCY-TT-010:

There were 2076 Hib-MenCY-TT and 691 Hib subjects fully co-vaccinated with Hib-MenCY-TT or Hib, *Pprevnar*®, *MMR*®_{1,1} and *Varivax*® 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: comments regarding meningococcal immunogenicity are deferred pending sponsor's response to CBER's CR letter.

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 15: 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 (source: sponsor’s Tables 32, Hib-MenCY-TT-010 clinical study report, page 194; Table 26, Hib-MenCY-TT-009 clinical study report, page 166; and Tables 1, 2 of the Effectiveness Information Amendment of January 8, 2010)

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-3 rd 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		
				n		95% CI		n		95% CI		Value	95% CI	
Antibody	Group	Timing	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
anti-PRP	HibMenCY Lots A, B, C combined	Post 3	469	469	100	99.2	100	451	96.2	94.0	97.7	10.802	9.767	11.947
		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	160	156	97.5	93.7	99.3	145	90.6	85.0	94.7	6.086	4.897	7.564
		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	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	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

HibMenCY = Hib-MenCY-TT + MMR_I® + Varivax® + Prevnar® in subjects who received 3 doses Hib-MenCY-TT + Pediarix® + Prevnar® in study Hib-MenCY-TT-009

Hib = PedvaxHIB® + MMR_{II} + Varivax + Prevnar in subjects who received 3 doses ActHIB® + Pediarix® + Prevnar® 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 + Pediarix®/Infanrix penta® (+ Prevnar®)

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 (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 μ g/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 μ g/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 μ g/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 μ g/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 16: Percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL and GMCs post-4th dose vaccination (source: sponsor’s Table 36, Hib-MenCY-TT-010 clinical study report, page 201)

Percentage of subjects with anti-PRP concentrations ≥ 0.15 mcg/mL and ≥ 1.0 mcg/mL and GMCs post-4 th dose vaccination (Fourth dose ATP Cohort for Immunogenicity, Cohort 1)													
			≥ 0.15 mcg/mL				≥ 1.0 mcg/mL				GMC		
					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

HibMenCY = Hib-MenCY-TT + MMR_{II}® + Varivax® + Prevnar® in subjects who received 3 doses Hib-MenCY-TT + Pediarix® + Prevnar® in study Hib-MenCY-TT-009

Hib = PedvaxHIB® + MMR_{II} + Varivax + Prevnar in subjects who received 3 doses ActHIB® + Pediarix® + Prevnar® 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

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 ≥ 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 ≥ 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.

Summary:

In study Hib-MenCY-TT-009, 258 SAEs were reported for 176 individuals [Hib-MenCY-TT n=126 subjects, 194 events; Hib n=50 subjects, 64 events]. Four deaths occurred during the ESFU, 3 in the HibMenCY-TT group and 1 in the Hib group. 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. From the clinical reviewer’s perspective, no meaningful differences were observed in the presented study population when comparing MenHibrix to the licensed control vaccine for local and systemic solicited adverse events, unsolicited AEs, and SAEs over the included reporting periods.

Due to the small sample size, no definite conclusions could be reached regarding concomitant influenza or hepatitis A vaccination.

Conclusions regarding meningococcal immunogenicity are deferred pending the sponsor's response to CBER's CR letter. The primary endpoints for the Hib vaccine component were met, although the poolability of the data from combined lots A, B, and C of MenHibrix remains in question.

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.

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. Please note that refrigerated *Varivax*® was used, and *Meningitec*® was used as the licensed MenC conjugate vaccine.

The study components relevant to U.S. licensure are the evaluations of the non-inferiority of co-administered MMR and V vaccines. Only the objectives germane to these evaluations are included below.

Objectives

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} and *Varivax*® 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*®_{II} and *Varivax*®. This comparison includes pooled data from Studies Hib-MenCY-TT-008 and -010.

Safety Objective:

In all participants:

- To evaluate the safety and reactogenicity of each vaccine, when co-administered with *MMR*®_{II} and *Varivax*®.

Study Design:

- The primary vaccination phase was an open, randomized (3:1:1), controlled multicenter study with 3 parallel groups. Infants were randomized to one of the following groups:
 - Hib-MenCY-TT group: Hib-MenCY-TT + *Infanrix*® *penta*† + *Prevenar*® [n=660]
 - Lic MenC group: *Meningitec*®* + *ActHIB*® + *Infanrix*® *penta*† + *Prevenar*® [n=220] (Not relevant to U.S. licensure)
 - *ActHIB*® group: *ActHIB*® + *Infanrix*® *penta*† + *Prevenar*® [n=220]
- The fourth dose vaccination phase was an open, randomized (3:1:1), controlled multicenter study with 3 parallel groups. Infants were randomized to one of the following groups:
 - Hib-MenCY-TT primed group: Hib-MenCY-TT + *MMR*®_{II} and *Varivax*® [n=660]
 - Lic MenC primed group: Hib-MenCY-TT + *MMR*®_{II} and *Varivax*® [n=220] (Not relevant to U.S. licensure)
 - *ActHIB*® primed group: *ActHIB*® + *MMR*®_{II} and *Varivax*® [n=220]

† trademark in the U.S. is *Pediarix*®

* Licensed in Australia, but not licensed in the U.S.

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)

March 6, 2006 – 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, ≥ 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 $<38^{\circ}\text{C}$, axillary $<37.5^{\circ}\text{C}$. A temperature greater than or equal to these cut-offs required deferral of vaccination 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 for the fourth dose vaccination phase of the study; these criteria were 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.

Reasons for deferring vaccination:

- Acute disease at the time of vaccination. (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 $<38^{\circ}\text{C}$, axillary temperature $<37.5^{\circ}\text{C}$).
- Fever at the time of vaccination (rectal temperature $\geq 38^{\circ}\text{C}$, axillary $\geq 37.5^{\circ}\text{C}$).

Vaccine administration

Infant participants received, intramuscularly, Hib-MenCY-TT or a monovalent Hib vaccine (*ActHIB*®) in the primary vaccination phase. The first 3 doses of Hib-MenCY-TT and the monovalent Hib vaccine were administered at two month intervals, at approximately 2, 4, and 6 months of age. Toddler participants received, intramuscularly, Hib-MenCY-TT or a monovalent Hib vaccine (*PedvaxHIB*®) at 12 to 15 months of age.

DTaP-HBV-IPV combination vaccine was mandated as a concomitant vaccine with the first 3 vaccinations and MMR, varicella, and PCV7 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, defined by the sponsor 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 ≥ 28 ED₅₀ in subjects with titer < 28 ED₅₀ 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 ≥ 10 IU/mL (ELISA, Enzygost®) in subjects seronegative (< 4 IU/mL) before vaccination.

*According to Dr. Rubin's review, CBER considers seroresponse using these assays to be defined as:

- Anti-measles seroresponse: anti-measles virus antibody concentration ≥ 200 mIU/mL in subject with a pre-vaccination antibody concentration of < 150 mIU/mL
- Anti-mumps seroresponse: anti-mumps virus neutralizing antibody titer $\geq 1:51$ in subjects with a pre-vaccination antibody titer of < 1:24
- Anti-rubella seroresponse: anti-rubella virus antibody concentration of ≥ 10 IU/mL (ELISA, Enzygost®) in subjects seronegative (< 4 IU/mL) before vaccination.

According to Dr. Tang's review, the relevant cut-off for the varicella assay may be $\geq 1:40$

Data using both definitions is included in the tables included in this review.

Secondary Endpoints:

Immunogenicity endpoints:

Fourth dose vaccination:

Forty-two days after the 4th vaccination in all subjects in the Hib-MenCY-TT, *Meningitec*®, and *ActHIB*® groups:

- Anti-PRP concentration ≥ 0.15 mcg/mL, ≥ 1.0 mcg/mL and concentration
- rSBA-MenC titer $\geq 1:8$ and $\geq 1:128$, and titers
- rSBA-MenY titer $\geq 1:8$ and $\geq 1:128$, and titers
- hSBA-MenC titer $\geq 1:4$ and titers
- hSBA-MenY titer $\geq 1:4$ and titers
- Anti-PSC concentration ≥ 0.3 mcg/mL and ≥ 2 mcg/mL, and concentration
- Anti-PSY concentration ≥ 0.3 mcg/mL and ≥ 2 mcg/mL, and concentration
- Anti-measles seroconversion and concentration
- Anti-mumps seroconversion and titers
- Anti-rubella seroresponse and concentration
- Anti-varicella seroconversion and concentration

Safety endpoints:

Safety endpoints included incidence of: solicited local and systemic symptoms within 4 days following each vaccine dose; unsolicited symptoms from dose 1 through Day 30 following dose 3 of Hib-MenCY-TT Vaccine and *ActHIB*®; SAEs (serious adverse events²) during the entire study; any of the following events, from enrollment up to last study contact at 18-21 months of age: SAEs, 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.

Randomization

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

Sub-randomization for serology

A sub-randomization list was generated and sent electronically to investigators. The list randomly assigned subjects in each of the 3 groups in a 3:1:1 ratio. In study Hib-MenCY-TT-007, 50% of the subjects in the Hib-MenCY-TT group, *Meningitec*® group, and *ActHIB*® group were allocated to have serological tests post-dose 2 for rSBA-MenC, rSBA-MenY, hSBA-MenC, hSBA-MenY, anti-PSC, anti-PSY, and anti-PRP; 50% of subjects were allocated to have serological tests post-dose 3 for anti-PRP, rSBA-MenC, rSBA-MenY, hSBA-MenC, hSBA-MenY, anti-PSC, and anti-PSY. hSBA-MenC and hSBA-MenY were assessed in the first 30% of the total samples (all groups pooled) at each timepoint.

Surveillance

Safety

Study participants were observed for 30 minutes post-vaccination and monitored for body temperature, local and systemic reactions for 3 days post-vaccination and for unsolicited adverse events for 30 days post-vaccination reported on daily diary cards by the subjects' guardians. Solicited adverse events included localized reactions, such as pain, redness, and swelling, as well as systemic symptoms, such as fever, irritability/fussiness, drowsiness, and loss of appetite. In the fourth dose vaccination phase, additional information was collected on the diary card regarding MMR and V specific solicited symptoms through day 42 post-4th dose vaccination. For each solicited and unsolicited symptom 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.

Regarding specific AEs of interest 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 entire study period (day 0 to 6 months) via diary cards days 0 - 30, study visits, and telephone contact at 18 - 21 months of age.

Effectiveness (immunogenicity):

Blood draws occurred just prior to administration of the 3rd dose, i.e., post-dose 2, in half of the subjects in each group and one month after the 3rd dose in the other half of subjects in each group, just prior to the 4th vaccination in all subjects, and 42 days after the 4th vaccination in all subjects. hSBA-MenC and hSBA-MenY were evaluated in the first 30% of the total samples (all groups pooled) at each timepoint. There was no similar subset selection for evaluation of anti-PRP response.

Statistical plan

Sample size calculations

The planned sample size of 1100 for the primary vaccination phase (Hib-MenCY-TT n=660, *ActHIB*® n=220, *Meningitec*® n=220) and of these subjects pooled with an additional 1280 subjects from the immunogenicity cohort from study Hib-MenCY-TT-009/010 for the fourth dose vaccination phase enabled at least 80% global power to detect meeting of the co-primary objectives.

A planned interim analysis of immunogenicity was performed when the immunogenicity data for at least 100 subjects at both the post-dose 2 and post-dose 3 timepoints were available. The analysis included all available data up to February 24, 2006 for subjects included in the Interim Immunogenicity Cohort (subjects with at least 1 immunogenicity datapoint available at the time of the interim analysis): 364 subjects (217 in the Hib-MenCY-TT group, 72 in the *Meningitec*® group, and 75 in the *ActHIB*® group). The exploratory analyses included in this interim analysis were: the percentage of subjects with antibody levels greater than or equal to proposed cut-offs with 95% CI and GMCs/GMTs with 95% CI for each vaccine antigen for which results were available; distribution of rSBA-MenC/Y titers, hSBA-MenC/Y titers, and anti-PSC/Y concentrations; reverse cumulative distribution curves for anti-PRP, rSBA-MenC/Y, hSBA-MenC/Y, and anti-PSC/Y antibodies. Non-overlapping of the 95% CI between the 3 groups was used as an indicator of statistically significant differences.

Populations analyzed

Fourth dose vaccination phase:

Pre- and post-4th dose vaccination immunogenicity analyses were performed on data pooled from 2 studies: study Hib-MenCY-TT-007/008 and the immunogenicity and safety cohort from a second study with the same ATP cohort definition, Hib-MenCY-TT-009/010. These analyses were also repeated within each study. The analysis of antibody

persistence and immunogenicity after the 4th dose Hib-MenCY-TT and MMR and V vaccination were based on the 4th dose ATP cohort for safety and the 4th dose ATP cohort for immunogenicity, respectively. If, for any vaccine group, the percentage of enrolled subjects with serological results excluded from an ATP cohort was higher than 5%, a second analysis based on the Total vaccinated cohort was performed to complement the ATP analysis. All safety analyses were based on the 4th dose total vaccinated cohort. Since in each vaccine group, the percentage of enrolled subjects excluded from the Fourth dose ATP cohort for safety was < 5%, no additional safety analyses based on the ATP cohort was performed. Since > 5% of the enrolled subjects with serological results were excluded from the Fourth dose ATP cohort for immunogenicity, an additional analysis was performed on the Fourth dose Total Vaccinated Cohort to complement the ATP analysis.

Total 4th dose vaccinated cohort:

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 concerning 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.

ATP 4th dose cohort for safety:

Included all eligible subjects who met all inclusion criteria and no exclusion criteria, received 3 doses in the primary vaccination phase, received the 4th vaccination, and who did not receive a vaccine forbidden or not specified in the protocol.

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_{II}*® and *Varivax*® 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_{II}*® and *Varivax*®.

This hypothesis would be supported by the data if the lower limit of the two-sided standardized asymptotic 95% CI on the difference in two proportions (pHib-MenCY-TTprimed – p*ActHIB*® primed) were:

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

Results:

Population

A total of 1104 subjects were enrolled and 1103 subjects were vaccinated in Hib-MenCY-TT-007 study (661 in group Hib-MenCY-TT, 221 in group *Meningitec*®, and 221 in group *ActHIB*®), 1078 completed the study (647 in group Hib-MenCY-TT, 215 in group *Meningitec*®, and 216 in group *ActHIB*®), and 1038 were enrolled in the ESFU (626 in group Hib-MenCY-TT, 206 in group *Meningitec*®, and 206 in group *ActHIB*®). Twenty-five subjects withdrew from study Hib-MenCY-TT-007 (14 Hib-MenCY-TT recipients, 6 *Meningitec*® subjects, and 5 *ActHIB*® participants). Three of these 25 subjects withdrew because of a SAE: 1 Hib-MenCY-TT subject had a hypotonic-hyporesponsive episode on the day of the first vaccination, 1 Hib-MenCY-TT subject had epilepsy 18 days post-2nd dose, and 1 Hib-MenCY-TT subject had a skull fracture. One subject withdrew because of a non-serious AE (fever in a Hib-MenCY-TT subject). Seven subjects withdrew consent (not due to an AE), and an additional 7 subjects moved from the study area. The study group breakdown for these 14 subjects was: Hib-MenCY-TT, 2 and 3; *Meningitec*®, 3 and 3; and *ActHIB*® 2 and 1, respectively. Five subjects were lost to follow-up, 3 in the Hib-MenCY-TT group and 2 in the *ActHIB*® group. One Hib-MenCY-TT recipient was withdrawn for “other reasons”, having not attended visits or returned the diary cards.

Of the total vaccinated cohort of 1103 subjects, 7 subjects were excluded from the ATP safety cohort due to protocol violations (6 in the Hib-MenCY-TT group and 1 in the *Meningitec*® group). An additional 99 subjects were excluded from the ATP cohort for immunogenicity, 3 for protocol violations (3 Hib-MenCY-TT subjects), 21 for non-compliance with vaccination or blood sampling schedules (13 Hib-MenCY-TT, 3 *Meningitec*®, and 5 *ActHIB*® subjects), and 75 for missing serological data (43 Hib-MenCY-TT, 13 *Meningitec*®, and 19 *ActHIB*® subjects).

There were 1038 subjects from study Hib-MenCY-TT-007 enrolled in Hib-MenCY-TT-008. Of the 66 subjects not enrolled in study Hib-MenCY-TT-008, 25 subjects (9 in group Hib-MenCY-TT, 7 in group Meningitec, 8 in group Hib, and 1 subject who was not assigned to a group in study Hib-MenCY-TT-007. Twelve subjects (8 in group Hib-MenCY-TT, 1 in group Meningitec, and 3 in group Hib) were lost to follow-up. Twenty-four subjects (14 in group Hib-MenCY-TT, 6 in group Meningitec, and 4 in group Hib) did not participate due to other reasons (e.g., migration from study area, parents withdrew subject from study). Subject 1515, who was withdrawn from study Hib-MenCY-TT-007 due to seizures did not participate in the 4th dose vaccination phase; this subject was classified as “not willing to participate due to other reason” by the investigator. Three subjects had a subject number allocated but were not vaccinated in study Hib-MenCY-TT-008: the parents of subject 1013 in the Hib group withdrew consent, and subjects 1024 (group Hib-MenCY-TT) and 1617 (group Hib) had a history of measles, mumps, rubella, or varicella. The parents/guardians or investigator of 5 subjects (4 in group Hib-MenCY-TT and 1 in group Meningitec) did not want the child to participate due to an AE or SAE. One of these 4 Hib-MenCY-TT recipients experienced generalized seizures 62 days post-3rd dose of Hib-MenCY-TT, Infanrix penta, and Prevnar. The child was hospitalized 4 days later, and neurological examination showed a focal disturbance of cerebral activities. The child was diagnosed as having epilepsy and was discharged 3 weeks after hospitalization. The event was unresolved. The child was seen in the ER 6 days post-discharge because of increased seizure activity and was sent home from the ER. Three and a half months later, the SAE was unresolved. The Meningitec participant who was withdrawn due to SAE experienced fever, decreased feeding, and pain 12 days post-dose 1 of Hib, Infanrix penta, Prevnar, and Meningitec. The child was hospitalized the next day and diagnosed with sepsis and underlying urinary reflux. The child was discharged from the hospital 5 days later and had recovered without sequelae 6 days later. Approximately 20 days later, the child developed fever, was hospitalized 2 days later, and was diagnosed with a viral illness. The child was discharged 2 days later, and the event resolved without sequelae the next day.

Of the 1035 subjects who were vaccinated during Hib-MenCY-TT-008 (625 in group Hib-MenCY-TT, 206 in group Meningitec, and 204 in group Hib), 1029 subjects completed the 4th dose vaccination study (623 in group Hib-MenCY-TT, 203 in groups Meningitec 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 Meningitec) migrated from the study area; 2 subjects (1 in group Meningitec 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 just delivered a new baby and was not available.

All 1038 subjects enrolled in study Hib-MenCY-TT-008 were included in the ESFU phase, and 1025 of them completed that phase of the study (620 in group Hib-MenCY-TT, 204 in group Meningitec, and 201 in group Hib). A total of 13 subjects withdrew before the end of the ESFU phase: 2 subjects (1 in group Hib-MenCY-TT and 1 in group Hib) withdrew consent; 6 subjects (4 in group Hib-MenCY-TT, 1 in group Hib, and 1 in group Meningitec) were lost to follow-up; additionally, 2 subjects (1 in group Meningitec and 1 in group Hib) were already lost to follow-up during the 4th dose phase of the study; 3 subjects were classified as other (1 Hib recipient died during the ESFU period, 1 Hib-MenCY-TT participant moved overseas and could not be contacted, and 1 Hib subject was withdrawn at the 4th dose phase due to history of varicella).

Of the total vaccinated cohort of 1035 subjects in study Hib-MenCY-TT-008, a number of protocol violations prompted exclusion of 37 subjects from the Fourth dose ATP cohort for safety: 17 subjects did not receive vaccine according to protocol; 17 subjects either did not receive the study vaccine according to protocol, had a protocol violation linked to inclusion/exclusion criteria, or were eliminated because of non-compliance with the vaccination schedule in study Hib-MenCY-TT-007; 3 subjects were vaccinated at an inappropriate age. 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, *Meningitec*[®] n=206, *ActHIB*[®] 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 *Meningitec*[®], and 201 in group *ActHIB*[®]).

4th dose immunogenicity population:

Analysis of 4th dose immunogenicity was based on the 4th dose ATP cohort for immunogenicity, which included 921 participants (Hib-MenCY-TT n=554, *Meningitec*[®] n=185, *ActHIB*[®] n=182). The demographics of the 3 treatment groups for the Fourth dose ATP cohort for immunogenicity were comparable with respect to mean age, gender, and racial distributions. The mean age at Visit 5 was 53.2 weeks, the overall distribution of females and males was 49.1% and 50.9%, respectively, and the population was predominantly White/Caucasian (95.5% of subjects).

Safety:Overall safety profile:

Following the fourth dose, the overall incidence of adverse events during the 4-day post-vaccination period was 89.3% [558/625], 88.3% [182/206], and 96.6% [197/204] in the Hib-MenCY-TT, Meningitec, and Hib groups, respectively. The confidence intervals for Hib-MenCY-TT and Hib did not overlap. The incidence of grade 3 adverse events overall/subject was 8.6%, 9.7%, and 15.7% among Hib-MenCY-TT, Meningitec, and Hib recipients, respectively. The clinical review of safety in this Phase II study focuses on SAEs and MMR and V solicited adverse events.

Serious adverse events during the 31 days post-vaccination period after the 4th MenHibrix dose:

14 SAEs were reported in 14 subjects: 10 in Hib-MenCY-TT subjects, 2 in Meningitec subjects, and 2 in Hib subjects. One Hib recipient reported urinary tract infection. All SAEs occurred in $\leq 0.5\%$ of subjects in each group. All SAEs during this time period resolved without sequelae.

Serious adverse events through the Extended Safety Follow Up (ESFU) period after the 4th dose:

Seventy-two SAEs were reported for 60 individuals [Hib-MenCY-TT n=40 subjects, 50 events; *Meningitec*[®] n=12 subjects, 13 events; Hib n=8 subjects, 9 events]. The most frequently reported SAEs were gastroenteritis (1.8%) and otitis media (1.3%) in group Hib-MenCY-TT and bronchiolitis (1.5%) in group *Meningitec*[®]. Other SAEs were reported in $< 1\%$ of the subjects of each group. Acute infection (bronchiolitis, croup, gastroenteritis, urinary tract infection, otitis media, pharyngeal abscess, pneumonia, tonsillitis, upper respiratory tract infection, and viral infection) accounted for 32/50 SAEs in Hib-MenCY-TT participants, 9/13 SAEs in *Meningitec*[®] subjects, and 5/9 SAEs in Hib recipients. One Hib recipient had urinary tract infection. All SAEs except 2 resolved without sequelae: a child diagnosed with acute lymphocytic leukemia 12 months post-4th dose of Hib-MenCY-TT and 1st doses of MMRII and Varivax (details of this SAE are provided below); a child diagnosed with sleep apnea 7 months post-4th dose of Hib-MenCY-TT and 1st doses of MMRII and Varivax whose sleep apnea resolved with sequelae 1 month later. No SAEs or AEs that started during study Hib-MenCY-TT-008 led to premature discontinuation of the study.

Pertinent case narratives

A 13 month-old Australian male developed urinary tract infection (UTI) 19 days post-dose 1 of PedvaxHIB, MMRII, and Varivax. He presented with fever, was diagnosed with tonsillitis, treated with penicillin, and then presented with persistent fever and rigors the following day. He was hospitalized. Blood and urine cultures were negative. Urinalysis obtained by unspecified method demonstrated > 1000 WBCs and > 100 RBCs. Renal ultrasound was normal. He was treated with trimethoprim and sulfamethoxazole, and the event resolved on day 7. The presence or absence of symptoms of Kawasaki disease is not mentioned. However, it is possible that his urine culture was negative because he had received 1 dose of penicillin prior to its collection.

A 12 month-old Australian male developed coryza, fever, respiratory distress, and petechial rash on the face and trunk 32 days post-4th dose of Hib-MenCY-TT and post-1st dose of MMRII and Varivax. He was tachypneic, tachycardia, and hypoxic in the ER, had widespread wheezing and crepitations with respiratory distress, and nasal aspirate was positive for Respiratory Syncytial Virus (RSV). The petechiae did not progress and resolved during hospitalization. Chest x-ray is reported as "consistent with bronchiolitis". He was hospitalized and treated with oxygen, salbutamol, and prednisolone. The event resolved day 14. Given the location and reported clinical course of the petechiae, they may be reasonably associated with the child's respiratory symptoms.

A 14 month-old Australian female with a family history of febrile seizures presented with rhinorrhea, cough, and irritability 67 days post-4th dose of Hib-MenCY-TT, post-1st dose of MMRII and Varivax. Approximately 6 days later, the child's mother noticed that she had a vacant look and seemed to twitch a couple of times while sitting in the car seat. She was unresponsive and floppy when picked up. The event lasted 1 – 2 minutes. In the ER, she was noted to have fever (39.5C), rhinorrhea, and slight tonsillar erythema. Blood cultures were negative, and urinalysis was normal. She was diagnosed with febrile seizure and upper respiratory tract infection, was hospitalized for observation, and was discharged the following day. The next day, she presented to the ER with persistent fever, vomiting, and refusal of oral fluids. White blood cell count was elevated, electrolytes, urine culture, nasopharyngeal aspiration, and chest x-ray were normal. She was hospitalized and treated with intravenous fluids. She was considered recovered and discharged 3 – 4 days later.

A 15 month-old Australian female experienced a febrile seizure 57 days post-4th dose of Hib-MenCY-TT, post-1st dose of MMRII and Varivax. She had developed cough, fever, and rhinorrhea the day before. The seizure lasted 30 seconds and resolved that day. She was hospitalized, discharged the next day, and the upper respiratory tract infection resolved approximately 2 days later. Electrolytes and complete blood count were reported as normal. An electroencephalogram (EEG) was not performed.

In study Hib-MenCY-TT-008, a 14 month-old Australian male with a family history of febrile seizures developed febrile seizure and vomiting 59 days post-4th dose of Hib-MenCY-TT and 1st dose of MMRII and Varivax. He had presented with fever the day prior and was started on antibiotics. He was hospitalized, found to have enlarged tonsils and tonsillar exudates. Throat swab was reportedly negative for bacterial infection. EEG was not performed. He was discharged the following day, and the tonsillitis resolved approximately 2 days post-discharge.

A 24 month old Australian female developed acute lymphocytic leukemia 12 months post-4th dose of Hib-MenCY-TT and post-1st dose of MMRII and Varivax. She presented approximately 2 months prior to diagnosis with limping after a fall. Transparent bone was noted on x-ray, and unspecified blood tests (presumably complete blood count) were “negative for signs of leukemia”. Over the next few weeks, she became tired more easily, lethargic, and “generally not herself”. No other information was presented, and the outcome is unknown. The diagnosis occurred after the conclusion of the ESFU but was noted when the investigator spoke with the child’s mother about a sibling enrolled in another study.

MMR and V solicited symptoms:

Fever was reported similarly across groups (52.1% of Hib-MenCY-TT subjects, 53.0% of Meningitec subjects, and 55.7% in Hib subjects) during the 42 day follow-up period. Fever peaked at approximately day 9 post-vaccination in all groups, and fever > 40.0C was reported infrequently (\leq 3.5% of subjects per group). No subject reported suspected signs of meningismus. Parotid/salivary gland swelling was reported in 5 subjects, 4 Hib-MenCY-TT recipients and 1 Meningitec participant. Rash was reported in 37.3%, 42.6%, and 32.8% of Hib-MenCY-TT, Meningitec, and Hib recipients, respectively. Rashes with more than 200 lesions were reported in 5.0%, 7.9%, and 3.5% of Hib-MenCY-TT, Meningitec, and Hib participants, respectively. Rashes with fever were reported in 19.8%, 25.7%, and 20.1% of the subjects in the Hib-MenCY-TT, Meningitec, and Hib groups, respectively. Rashes reportedly assessed as measles/rubella-like or varicella-like were reported in 8.5% and 15.2% of Hib-MenCY-TT subjects, 12.6% and 14.6% of Meningitec participants, and 10.3% and 11.3% of Hib subjects, respectively.

Immune responses to MMR and V vaccine components:

Table 17: Percentages of subjects with anti-measles, anti-mumps, anti-rubella, and anti-varicella titers meeting pre-specified immune response cut-offs (source: sponsor’s Tables 30, 32, 33, 34 in Hib-MenCY-TT-010 clinical study report, page 130 – 134)

Percentage of subjects with anti-measles concentrations ≥ 150 mIU/mL and ≥ 200 mIU/mL and GMCs post-4 th dose vaccination													
			≥ 150 mIU/mL				≥ 200 mIU/mL				GMC		
			95% CI				95% CI				95% CI		
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
Anti-measles	HibMenCY	501	469	93.6	91.1	95.6	466	93.0	90.4	95.1	1627.494	1469.996	1801.866
	Hib	171	163	95.3	91.0	98.0	162	94.7	90.2	97.6	1786.404	1523.083	2095.250
Percentage of subjects with anti-mumps titers ≥ 28 ED50 and ≥ 51 ED50 and GMTs post-4 th dose vaccination													
			≥ 28 ED50				≥ 51 ED50				GMT		
			95% CI				95% CI				95% CI		
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
Anti-mumps	HibMenCY	332	330	99.4	97.8	99.9	-	-	-	-	121.825	113.250	131.050
	Hib	110	110	100	96.7	100	-	-	-	-	119.613	105.928	135.065
Percentage of subjects with anti-rubella concentrations ≥ 4 IU/mL and ≥ 10 IU/mL and GMCs post-4 th dose vaccination													
			≥ 4 IU/mL				≥ 10 IU/mL				GMC		
			95% CI				95% CI				95% CI		
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
Anti-rubella	HibMenCY	500	500	100	99.3	100	498	99.6	98.6	100	78.779	73.941	83.932
	Hib	171	171	100	97.9	100	171	100	97.9	100	76.691	69.019	85.217
Percentage of subjects with anti-varicella titers $\geq 1:5$ and $\geq 1:40$ and GMTs post-4 th dose vaccination													
			$\geq 1:5$				$\geq 1:40$				GMT		
			95% CI				95% CI				95% CI		
Antibody	Group	N	n	%	LL	UL	n	%	LL	UL	Value	LL	UL
Anti-varicella	HibMenCY	404	403	99.8	98.6	100	403	99.8	98.6	100	414.633	391.361	439.288
	Hib	119	119	100	96.9	100	119	100	96.9	100	438.280	394.261	487.214

Table 18: Ratios (group Hib-MenCY-TT/group Hib) of anti-measles, anti-mumps, anti-rubella, anti-varicella GMC/Ts 42 days post-vaccination with 4th dose (source: sponsor's Supplement 54, Hib-MenCY-TT-008 clinical study report, page 210)

Ratios (group Hib-MenCY-TT/group Hib) of anti-measles, anti-mumps, anti-rubella, anti-varicella GMC/Ts 42 days post-vaccination (Fourth dose ATP Cohort for Immunogenicity)							
Antibody	Hib-MenCY		Hib		GMC/T ratio (HibMenCY/Hib)		
	N	GMC/T	N	GMC/T	Value	95% CI	
						LL	UL
Anti-measles (mIU/mL)	542	1678.4	178	1820.0	0.92	0.76	1.11
Anti-mumps (U/mL)	509	125.1	165	127.3	0.98	0.87	1.11
Anti-rubella (IU/mL)	540	77.9	177	76.0	1.03	0.91	1.16
Anti-varicella	548	421.1	179	431.2	0.98	0.88	1.08

One Hib-MenCY-TT participant in was diagnosed clinically with mumps parotiditis approximately 2 years and 8.5 months post-vaccination with the 4th dose of Hib-MenCY-TT and the 1st dose of MMRII and Varivax. Reportedly, 3 days after onset, the child was evaluated by the physician for a 3 day course of illness, with fever and initially unilateral facial swelling, which had become bilateral by the physician visit. No blood tests or other diagnostic tests were performed, and the child was improved and had not developed any complications by telephone review 6 days later. Anti-mumps titer of 526 was noted 42 days post-vaccination.

Summary and Conclusions:

For purposes of U.S. licensure, this study provided data to support concomitant use of MenHibrix with MMR and varicella vaccines in 12 month old toddlers. Pre-specified co-primary endpoints were based on pooled safety and immunogenicity data from this study and study Hib-MenCY-TT-010. CBER agreed to assessment based on pooled data if the respective endpoints were met in the individual studies. Therefore, concomitant immunogenicity data were presented for each individual study. Based on the available data from study Hib-MenCY-TT-008, concomitant vaccine responses to measles, mumps, rubella, and varicella components were similar among study groups receiving MenHibrix or Hib. Immunogenicity data from study Hib-MenCY-TT-010 and the pooled analysis will be presented in the full clinical review following the sponsor's response to CBER's CR letter.

The groups receiving MenHibrix or Hib with concomitant vaccines were similar in proportions of subjects reporting any adverse event, local adverse event, systemic adverse event, and adverse events of special interest during the ESFU. One subject in the Hib group had cardiomyopathy reported during the ESFU and died at 17 months of age. Due to the timing and nature of the disease, it is unlikely that this death was related to vaccination.

Study 101858 Hib-MenCY-TT-005 (Primary vaccination)/ Study 102015 Hib-MenCY-TT-006 (Booster vaccination): review deferred pending response to CR letter.

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 an active primary vaccination phase through 1 month after the 3rd vaccination and an active 4th dose vaccination phase from administration of the 4th dose to day 31 post-vaccination. The extended follow-up phases were an extended safety follow-up (ESFU) phase for primary vaccination from the end of the active primary vaccination phase (one month post-dose 3) to the 4th dose and an ESFU phase for 4th dose vaccination from the end of the active 4th dose vaccination phase (one month post-4th dose) through Month 5 post-4th dose.

Objectives

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

- To evaluate occurrence of serious adverse events (SAEs), new onset of chronic disease (NOCD), rash, and emergency room (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: Initiation: September 15, 2006

Completion ESFU: March 28, 2008

Study Period for Hib-MenCY-TT-012: Initiation: July 13, 2007

Completion ESFU: November 12, 2008

Population

The study was conducted at 59 centers in the U.S. and 2 centers in Mexico. One U.S. site was excluded due to Good Clinical Practice (GCP) violations.

Inclusion criteria

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

Exclusion criteria

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

Reasons for deferring vaccination:

- Acute disease, defined as moderate or severe illness with or without fever.
- Fever [defined as rectal temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$), axillary/oral temperature $\geq 37.5^{\circ}\text{C}$ ($\geq 99.5^{\circ}\text{F}$), tympanic temperature on oral setting $\geq 37.5^{\circ}\text{C}$ ($\geq 99.5^{\circ}\text{F}$), or tympanic temperature on rectal setting $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)].

Vaccine administration

Participants received, intramuscularly, Hib-MenCY-TT or a monovalent Hib vaccine. For the primary vaccination phase, ActHIB was administered. PedvaxHIB was preferred for the fourth Hib vaccination, but ActHIB was an acceptable alternative. Pediarix was administered concomitantly, and Prevnar was given concomitantly to all subjects receiving monovalent Hib and to subjects receiving Hib-MenCY-TT if Prevnar was available.

As in study Hib-MenCY-TT-009/010, PCV7 (4th dose), MMR, and varicella vaccines were provided as study vaccines for the U.S. safety and immunogenicity cohort (cohort 1). MMR and varicella vaccines were not mandated as concomitant vaccines for the safety only cohort (cohort 2) and the Mexico safety and immunogenicity cohort (cohort 3), but their administration was permitted 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, labeled indications, and availability. GSK provided Prevnar to Mexican sites for study Hib-MenCY-TT-011. Synagis and influenza and rotavirus vaccines were permitted to be co-administered with primary immunization according to local recommendations. For study Hib-MenCY-TT-012, PCV7, MMR, and varicella were provided as study vaccines, while Hepatitis A and influenza vaccines were permitted vaccines.

Endpoints

Primary endpoints: pooled dataset of all 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: pooled dataset of all 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. Solicited adverse events (AEs) and non-serious, unexpected AEs (other than those defined as a medically significant AE) were not collected in this trial.

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:

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

Actual number of enrolled (evaluable) participants:

<u>Study #</u>	<u>Hib-MenCY-TT</u>	<u>Monovalent Hib</u>
Hib-MenCY-TT 009	3136*	1044
Hib-MenCY-TT 011	3308*	1123*
Total	6638	2234

* 261 subjects in Hib-MenCY-TT-009 and 40 subjects in Hib-MenCY-TT-011 who participated at one U.S. center were eliminated from all analyses due to Good Clinical Practice (GCP) violations and non-compliance at the center. Also, 1 enrolled subject in Hib-MenCY-TT-011 was not assigned a group or vaccinated.

The planned pooled 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%. Planned sample size for study Hib-MenCY-TT alone enabled >80% power to detect a doubling in AE rate after Hib-MenCY-TT vaccination, assuming that the incidence of the adverse event in the monovalent Hib group was > 2.5%.

Analysis of the secondary objective was based on a pooled dataset from all participants in studies Hib-MenCY-TT-010 and Hib-MenCY-TT-012.

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.

According-to-Protocol (ATP) cohort:

The ATP cohort for the primary vaccination study period included all eligible participants who 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 ATP cohort for the fourth dose vaccination included all eligible participants who received 3 doses in the primary vaccination course and the fourth dose and who had not received a vaccine not specified in the protocol. Secondary analyses based on the ATP cohort were performed because more than 5% of the subjects in the total vaccinated cohort were not eligible for inclusion in the fourth dose ATP cohort for safety.

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. Separate analyses by country were also provided.

Changes in the conduct of the study or planned analyses:

Prevnar (4th dose), M-M-R II, and Varivax were provided as study vaccines and administered according to US labeling and ACIP recommendations. Contraindications to MMRII and Varivax immunization were added to the exclusion criteria for study enrollment.

Changes between the Report Analysis Plan (RAP) and protocol were made to align the definitions of the fourth dose ATP cohort for safety with the Hib-MenCY-TT-010 study so that the datasets could be pooled. The definition of the fourth dose ATP cohort for safety was modified as follows: “who have safety data available” was replaced with “who were not excluded from the primary ATP cohort for immunogenicity”. To restrict the number of primary endpoints, for the pooled datasets, the following endpoints: 1) occurrence of SAEs; 2) occurrence of NOCD; 3) occurrence of rash; and 4) occurrence of ER visits, during the period from dose 1 up to day 30 after dose 3, was only to be reported in the within group analyses, but not in the between group analyses. No comparison between the Hib-MenCY-TT and Hib groups between dose 1/4th dose up to day 30 after dose 3/4th dose was to be performed.

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). Comparisons of safety endpoints between the treated groups were to be performed on the basis of differences in incidences. As per CBER recommendations, the differences in country effect were quantified in terms of relative risk differences.

The majority of Mexican subjects in the Hib group did not receive their PedvaxHIB according to protocol, as they received commercial PedvaxHIB due to temperature deviation noted for the shipment of PedvaxHIB from the applicant to Mexican study sites. Commercially available PedvaxHIB was administered to prevent delay of Hib vaccination in study subjects. These subjects were noted as protocol deviations but were not eliminated from the ATP cohorts.

Changes in the Report Analysis Plan (RAP):

In the RAP, analyses by co-vaccination status for the Hib-MenCY-TT study were to be performed for Mexican and US subjects, or for US subjects, depending on whether more than 10% of Mexican subjects were co-vaccinated. Because the inclusion of a country with a large majority of subjects in a single category could bias the results, the inclusion of subjects from Mexico in these analyses was determined based on the following criterion: Mexican subjects were to be included in the analysis if there were no more than 90% of Mexican subjects in one co-vaccination category. Similarly for the pooled analyses, Australian subjects were included in the analysis if there were no more than 90% of Australian subjects in one co-vaccination category and Mexican subjects were included in the analysis if there were no more than 90% of Mexican subjects in one co-vaccination category.

Consistent with local country recommendation, an Australian-licensed meningococcal serogroup C conjugate vaccine was given to the control group in Australia at 12months of age.

Results:**Safety:**

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. For the pooled datasets from Hib-MenCY-TT-009 and Hib-MenCY-TT-011, 6002 and 2099 subjects in the Hib-MenCY-TT and Hib groups, respectively, completed the studies. The number of subjects withdrawn due to SAEs and AEs, respectively, was 16 and 3 in the Hib-MenCY-TT group and 5 and 2 in the Hib group.

The demographic characteristics of subjects in the Hib-MenCY-TT and monovalent Hib groups were similar, both for study Hib-MenCY-TT-011 and for the pooled dataset of subjects from Hib-MenCY-TT-011 and Hib-MenCY-TT-009. In study Hib-MenCY-TT-011, greater than two-thirds of subjects were Hispanic, and almost one quarter of subjects was of Caucasian/European heritage. For the pooled dataset, the predominant race was Hispanic (~46%), followed by Caucasian (~44%), and African heritage (~4.5%).

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. The most common reason for the 34 withdrawals was “lost to follow up” in both groups, occurring in 19 and 7 subjects with complete vaccination courses in the Hib-MenCY-TT and Hib groups, respectively. The other reason for withdrawal was “others”, occurring in 6 Hib-MenCY-TT recipients and 2 Hib participants. There were no withdrawals for SAEs or AEs. *Approximately half the subjects were fully co-vaccinated in both treatment groups (i.e., study vaccine, MMR, Varivax, and Prevnar administered concomitantly).* In the U.S., 94.3% of subjects from the Fourth dose Total Vaccinated cohort were fully co-vaccinated, while in Mexico, this percentage was 37.9%. Overall, percentage of subjects co-vaccinated with MMR was 98.3%, 54.9% for Varivax, 66.4% for Prevnar, 23.0% for influenza, and 2.5% for Hepatitis A (all hepatitis A co-vaccination was in the U.S.). Out of the 4021 subjects enrolled in Hib-MenCY-TT-012, 136 did not attend the concluding visit/contact of the ESFU phase and were not included in the fourth dose ESFU phase; 133 of these subjects were lost to follow up, and 3 withdrew consent. Of the 4020 subjects included in the fourth dose Total Vaccinated cohort, 444 were eliminated from the Fourth dose ATP Safety cohort: 6 for receiving a protocol-prohibited vaccine, 256 for receiving the fourth dose “not according to protocol”, 174 because they had been eliminated from the Hib-MenCY-TT-011 ESFU phase, and 8 subjects for being outside of the protocol defined intervals for age at the time of the fourth vaccination. Therefore, 3576 subjects were included in the Fourth dose ATP Cohort for Safety. For the pooled ESFU datasets from Hib-MenCY-TT-010 and Hib-MenCY-TT-012, 5779 and 1933 subjects received Hib-MenCY-TT and Hib, respectively, and 5667 and 1900 subjects in the Hib-MenCY-TT and Hib groups, respectively, completed the studies. The number of subjects withdrawn due to SAEs was 1 in the Hib-MenCY-TT group and 0 in the Hib group. Therefore, 7416 subjects completed the Pooled Fourth Dose ESFU, 5548 in the Hib-MenCY-TT group, and 1868 in the Hib group. The predominant reason for withdrawal prior to completion of the ESFU was lost to follow-up or withdrawal of consent. In the Pooled Fourth Dose Total Vaccinated cohort, 71.3% of subjects were fully co-vaccinated (similar between groups).

The demographic characteristics of subjects in the Hib-MenCY-TT and monovalent Hib groups were similar, both for study Hib-MenCY-TT-012 and for the pooled dataset of subjects from Hib-MenCY-TT-012 and Hib-MenCY-TT-010. In study Hib-MenCY-TT-012, greater than two-thirds of subjects were Hispanic, and almost one quarter of subjects was of Caucasian/European heritage. For the pooled dataset, the predominant race was Hispanic (~48%), followed by Caucasian (~44%), and African heritage (~4%).

Study Hib-MenCY-TT-011:

Table 18: 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 (source: sponsor’s Supplement 33, Hib-MenCY-TT-011 clinical study report, page 165 and Table 19, Hib-MenCY-TT-011 clinical study report, page 79)

Percentage of subjects in study Hib-MenCY-TT-011 with at least one symptom, SAE, NOCD, rash, or ER visit 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				
		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

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 \leq 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 \leq 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 \leq 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-MenCY-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 pneumonia and pharyngitis). The investigator determined these deaths to be unrelated to study vaccines; number of days post-vaccination ranged from 10 to 77 days.

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

Table 19: 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 (source: sponsor's Tables 26 Hib-MenCY-TT-011 clinical study report, page 99 and Table 27, Hib-MenCY-TT-011 clinical study report, page 100)

Percentage of subjects with SAEs, NOCD, rash, ER visits from day 0 through day 30 after dose 3 and from day 0 through the ESFU (pooled studies Hib-MenCY-TT-009 and -011, Primary Total Vaccinated Cohort)												
AE category	Time period	HibMenCY N = 6414				Hib N = 2157				Relative Risk (HibMenCY/Hib)		
				95% CI				95% CI		RR	95% CI	
		n	%	LL	UL	N	%	LL	UL		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

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, Prevnar, and Pediarix 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 Pediarix, Prevnar, influenza, and RotaTeq 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, 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%). Additional information about these cases was requested, including identification of cases with positive urine cultures and cases of sterile pyuria and screening for presence of symptoms of Kawasaki disease. Currently there is insufficient information to determine why such a case imbalance would occur in a randomized trial. 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 $\leq 1.3\%$ 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. Non-palpable purpura are less likely to be a manifestation of vasculitis. 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, 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.

Study Hib-MenCY-TT-012:

Table 20: 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 (source: sponsor’s Synopsis Table 2, Supplement 42, Hib-MenCY-TT-012 clinical study report, pages 9 and 195)

Percentage of subjects in study Hib-MenCY-TT-012 with at least one symptom, SAE, NOCD, rash, or ER visit from Day 0 through day 30 following dose 3 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

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-MenCY-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.

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

Table 21: 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 (source: sponsor's Synopsis Tables 3 and 4, Hib-MenCY-TT-012 clinical study report, page 12)

Percentage of subjects with SAEs, NOCD, rash, ER visits from day 0 through day 30 after dose 3 and from day 0 through the ESFU (pooled studies Hib-MenCY-TT-010 and -012, Fourth Dose Total Vaccinated Cohort)												
AE category	Time period	HibMenCY N = 5779				Hib N = 1933				Relative Risk (HibMenCY/Hib)		
				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

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, 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. Eczema 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-MenCY-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 sponsor 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 22: 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 (source: Supplements 12 – 16, 9-10-11-12-report body.pdf, pages 68, 72, 79, 83, 85)

Percentage of subjects with SAEs from day 0 through day 30 after dose 3 and from day 0 through the ESFU and NOCD, rash, ER visits from day 0 through the ESFU (pooled studies Hib-MenCY-TT-009, Hib-MenCY-TT-010, Hib-MenCY-TT-011, and Hib-MenCY-TT-012, Fourth Dose Total Vaccinated Cohort)												
AE category	Time period	HibMenCY N = 6414				Hib N = 2157				Relative Risk (HibMenCY/Hib)		
				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

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, MMR2, Varivax, and Prevnar. 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 Prevnar, 1st doses of MMR2 and Varivax. He was hospitalized the day he presented and found to have a platelet count of 2300mm³. On further review, the platelet count was reported as 16000mm³. 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, MMR2, Varivax, and Prevnar 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 Prevnar and post-1st doses of MMR2 and Varivax, 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, Pediarix, and Prevnar. 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%). The reason for the case imbalance cannot be determined at this time. Initially, many SAE narratives did not include information regarding urine culture results, so CBER was concerned that these children may have had sterile pyuria which might suggest Kawasaki disease. However, based on review of

additional information provided by the sponsor, it seems likely that the majority of the children indeed had UTI or pyelonephritis. In the case of 2 Hib-MenCY-TT recipients, there was insufficient detail available to rule out the possibility of Kawasaki disease. 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 sponsor:

- ❖ A 2-month old U.S. female in study Hib-MenCY-TT-009 developed UTI 4 days post-dose 1 of Hib-MenCY-TT, Pediarix, and Prevnar. She had fever to 40.1C 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, Pediarix, and Prevnar. 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, Pediarix, and Prevnar. 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, Pediarix, and Prevnar. 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. Mild petechial rash on the trunk may have been caused by cough.
- ❖ A 2-month old U.S. male in study Hib-MenCY-TT-009 developed UTI 28 days post-dose 1 of Hib-MenCY-TT, Pediarix, and Prevnar. He presented with cough, congestion, fever of 40.3C, 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 urinary tract infection 20 days post-dose 2 of Hib-MenCY-TT, Pediarix, and Prevnar and 20 days post-dose 1 of Rotateg. 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. It cannot be determined whether the apparently sterile pyuria was due to fever or, potentially, to Kawasaki disease. However, given that no other Kawasaki symptoms were described, it may be 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, Pediarix, and Prevnar. 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*. Given the positive urine culture, this subject most likely did have a 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 Prevnar. 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, Pediarix, and Prevnar. 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 Prevnar. 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. The absence of a urine culture to diagnose UTI and lack of other information regarding symptoms of Kawasaki disease give us insufficient information to rule out this possibility.
 - ❖ A 7 month-old Australian male in study Hib-MenCY-TT-009 developed UTI 35 days post-3rd dose of Hib-MenCY-TT, Pediarix, and Prevnar. 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 Prevnar. She presented with fever of 38.9C and was hospitalized. Urine catheterization 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 Prevnar. 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 extremities, 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, Pediarix, and Prevnar. 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 Prevnar. 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 Prevnar. 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 Prevnar. 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, Pediarix, and Prevnar. 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, Pediarix, and Prevnar. 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, Pediarix, and Prevnar, 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, although not all, of the symptoms associated with Kawasaki disease is reassuring, although not entirely convincing. Although Kawasaki disease cannot be ruled out in this case, it is the clinical reviewer’s opinion that it is unlikely.
- ❖ A 2 month-old U.S. female developed irritability 20 days post-dose 1 of Hib-MenCY-TT, Pediarix, and Prevnar. 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, 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, Pediarix, and Prevnar. 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.
- ❖ A 4-month old U.S. male developed viral syndrome and fever to 38.56C 30 days post-dose 1 of Hib, Pediarix, and Prevnar. He had a 2-day history of irritability. 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, Pediarix, and Prevnar. 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. While sepsis and/or congenital coagulopathy are possible etiologies, there is insufficient information to determine that the event was unrelated to vaccination.

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, Pediarix, and Prevnar. 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, MMR2, Varivax, and Prevnar. 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 was 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, MMR2, Varivax, and Prevnar 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 Prevnar. 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 nystagmus 8 days post-dose 1 of Hib-MenCY-TT, Infanrix penta, and Prevnar. Incidentally, this presentation occurred 3 days after the case mentioned above. 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, Pediarix, and Pevnar. 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, Pediarix, and Pevnar. The child’s mother was holding him when he had several “jerkings 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. By description, if the child was attentive after the episode, without post-ictal period, it is reasonable to assume that seizure was unlikely.
- ❖ 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 Pevnar. 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 Pevnar. 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 Pevnar. 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” although it seems 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, Pediarix, and Pevnar, 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 Pevnar. 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, Pediarix, and Pevnar. 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 Pevnar. 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 Pevnar. 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, Varivax, and Pevnar. 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, MMR2, Varivax, and Prevnar. 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, MMR2, Varivax, and Prevnar 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, MMR2, Varivax, and Prevnar and 2.5 and 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 outpatient, 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, MMR2, Varivax, and Prevnar. 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, MMR2, Varivax, and Prevnar 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 Prevnar. 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. It is unlikely that the seizure was related to vaccination and more likely that it was related to fever secondary to gastroenteritis.
 - ❖ 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, Pediarix, and Prevnar. Chest x-ray, lumbar puncture, influenza test were performed, and pneumonia was diagnosed. EEG was abnormal, with 3 bursts of sharp slow 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, Pediarix, and Prevnar. 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 resuscitation, 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, MMR2, Varivax, and Prevnar 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, Varivax, and Prevnar. 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, Pediarix, and Prevnar. 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.

Deaths:

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, Pediarix, and Prevnar. One blanket with a wrapped piece of candy was found in her crib. One part of her sleeper was moist in the posterior neck-upper back area and had the odor of formula. 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, Infanrix penta, and Prevnar. He had vomited an abundant amount of yellow liquid and became very pale. The mother brought the child to a doctor who referred her to the hospital. In the ER, he was pale, cyanotic, motionless, and apparently without respiratory effort or pulse. 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, Infanrix penta, and Prevnar. She was breastfed at 3 am and put to bed. At 6 am, she was found motionless, cyanotic, and cold, was brought to a doctor (who felt the baby was dead), and then to the ER, where she was rigid, blue, and cold without vital signs. 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, Pediarix, and Prevnar. The baby's parent found him dead, lying on his stomach on the couch in the morning. He was seen by a doctor. 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, Infanrix penta, and Prevnar. She was sleeping with her parents, breastfed at 3 am and 6 am. At 9 am, her mother found her in bed, on her side, with 2 covers/blankets. She was cyanotic, rigid, and unresponsive. 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, Infanrix penta, and Prevnar. At 3 am, she breastfed. At 5 am, her father found her pale, cold, and unresponsive. 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 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, Infanrix penta, and Prevnar. He died 7 days later. According to the SAE narrative, the investigator reported that it was not possible to obtain more information. Insufficient information was provided to determine definitively that his death was unrelated to vaccination. However, given his diagnosis of pneumonia, it is possible that his death was due to infection.
- ❖ 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, Infanrix penta, and Prevnar. He presented with cough, tachypnea, respiratory distress, and fever (40C). On day 5 of the illness, he was hospitalized. He received furosemide, spironolactone, captopril, and cefuroxime. Chest x-ray results reported as cardiomegaly, cardiothoracic index of 0.6, right basal infiltrate, and increased bronchovascular markings. Blood and urine cultures were negative. Approximately 8 days later, he had improved and was discharged. Fever recurred the day after discharge, and he was treated with amikacin, secnidazole, dipyrrone, 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. Given the child's medical history of total anomalous pulmonary venous return and pulmonary hypertension, it is reasonable to assess the child's congestive heart failure and death as unrelated to vaccination.

- ❖ An 8 month-old Mexican female in study Hib-MenCY-TT-009 developed bronchial aspiration approximately 89 days post-3rd dose of Hib, Pediarix, and Prevnar and 1.5 months and 12 days post-1st and 2nd doses of Fluzone. At 00:45, she drank 8 oz of milk and went to sleep at 01:10. At 04:00, the mother noticed the baby was “complaining and agitating” with respiratory distress. She brought the child 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). In the absence of an autopsy, it is difficult to state definitively that aspiration caused the child’s death. It is possible that aspiration caused respiratory distress that precipitated death. Given the interval between vaccination and death, it is reasonable to assess the child’s death as unrelated to vaccination.
- ❖ 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, Infanrix penta, and Prevnar. 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. An oxygen saturation from that day is reported as 79.5%. The day after hospitalization, sepsis, gastrointestinal bleeding, and anemia were diagnosed, as well. During the hospitalization, he was treated with midazolam, vecuronium, salbutamol + ipratropium, budesonide, prednisolone, epinephrine, aminophylline, blood transfusion, furosemide, vitamin K, amikacin, cefotaxime, vancomycin, dobutamine, and atropine. 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. Given the nature and timing of his illness, it is reasonable to assess the child’s death as unrelated to vaccination.
- ❖ A 13 month-old U.S. female in study Hib-MenCY-TT-010 died 29 days post-4th dose of Hib-MenCY-TT and Prevnar and post-1st dose of MMRII and Varivax due to trauma suffered during a motor vehicle accident. She was pronounced dead at the scene of the accident. Given the nature of the child’s death, it is reasonable to assess the event as unrelated to vaccination.

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 sponsor 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).

Immunogenicity: Not applicable.

Summary:

Studies Hib-MenCY-TT-011 and Hib-MenCY-TT-012 were trials to evaluate 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. Data analysis was performed on the individual databases from these trials and on the pooled databases from studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011 and studies Hib-MenCY-TT-010 and Hib-MenCY-TT-012, respectively.

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. There is an apparently greater incidence of vasculitic phenomena in the Hib-MenCY-TT recipients. However, it is difficult to evaluate this fully based on the currently available data, and it is important to remember that subjects were randomized 3:1.

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.

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

Study 107824: Hib-MenCY-TT-013: review of this antibody persistence study is deferred pending review of response to CR letter.

Supportive Clinical Studies:

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 booster vaccination phase (792014/002 [Hib-MenCY-TT-002]).
#Menjugate was used instead of Meningitec

Pertinent Study Design Elements: 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 + Prevenar®, Hib-MenCY (5/10/10) + Infanrix® penta + Prevenar®, Hib-MenCY (5/5/5) + Infanrix® penta + Prevenar®, Menjugate® + ActHIB® + Infanrix® penta, or ActHIB® + Infanrix® penta + Prevenar®. 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 and functional anti-meningococcal serogroup C and Y activity (SBA-MenC and SBA-MenY). The serum bactericidal assay used a rabbit complement source.

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

Results:

Safety: Of 409 enrolled participants, 407 participants were included in the total vaccinated 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 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 baby rabbit complement to be an unreliable predictor of inferred effectiveness in children younger than 2 years old.

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

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 booster vaccination phase (792014/002 [Hib-MenCY-TT-002]).
#Menjugate was used instead of Meningitec for infant immunization

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 Infanrix® penta + Prevenar®) at three study centers in Australia. 394 participants 11-14 months of age were enrolled. Children who had been vaccinated in Study 001 with Infanrix® penta and one of the three Hib-MenCY formulations or Menjugate® + ActHIB® or Prevenar® + 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 rabbit 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 effectiveness in children younger than 2 years old.

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

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.

Pertinent Study Design Elements: 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. Safety evaluation was the same as for Hib-MenCY-TT-001. 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, rSBA-MenC and rSBA-MenY.

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 death was 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 ≥ 0.15 µg /mL. The percentage (95% CI) in each study group achieving ≥ 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 effectiveness 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 (10µg 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.

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. Safety evaluation was the same as for Hib-MenCY-TT-001. 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.

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>39.5C, 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. 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.

7 Overview of Immunogenicity (Effectiveness) Across Trials

Deferred pending review of responses to CR letter comments

8 Overview of Safety Across Trials

Deferred pending review of responses to CR letter comments

9.0 PREA requirements

The applicant requested a waiver to conduct studies of MenHibrix in children 0 to <6 weeks of age and in children 5 to 17 years of age because in these age groups, use of MenHibrix is not thought to represent a meaningful therapeutic benefit over existing vaccination schedules, and MenHibrix is not likely to be used in a substantial number of patients. In addition, for children 5 to 17 years of age, studies with MenHibrix would be impossible or highly impracticable. *Final decisions regarding PREA requirements are deferred pending presentation to the PERC committee.*

10 Conclusions—Overall

Final conclusions and recommendations are pending review of the sponsor's response to CBER issued complete response comments.

The following clinical comments are not anticipated to change the overall clinical conclusions; rather, the comments are intended to be information requests within the context of the Complete Response letter:

1. We note your inclusion of the sensitivity analyses with and without the safety data from Dr. Naz's site. Please provide separate tabular summaries of demographic characteristics for Dr. Naz's site, compared to the total enrolled population in -009 and -010, respectively.
2. In study Hib-MenCY-009 Table 12, we note that 2898 MenHibrix recipients and 955 Hib recipients in the Total Vaccinated Cohort (TVC) completed the extended safety follow-up (ESFU). However, fewer TVC MenHibrix (n=2888) and Hib (n=961) recipients completed the safety follow-up through one month post-dose 3 (table 11). Please explain why the number of vaccinated participants completing the ESFU is more than the number of participants who completed the primary active phase.
3. Please clarify if the eleven Hib-MenCY-TT-009 subjects (n=10 MenHibrix, n=1 Hib) who withdrew or prematurely discontinued from the study completed the ESFU.
4. Please clarify how safety data were categorized by treatment assignment for the sensitivity analysis if one reason for excluding Dr. Naz's site data was inability to confirm treatment assignment.
5. Please clarify in study Hib-MenCY-TT-011, during the period from day 0 after dose 1 through day 30 after dose 3, the number of subjects in each treatment group reporting AEs leading to ER visits and the number of reported events of this nature.

6.Regarding subject 04863, the 10 month-old U.S. male in study Hib-MenCY-TT-009 with family and personal history of developmental delay developed seizure 5 months post-dose 3 study vaccines: the SAE narrative first states Hib-MenCY was given but later states that ActHIB was given. Please clarify which study vaccines the subject received.

7. Please provide a clinical summary and table describing the reported occurrence of SAEs, NOCD, rash, and AEs resulting in ER visits for study Hib-MenCY-TT-009 within 30 days of vaccination. The table should include the number and percentage of subjects reporting these events, with 95% confidence intervals for each treatment group, and the relative risk (HibMenCY-TT/Hib), with corresponding 95% CI.

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