

OBE BLA REVIEW

STN: 125363 / 0
PRODUCT: MenHibRix® (Hib-MenCY-TT)
Haemophilus influenzae type b
Neisseria meningitidis serogroups C and Y-tetanus toxoid (TT) conjugate

MANUFACTURER: GlaxoSmithKline
SUBMISSION DATE: 12-AUG-2009
FINAL REVIEW DUE DATE: 07-MAY-2010
ACTION DUE DATE: 12-JUN-2010

REVIEWER: Patricia J. Rohan, MD

THRU: David Martin, MD, MPH

Rickey Wilson, MD, MS, JD

REVIEWED

By Patricia Rohan, MD at 8:54 am, May 07, 2010

APPROVED

By David Martin, MD, MPH, FACOEM at 12:56 pm, May 07, 2010

APPROVED

By Rickey Wilson MD MS JD at 5:01 pm, May 10, 2010

PROPOSED USE: Hib-MenCY-TT vaccine is proposed to be indicated for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y.

DOSE SCHEDULE: 0.5 ml intramuscular dose at 2, 3, 6 and 12-15 months of age. The first dose may be given as early as 6 weeks of age.

MATERIALS REVIEWED: 125363.0000
Module 1.16 Risk Management Plans
Module 2.7.4 Summary of Clinical Safety
Module 5.3.5.1 Active-control-without-placebo
Office visits: HibMenCY 005, 006, 007, 008, 009, 010
Module 5.3.6 Reports of Postmarketing Experience

BACKGROUND:

Regulatory

The Hib-MenCY-TT vaccine is not currently licensed in any country.

The *Haemophilus* b capsular polysaccharide (polyribosyl-ribitol-phosphate [PRP]) and MenC component antigens are included in other conjugate vaccines marketed outside the US [*Hiberix* (*Haemophilus influenzae* type b conjugate vaccine) for the PRP component and *Menitorix* (*Haemophilus influenzae* type b and *Neisseria meningitidis* serogroup C conjugate vaccine) for the PRP and MenC components].

Clinical

1. *Haemophilus influenzae* type B

Prior to introduction of effective vaccines, *Haemophilus influenzae* type b (Hib) was the leading cause of invasive bacterial disease in US children affecting 0.5% of those 5 years of age and under - two-thirds of pediatric Hib infections in those less than 15 months of age. A large proportion of these children (60%)

had meningitis with a mortality rate of 3-6% and permanent neurologic sequelae in 20-30%. Hib accounted for 95% of all cases of invasive *H. influenzae* disease in this pediatric population. Comparator studies have demonstrated 93-100% Hib vaccine efficacy. (CDC ACIP 2010)

The Advisory Committee on Immunization Practices (ACIP) recommends that all children receive one of the conjugate vaccines licensed for infant use (HbOC or PRP-OMP), beginning routinely at 2 months of age. Administration of the vaccine series may be initiated as early as age 6 weeks. This recommendation was first made in 1991, and while the number of reported cases of invasive *Haemophilus influenzae* Type b has decreased, over the same period the number of cases of invasive non-B, and non-typeable *Haemophilus influenzae* have risen. Of note, the latter two types of invasive *Haemophilus influenzae* represent the majority of invasive *Haemophilus influenzae* cases. (CDC Active Bacterial Core surveillance or ABC, 1997-2007).

2. Meningococcal Disease

Following reduction in the incidences of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (HiB) as the result of conjugate vaccines, *Neisseria meningitidis* has emerged as a leading cause of bacterial meningitis in the US, with an estimated annual incidence of 0.5-1.1/100,000 persons (1,400-2,800 cases). The fatality rate for meningococcal disease is 10%--14% (CDC, unpublished data, 2004). Meningococcal disease also causes substantial morbidity; 11%--19% of survivors have sequelae (e.g., neurologic disability, limb loss, and hearing loss) (DCD, ACIP 2010)

Studies of serogroups A and C vaccines have demonstrated estimated clinical efficacies of $\geq 85\%$ among school-aged children and adults. Efficacy has not been evaluated for serogroups Y and W-135 polysaccharides, but these vaccines have demonstrated immunogenicity in adults and children aged >2 years, i.e., production of bactericidal antibodies.

The Advisory Committee on Immunization Practices (ACIP) recommends

- Routine vaccination of young adolescents (defined in this report as persons aged 11--12 years) with MCV4 at the preadolescent health-care visit (i.e., a visit to a health-care provider at age 11--12 years, at which time ACIP and other professional organizations [e.g., AAP and the American Medical Association] recommend that persons aged 11--12 years receive appropriate vaccinations and other preventive services [106--109]). Introducing a recommendation for MCV4 vaccination among persons aged 11--12 years might strengthen the role of the preadolescent health-care visit and have a positive effect on vaccine coverage during adolescence. For those adolescents who have not previously received MCV4, ACIP recommends vaccination before high school entry (at approximately age 15 years) as an effective strategy to reduce meningococcal disease incidence among adolescents and young adults. By 2008, the goal will be routine vaccination with MCV4 of all adolescents beginning at age 11 years. Other adolescents who wish to decrease their risk for meningococcal disease may elect to receive vaccine.
- Routine vaccination with meningococcal vaccine also is recommended for college freshmen living in dormitories and for other populations at increased risk (i.e., military recruits, travelers to areas in which meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency). Other adolescents, college students, and persons infected with human immunodeficiency virus who wish to decrease their risk for meningococcal disease may elect to receive vaccine.

OVERVIEW OF CLINICAL EXPERIENCE WITH Hib-MenCY-TT:

The vaccine, Hib-MenCY-TT, has been evaluated in 6 primary vaccination studies of a 3-dose schedule, at 0, 2 and 6 month (Table 1) and 5 studies of a 4th dose (Table 2). In addition two studies are reported as ongoing, one of which involves a related vaccine, MenACW-135Y-TT in which subjects received a 4th dose of Hib-MenCY-TT (Table 3).

3-dose schedule

7,521 infants received at least one dose of the Hib-MenCY-TT vaccine as part of the 3-dose primary vaccination course starting from 6 weeks of age and a total of 21,943 doses of the Hib- MenCY-TT vaccine have been administered in these studies.

4th dose

7,023 subjects have received Hib-MenCY-TT as a 4th dose in a series; 6,686 subjects had previously received 3 doses of Hib-MenCY-TT, and 337 subjects from study 008 had previously received 3 doses of Hib vaccine and 3 doses of serogroup C conjugate vaccine, Meningitec (licensed in Australia).

Overall

9,148 subjects have received at least one dose of the Hib-MenCY-TT vaccine licensure formulation (7,858 subjects in the Hib-MenCY-TT vaccine clinical development and approximately 1,290 subjects in the ongoing study MenACWYTT- 057).

Safety Database

The total pre-licensure safety database for the Hib-MenCY-TT vaccine includes approximately 9,465 subjects in the target age group who have received at least one dose of any formulation of the Hib-MenCY-TT vaccine.

Non-serious adverse events / serious adverse events leading to study discontinuation:

- Recorded during the active phase follow-up (Day 0 to Day 30 after last vaccination)
- Information on discontinuation from the ESFU phase due to AE/SAE was not collected Studies Hib-MenCY-TT-005/006, -007/008, -009/010 and -011/012 and subjects withdrawn from the active phase could participate in the ESFU phase.
- Data from all subjects enrolled in US studies Hib-MenCY-TT-009 (Center 24660), -010 (Center 34932), -011 (Center 35785) and -012 (Center 39451) were excluded from all analyses due to repeated GCP violations and protocol non-compliance in spite of intense monitoring and remediation efforts by the sponsor.
 - Certain key data points, such as vaccine accountability, could not be fully reconciled at the site, resulting in exclusion of 261 subjects in study Hib-MenCY-TT-009, 189 subjects in study Hib-MenCY-TT-010, 40 subjects in study Hib- MenCY-TT-011 and 27 subjects in study Hib-MenCY-TT-012.
 - Individual subject data are included separately in the line listing of the respective study reports.
 - Based upon CBER's recommendation at a teleconference held on March 23, 2009, the sponsor conducted a sensitivity analyses for fever and specific unsolicited AEs by comparing the results obtained including and excluding subjects from this location (Center 24660 in study -009 and Center 34932 in study -010) and demonstrated that no bias was detected.

The Hib-MenCY-TT vaccine completed primary vaccination and fourth dose studies, and ongoing studies are summarized, respectively, in Tables 1-3 below.

Table 1: Completed primary vaccination phase studies providing data with the Hib-MenCY-TT candidate vaccine

Study number Study Location Type	Population Age at Dose 1 (Dose Schedule)	Safety Objectives	Study Design / Vaccine Cohorts	Total Vaccinated Cohort
Hib-MenCY-TT-001 Australia (multicenter) Non-pivotal study Immunogenicity Safety/Reactogenicity	Healthy infants 6-12 weeks (2, 4, 6 months)	Secondary objective: Reactogenicity and safety.	Phase 2, partially DB, RC, primary vaccination	407
			Group Hib-MenCY 2.5/5/5 + <i>Pediarix</i> + <i>Prevnar</i>	82
			Group Hib-MenCY 5/10/10 + <i>Pediarix</i> + <i>Prevnar</i>	82
			Group Hib-MenCY 5/5/5 + <i>Pediarix</i> + <i>Prevnar</i>	80
			Group <i>Menjugate</i> + <i>ActHIB</i> + <i>Pediarix</i>	81
			Group <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	82
Hib-MenCY-TT-003 Belgium, Germany Non-pivotal study Immunogenicity Safety/Reactogenicity	Healthy infants 6-12 weeks (2, 3, 4 months)	Secondary objective: Reactogenicity and safety.	Phase 2, partially DB, RC, primary vaccination	388
			Group Hib-MenCY 2.5/5/5 + <i>Pediarix</i>	78
			Group Hib-MenCY 5/10/10 + <i>Pediarix</i>	77
			Group Hib-MenCY 5/5/5 + <i>Pediarix</i>	78
			Group Hib-MenC 5/5 + <i>Pediarix</i>	78
			Group <i>Menjugate</i> + <i>Infanrix hexa</i>	77
Hib-MenCY-TT-005 US (multicenter) Pivotal study Immunogenicity, Safety/Reactogenicity	Healthy infants 6-12 weeks (2, 4, 6 months) Healthy children 3-5 years (1 dose)	Secondary objective: Reactogenicity and safety.	Phase 2, SBRC, primary vaccination	756
			Group Hib-MenCY + <i>Pediarix</i> + <i>Prevnar</i>	287
			Group <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	319
			Group <i>Menomune</i>	150
Hib-MenCY-TT-007 Australia Pivotal study Immunogenicity, Safety/Reactogenicity	Healthy infants 6-13 weeks (2, 4, 6 months)	Secondary objective: Reactogenicity and safety.	Phase 2, open RC primary vaccination study	1103
			Group Hib-MenCY + <i>Pediarix</i> + <i>Prevnar</i>	661
			Group <i>Meningitec</i> + <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	221
			Group <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	221
Hib-MenCY-TT-009 US, Australia, Mexico Pivotal study Lot-to-lot consistency, immunogenicity, Safety/Reactogenicity	Healthy infants 5-16 weeks (2, 4, 6 months)	Secondary objectives: Reactogenicity and safety; Incidence of fever >39.5°C w/in 4 days after any vaccine dose.	Phase 3 DB Hib-MenCY-TT lot consistency / SB Hib-MenCY-TT vs. monovalent Hib vaccine, RC primary vaccination	4180
			Group Hib-MenCY Lot A + <i>Pediarix</i>	1041
			Group Hib-MenCY Lot B + <i>Pediarix</i>	1046
			Group Hib-MenCY Lot C + <i>Pediarix</i>	1049
			Group <i>ActHIB</i> + <i>Pediarix</i>	1044
			± <i>Prevnar</i> / influenza vaccine / <i>RotaTeq</i> / <i>Synagis</i>	
Hib-MenCY-TT-011 US, Mexico Pivotal study Safety	Healthy infants 6-13 weeks (2, 4, 6 months)	Primary objective: (Hib-MenCY-TT-011 and 009 pooled data) SAEs, ER visits New onset chronic diseases, e.g. autoimmune disorders, asthma, diabetes, allergies, rash (e.g. hives, ITP, petechiae)	SBRC primary vaccination study	4391
			Group Hib-MenCY + <i>Pediarix</i>	3278
			Group <i>ActHIB</i> + <i>Pediarix</i>	1113
			± <i>Prevnar</i> / influenza vaccine / <i>RotaTeq</i> / <i>Synagis</i>	
Total number of subjects exposed to Hib-MenCY group (TVC)				7,522
Hib-MenCY 5/10/10 and 5/5/5 are earlier formulations (Studies 001 and 003); Hib-MenCY 2.5/5/5 (Studies 001 and 003) and Hib-MenCY refer to the licensed formulation. 7,522 subjects in Hib-MenCY TVC include 7,521 subjects who received Hib-MenCY-TT and one subject (study 011) who did not receive Hib-MenCY-TT vaccine. SB = single blinded; DB =double-blinded; R = randomized; C = controlled				
STN 1253633/0, Section 1.16, PVP, Table 1				

Table 2: Completed fourth dose phase studies providing data with the Hib-MenCY-TT candidate vaccine

Study number Study Location / Type	Age at Dose 4 (Actual Range)	Safety Objectives	Study Design / Vaccine Cohorts	Total Cohort
Hib-MenCY-TT-004 Germany Non-pivotal Extension Immunogenicity Safety and Reactogenicity	Healthy toddlers 12 months (11-18 months)	Secondary objectives: Reactogenicity and safety.	Phase 2 partially DBC, non-randomized extension of Hib-MenCY-TT-003	221
			Group Hib-MenCY 2.5/5/5 + <i>Pediarix</i>	47
			Group Hib-MenCY 5/10/10 + <i>Pediarix</i>	42
			Group Hib-MenCY 5/5/5 + <i>Pediarix</i>	44
			Group Hib-MenC 5/5 + <i>Pediarix</i>	44
			Group <i>Menjugate</i> + <i>Infanrix hexa</i>	44
Hib-MenCY-TT-006 US / Pivotal study Immunogenicity Safety and reactogenicity	Healthy toddlers 12 months (11-16 months)	Secondary objectives: Reactogenicity and safety.	Phase II, SBC (re-randomized from Hib-MenCY-TT-005)	498
			Group Hib-MenCY: Hib-MenCY-TT + <i>Prevnar</i> /priming w/ Hib-MenCY-TT + <i>Prevnar</i> + <i>Pediarix</i>	236*
			Group <i>ActHIB</i> _ <i>ActHIB</i> : <i>ActHIB</i> + <i>Prevnar</i> / priming with <i>ActHIB</i> + <i>Prevnar</i> + <i>Pediarix</i>	130
			Group <i>ActHIB</i> _Hib-MenCY: Hib-MenCY-TT + <i>Prevnar</i> /priming with <i>ActHIB</i> + <i>Prevnar</i> + <i>Pediarix</i>	132
Hib-MenCY-TT-008 Australia Pivotal study Immunogenicity Safety and reactogenicity	Healthy toddlers 12 months (11-15 months)	Secondary objectives: Reactogenicity and safety.	Phase 3, open, RC 4 th dose extension of Hib-MenCY-TT-007	1035
			Group Hib-MenCY: Hib-MenCY-T, 4th dose + <i>M-M-R</i> + <i>Varivax</i> after priming with Hib-MenCY-TT + <i>Pediarix</i> + <i>Prevnar</i>	625
			Group LicMenC: Hib-MenCY-TT, single dose + <i>M-M-R</i> + <i>Varivax</i> after priming with <i>Meningitec</i> + <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	206
			Group Hib: <i>PedvaxHIB</i> , 4th dose + <i>M-M-R</i> + <i>Varivax</i> after priming with <i>ActHIB</i> + <i>Pediarix</i> + <i>Prevnar</i>	204
Hib-MenCY-TT-010 US, Australia, Mexico Pivotal study Immunogenicity, Safety and reactogenicity	Healthy toddlers 12 months (11-17 months)	Secondary objectives: Fever >39.5°C/103.1°F, within 4-days after 4 th dose Safety and reactogenicity.	Phase 3, SBRC 4 th dose extension of Hib-MenCY-TT-009	3692
			Group Hib-MenCY: Hib-MenCY-TT after priming with Hib-MenCY-TT + <i>Pediarix</i>	2769
			Group Hib: <i>PedvaxHIB</i> , 4 th dose after priming with <i>ActHIB</i> + <i>Pediarix</i>	923
			± hepatitis A vaccine and influenza vaccine; ±4 th dose <i>Prevnar</i> , <i>M-M-R</i> , <i>Varivax</i>	
Hib-MenCY-TT-012 US, Mexico Pivotal study Safety data	Healthy toddlers 12 months (11-17 months)	Secondary objective: SAEs, NOCD*, rash (e.g. hives, ITP, petechiae), ER visits	Phase 3, SBRC 4th dose, extension of Hib-MenCY-TT-011	4020
			Group Hib-MenCY: Hib-MenCY-TT / priming with Hib-MenCY-TT + <i>Pediarix</i>	3010
			Group Hib: <i>PedvaxHIB</i> / priming with <i>ActHIB</i> + <i>Pediarix</i>	1010
			±4 th dose of <i>Prevnar</i> , <i>M-M-R</i> , <i>Varivax</i> , hepatitis A and influenza vaccine	
Total number of subjects in the Hib-MenCY group (TVC)				7,025
Hib-MenCY 5/10/10 and 5/5/5 are earlier formulations (Study 004); Hib-MenCY refers to the licensed formulation. Study 006: After database lock and completion of analyses, it was discovered that one subject was incorrectly assigned to Hib-MenCY group after having received 3 doses of <i>ActHIB</i> SB = single blinded; DB =double-blinded; R = randomized; C = controlled				
STN 1253633/0, Section 1.16, PVP, Table 2				

Table 3: Ongoing studies with the Hib-MenCY-TT candidate vaccine

Study number Study Location / Type	Population Age at Enrollment (Schedule)	Safety Objectives	Study Design / Vaccine Cohorts	Planned enrollment
Hib-MenCY-TT-014 US (multicenter) Observation Immune Persistence	Healthy children 4 years (no vaccination)	None	Phase 3, open, controlled extension of study 005 / 006	320*
			Group Hib-MenCY (4 doses)	160
			Group <i>ActHIB</i> (4 doses)	80
			Group <i>ActHIB</i> _Hib-MenCY (<i>ActHIB</i> 3 doses, Hib-MenCY-TT 4 th dose	80
MenACWY-TT-057 US (multicenter) primary phase	Healthy infants 6-12 weeks (2, 4, 6 months)	Secondary objective: Safety	Phase 3, RC	1548
			Group Hib-MenCY-TT + <i>Pediarix</i>	1290
			Group <i>ActHIB</i> + <i>Pediarix</i>	258
			± <i>Prevnar</i> , influenza vaccine, rotavirus vaccine	
MenACWY-TT-057 US (multicenter) booster phase	Healthy toddlers 12-15 months (12- 15, 15-18 months)	Secondary objective: Safety and reactogenicity.	Phase 3, re-randomized, C controlled extension of study 057	1548
			Group MenACWY-TT at 12-15 months / Infanrix at 15-18 months	516
			Group Hib-MenCY-TT at 12-15 months / Infanrix at 15-18 months	258
			Group MenACWY-TT + Infanrix at 15-18 months of age.	516
			Group Infanrix at 15-18 months of age.	258
*Planned enrollment in study Hib-MenCY-TT-014 (Year 3 follow-up of study Hib-MenCY-TT-005/006) is more than the number of subjects who participated in study Hib- MenCY-TT-013 (Year 1 follow-up of study Hib-MenCY-TT-005/006) because subjects could participate in each persistence time point independent of other persistence time points.				
STN 1253633/0, Section 1.16, PVP, Table 4				

Demographics:

The age, race and gender distributions are comparable between the Hib-MenCY and Hib vaccine cohorts for both the primary vaccination series and the fourth dose vaccination studies as shown in Table 4. The relatively large proportion (37-42%) of Hispanic subjects is due to study sites in Mexico.

Table 4: Demographic characteristics of Hib-MenCY and Hib vaccine groups

Characteristics	Parameters or Categories	Hib-MenCY (N = 7522)		Hib (N = 2779)	
Pooled primary vaccination phase studies Hib-MenCY-TT-001, -003, -005, -007, -009, and -011*					
		Value or n	%	Value or n	%
Age at first dose (days)	Mean	61.1	-	61.5	-
	SD	9.42	-	9.31	-
	Median	62.0	-	62.0	-
	Minimum	37	-	40	-
	Maximum	111	-	116	-
Age at third dose (days)	Mean	185.9	-	186.8	-
	SD	14.98	-	13.72	-
	Median	185.0	-	186.0	-
	Minimum	99	-	133	-
	Maximum	322	-	312	-
	Unknown	357	-	143	-
Gender	Female	3637	48.4	1361	49.0
	Male	3885	51.6	1418	51.0
Race	White / Caucasian	3789	50.4	1496	53.8
	African American / Black	332	4.4	139	5.0
	Hispanic	3068	40.8	1027	37.0
	Arabic / North African	7	0.1	1	0.0
	Asian	62	0.8	20	0.7
	Other	264	3.5	96	3.5
Pooled fourth dose phase studies Hib-MenCY-TT-004, -006, -008, -010, and -012**					
Characteristics	Parameters or Categories	Hib-MenCY (N = 6687)		Hib (N = 2267)	
		Value or n	%	Value or n	%
Age (months)	Mean	12.1	-	12.1	-
	SD	0.45	-	0.47	-
	Median	12.0	-	12.0	-
	Minimum	11	-	12	-
	Maximum	17	-	17	-
Gender	Female	3241	48.5	1108	48.9
	Male	3446	51.5	1159	51.1
Race	White / Caucasian	3308	49.5	1155	50.9
	African American / Black	266	4.0	87	3.8
	Hispanic	2835	42.4	942	41.6
	Arabic / North African	5	0.1	1	0.0
	Asian	51	0.8	12	0.5
	Other	222	3.3	70	3.1
N = total number of subjects in Total Vaccine Cohort (TVC) Value = value of the considered parameter		n / % = number / percentage of subjects in a given category SD = standard deviation			
*STN 1253633/0, Section 2.7.4, Table 21		**STN 1253633/0, Section 2.7.4, Table 21			

Integrated summary of safety (ISS) analysis

An integrated summary of safety (ISS) analysis was performed across the 3-dose and the 4th dose studies of Hib-MenCY-TT vaccine. Groups receiving the Hib-MenCY-TT vaccine or Hib vaccine (control group) were compared by pooling data from studies that included a control group receiving a US-licensed monovalent Hib vaccine (*ActHIB* or *PedvaxHIB*). Note that studies that did not include a US-licensed monovalent Hib vaccine control (Hib-MenCY-TT-003 and -004) and subjects in studies in which a single dose of the Hib-MenCY-TT vaccine was administered at approximately 12 to 15 months of age (Hib-MenCY-TT-006 and -008) after 3 doses of a Hib vaccine (and an Australian-licensed meningococcal serogroup C conjugate vaccine, *Meningitec*, in study -008) at 2, 4 and 6 months are excluded from the respective analyses.

The safety database includes 9,465 subjects who have received ≥1 dose of any formulation of the Hib-MenCY-TT vaccine.

Solicited AEs

The following symptoms were solicited in all studies except Hib-MenCY-TT-011 and -012:

- Local solicited events: pain, redness and swelling at each injection site
- General solicited events: drowsiness, fever, irritability/fussiness and loss of appetite

Additionally, increase in mid-limb circumference was solicited in fourth dose phase studies Hib-MenCY-TT-006 and -010

Solicited general AEs specific to co-administered *M-M-R/II* and *Varivax* vaccines were solicited in studies Hib-MenCY-TT-008 and -010 (US Safety and Immunogenicity Cohort) and are described in the section on adverse events of interest, below.

As summarized in Tables 5 and 6, below, statistically significant higher rates (**bolded**) of several solicited and general AEs were seen in the Hib cohorts in either the primary vaccination series or fourth dose vaccination studies in the Hib cohorts. While no adjustment was made for multiple comparison, it should be noted that there was no solicited AE found to be statistically significantly higher in the Hib-MenCY cohorts.

Table 5: Solicited local AEs reported within the 4-day (Days 0-3) post-vaccination period

Symptom	Type	Hib-MenCY			Hib			Relative Risk (Hib-MenCY over Hib)			P-value	P-value interact
		N	n	%	N	n	%	RR	95% CI			
									LL	UL		
Pooled primary vaccination studies Hib-MenCY-TT-001, -005, -007, and -009*												
Pain	All	4113	3034	73.8	1635	1202	73.5	0.95	0.89	1.02	0.1785	0.6742
	Grade 2-3	4113	1631	39.7	1635	752	46.0	0.80	0.73	0.88	<0.0001	0.9563
	Grade 3	4113	518	12.6	1635	303	18.5	0.62	0.54	0.72	<0.0001	0.0554
Redness	All	4113	2787	67.8	1635	1097	67.1	0.97	0.90	1.04	0.3485	0.7126
	>10.0 mm	4113	754	18.3	1635	317	19.4	0.90	0.79	1.03	0.1368	0.9365
	>30.0 mm	4113	126	3.1	1635	72	4.4	0.66	0.49	0.90	0.0076	0.1743
Swelling	All	4113	2342	56.9	1635	902	55.2	0.98	0.91	1.06	0.6102	0.9483
	>10.0 mm	4113	689	16.8	1635	257	15.7	1.02	0.88	1.18	0.8482	0.7308
	>30.0 mm	4113	145	3.5	1635	76	4.6	0.70	0.53	0.94	0.0182	0.1148
Pooled fourth dose vaccination studies Hib-MenCY-TT-006, -008, and -010**												
Pain	All	3382	1615	47.8	1159	636	54.9	0.86	0.78	0.94	0.0014	0.1490
	Grade 2-3	3382	506	15.0	1159	271	23.4	0.63	0.54	0.73	<0.0001	0.0088
	Grade 3	3382	65	1.9	1159	64	5.5	0.34	0.24	0.49	<0.0001	0.2877
Redness	All	3382	1673	49.5	1160	660	56.9	0.86	0.78	0.94	0.0009	0.2654
	>10.0 mm	3382	305	9.0	1160	164	14.1	0.63	0.52	0.76	<0.0001	0.0196
	>30.0 mm	3382	83	2.5	1160	34	2.9	0.83	0.55	1.27	0.4079	0.4696
Swelling	All	3380	1210	35.8	1159	476	41.1	0.85	0.77	0.95	0.0039	0.0005
	>10.0 mm	3380	254	7.5	1159	124	10.7	0.68	0.55	0.85	0.0008	<0.0001
	>30.0 mm	3380	66	2.0	1159	35	3.0	0.63	0.41	0.98	0.0384	0.0410

Note: Includes local symptoms at any injection site following the study vaccine as well as co-administered vaccines

N = number of subjects with at least one documented dose; n/% = number/percentage of subjects reporting the symptom at least once

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

limit, UL = upper limit

P-value: 2-sided Exact Stratified Test conditional to no. of cases; P-value interact: 2-sided Exact Breslow & Day Test for heterogeneity across studies

Grade 2 pain = Cried/protested on touch

Grade 3 pain = Cried when limb was moved/spontaneously painful

Redness/swelling >10.0 mm = grade 2 and grade 3 Redness/swelling > 30.0 mm = grade 3

*STN 1253633/0, Section 2.7.4, Table 26

** STN 1253633/0, Section 2.7.4, Table 27

Table 6: Solicited general AEs reported within the 4-day (Days 0-3) post-vaccination period

Symptom	Type	Hib-MenCY			Hib			Relative Risk (Hib-MenCY over Hib)			P-value	P-value interact
		N	n	%	N	n	%	RR	95% CI			
									LL	UL		
Pooled primary vaccination studies Hib-MenCY-TT-001, -005, -007, and -009*												
Drowsiness	All	4114	3198	77.7	1634	1270	77.7	0.98	0.92	1.05	0.6134	0.8992
	Grade 2-3	4114	1194	29.0	1634	555	34.0	0.85	0.77	0.95	0.0026	0.6905
	Grade 3	4114	229	5.6	1634	111	6.8	0.78	0.62	0.99	0.0450	0.1051
Irritability	All	4114	3648	88.7	1634	1485	90.9	0.96	0.90	1.02	0.2301	0.8842
	Grade 2-3	4114	2105	51.2	1634	944	57.8	0.88	0.81	0.95	0.0010	0.9801
	Grade 3	4114	454	11.0	1634	255	15.6	0.70	0.60	0.83	<0.0001	0.3250
Fever	All	4115	1751	42.6	1634	711	43.5	0.96	0.87	1.05	0.3222	0.0995
	> 38.5°C	4115	624	15.2	1634	274	16.8	0.87	0.75	1.01	0.0586	0.6673
	> 39.0°C	4115	186	4.5	1634	71	4.3	1.00	0.75	1.34	1.0000	0.8726
	> 39.5°C	4115	57	1.4	1634	22	1.3	0.92	0.55	1.59	1.0000	0.8726
	> 40.0°C	4115	10	0.2	1634	3	0.2	1.10	0.28	6.20	0.8194	0.8080
Loss of appetite	All	4114	2351	57.1	1634	959	58.7	0.95	0.88	1.03	0.2146	0.7646
	Grade 2-3	4114	661	16.1	1634	300	18.4	0.86	0.75	1.00	0.0460	0.7527
	Grade 3	4114	55	1.3	1634	25	1.5	0.87	0.53	1.48	0.6535	0.5116
Pooled fourth dose vaccination studies Hib-MenCY-TT-006, -008, and -010**												
Drowsiness	All	3380	1356	40.1	1157	500	43.2	0.92	0.83	1.02	0.1259	0.7350
	Grade 2-3	3380	336	9.9	1157	125	10.8	0.91	0.74	1.13	0.4036	0.2981
	Grade 3	3380	50	1.5	1157	14	1.2	1.20	0.65	2.36	0.6536	0.5697
Irritability	All	3380	1957	57.9	1157	716	61.9	0.93	0.85	1.01	0.0992	0.7533
	Grade 2-3	3380	702	20.8	1157	285	24.6	0.84	0.73	0.96	0.0139	0.2785
	Grade 3	3380	102	3.0	1157	38	3.3	0.92	0.62	1.37	0.7026	0.0220
Fever	All	3381	429	12.7	1158	178	15.4	0.82	0.69	0.98	0.0315	0.2621
	> 38.5°C	3381	156	4.6	1158	68	5.9	0.77	0.57	1.04	0.0844	0.2474
	> 39.0°C	3381	63	1.9	1158	23	2.0	0.92	0.56	1.55	0.7962	0.3668
	> 39.5°C	3381	23	0.7	1158	7	0.6	1.10	0.46	3.03	1.0000	0.7401
	> 40.0°C	3380	4	0.1	1158	2	0.2	0.66	0.09	7.25	0.9175	0.3295
Loss of appetite	All	3380	1095	32.4	1157	383	33.1	0.97	0.86	1.09	0.5676	0.1896
	Grade 2-3	3380	221	6.5	1157	96	8.3	0.77	0.60	0.99	0.0395	0.0783
	Grade 3	3380	43	1.3	1157	16	1.4	0.89	0.49	1.69	0.7856	0.7902
N = number of subjects with at least one documented dose n/% = number/percentage of subjects reporting the symptom at least once 95% CI = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases), LL = lower limit, UL = upper limit P-value: 2-sided Exact Stratified Test conditional to no. of cases; P-value Interact: 2-sided Exact Breslow & Day Test - heterogeneity across studies All = all events irrespective of intensity Incidence of fever is tabulated by 0.5° increments Fever = rectal or axillary/tympanic temperature ≥38.0°C Grade 2 = drowsiness interfered with normal activity; temperature >39.0°C to ≤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												
*STN 1253633/0, Section 2.7.4, Table 29												
** STN 1253633/0, Section 2.7.4, Table 30												

Unsolicited Adverse Events Days 0-30 Post-vaccination

Adverse events other than the specified solicited symptoms with onset Day 0-30 post-vaccination as well as solicited AEs with onset outside the 4- or 8-day follow-up period were recorded for studies Hib-MenCY-TT-001, -005, -007, and -009, but not for Hib-MenCY-TT-011 and -012..

While a statistical imbalance was observed in several unsolicited AEs, these analyses were conducted without adjustment for multiplicity. No consistent pattern of AEs is identified. Except for lethargy (higher rate in the Hib vaccine group after the 4th dose); the imbalances in AEs of all grades were not reflected in the corresponding grade 3 subset for each of these events. Additional grade 3 AEs were reported to have a statistical imbalance included: 1.) Grade 3 upper respiratory infection after the 4th dose (1.3% of Hib-MenCY and 0.6% of Hib groups with a P-value of 0.0374), none of which were reported as an SAE, while overall upper respiratory infection rates were similar (9.1% in Hib-MenCY group and 8.7% in the Hib group, P-value 0.7437); and 2.) Grade 3 crying across the entire four dose series (0.0% in the Hib-MenCY group vs. 0.3% of subjects in the Hib group, P-value = 0.0311)

Table 7: Unsolicited AEs within 30 days Post-vaccination with statistical imbalance between vaccine groups overall and their corresponding grade 3 events

AE	Grade	Hib-MenCY	Hib	P-value
Primary Vaccination Studies				
Bronchitis	All	0.5%	0.1%	0.0461
	3	0.1%	0.1%	0.8208
Croup infectious	All	0.8%	1.5%	0.0293
	3	0.3%	0.5%	0.1956
Oral candidiasis*	All	0.7%	0.3%	0.0444
	3	0.0%	0.0%	1.0000
Rash	All	4.5%	3.1%	0.0412
	3	0.1%	0.1%	0.9323
Fourth Dose Vaccination Studies				
Injection site nodule	All	0.1%	0.8%	0.0015
	3	0.0%	0.0%	1.0000
Gastroenteritis rotavirus	All	0.0%	0.2%	0.0308
	3	0.0%	0.0%	1.0000
Lethargy	All	0.1%	0.6%	0.0008
	3	0.0%	0.2%	0.0303
Somnolence	All	0.3%	1.0%	0.0133
	3	0.1%	0.2%	1.0000
Eczema	All	1.1%	0.3%	0.0141
	3	0.1%	0.0%	1.0000
Across Entire 4-dose Series				
Constipation	All	3.3%	2.0%	0.0482
	3	0.3%	0.3%	1.0000
Insomnia	All	0.7%	1.5%	0.0403
	3	0.2%	0.3%	0.6416
Rhinitis allergic	All	0.5%	1.2%	0.0427
	3	0.0%	0.1%	0.4993
Croup infectious	All	1.0%	2.0%	0.0208
	3	0.4%	0.7%	0.3486
Crying	All	0.2%	0.7%	0.0483
	3	0.0%	0.3%	0.0311
* Overall and grade 3 candidiasis (including oral candidiasis) showed no statistical imbalance.				
STN 1253633/0, Section 2.7.4, pages 146, 177, 199; Tables 61, 62 and 64				

Additional AEs of Interest

1. Prespecified AEs of Interest

No statistical imbalances were observed in the rates of reported new onset chronic disease (NOCD), rash and AEs resulting in ER visit across studies. The most frequently reported NOCD was eczema (2.6% of subjects in the Hib-MenCY group and 2.1% of subjects in the Hib group). Asthma was reported in 0.4% of subjects for both treatment groups.

Table 8: New Onset Chronic Disease, rash and AEs resulting in an ER visit Day 0 after Dose 1 through the day preceding administration of Dose 4 (Studies Hib-MenCYTT-005, -007, -009, and -011)

Event	Hib-MenCY N = 7362				Hib N = 2697				Relative Risk (Hib-MenCY over Hib)			P-value	P-value interact
			95% CI				95% CI			95% CI*			
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL		
NOCD	355	4.8	4.3	5.3	118	4.4	3.6	5.2	1.03	0.83	1.28	0.8355	0.6424
Rash	1082	14.7	13.9	15.5	394	14.6	13.3	16	1.02	0.91	1.15	0.7559	0.8613
AEs w/ ER visit	521	7.1	6.5	7.7	186	6.9	6	7.9	1.05	0.89	1.26	0.5727	0.1339
NOCD = new onset chronic disease N = number of subjects with at least one administered dose n/% = no./percentage of subjects reporting symptom 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) P-value = 2-sided Exact Stratified Test conditional to number of cases NA = Not Applicable as all events are in one strata P-value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies													
STN 1253633/0, Section 2.7.4, Table 65													

Prespecified AEs of Interest by Country

The reported rates of NOCD, rash and AEs resulting in ER visits were comparable in the US and Australia, and the reported rates were lower in Mexico. The reported rates of SAEs were similar in the three countries. There were no statistical imbalances detected from the Breslow and Day test indicating that the imbalances between Hib-MenCY and Hib groups (as measured by Relative Risks) or the absence thereof did not vary significantly across countries.

2. Frequent AEs

A meta-analysis of frequently reported AEs (i.e., AE reported in >5% of either the Hib-MenCY or the Hib group) was conducted to unsolicited AEs reported within the 31-day post-vaccination period across studies Hib-MenCY-TT-005/006, -007/008 and -009/010, to assess for study or country effect. No statistical imbalances detected by the Breslow and Day test in any analysis, except for:

- Rhinitis within 31 days of any vaccination
1.9% in the Hib-MenCY group and 1.5% in the Hib group, P-value interact = 0.0463
This result is due to a statistical imbalance in the rates of rhinitis in Hib-MenCY-TT-007/008 (Australian study), with 2.9% of subjects in the Hib-MenCY group and 0.5% of subjects in the Hib group with rhinitis (RR = 6.35, P-value = 0.0480). This result is in contrast to that for the Australian population in HibMenCY-TT-009/010, the observed RR for rhinitis was 0.53. No statistical imbalances were noted in the incidence of rhinitis in the other study populations in the ISS.
- Cough within 31 days of any vaccination
6.8% in the Hib-MenCY group and 6.6% in the Hib group, P-value interact = 0.0489
This result is due to a statistical imbalance in the Australian subjects in Hib-MenCY-TT-009/010, with 6.4% of subjects in the Hib-MenCY group and 13.2% of subjects in the Hib group with cough (RR = 0.48, P-value = 0.0217). No statistical imbalances were noted in the incidence of cough in the other study populations in the ISS.

3. Medication and Anti-Pyretic Use

Medication use was at the discretion of each study investigator and concomitant medications were recorded for all studies except for Hib-MenCY-TT-001 and -012. In the latter two studies all medications used for treatment of AEs and SAEs were recorded. The percentages of subjects who used concomitant medications, antipyretics or prophylactic antipyretics during the 4-day (Days 0-3) post-

vaccination period were evaluated and found similar in the Hib-MenCY group and the Hib group after each dose of the primary vaccination course and overall. A trend of lower usage was seen with subsequent vaccinations.

4. Prospective Non-inferiority Safety Endpoints

Study 009 safety endpoint comparing the frequency of fever overall for all subjects failed to demonstrate non-inferiority of the Hib-MenCY-TT group to the ActHib group (**bolded** in Table 9), although comparisons fever after each dose and overall/dose met the statistical definition of non-inferiority. No other endpoints failed to demonstrate non-inferiority as defined.

Table 9: Safety Endpoints in Hib-MenCY-TT Studies

Endpoint / Type		Comparison	Results	
Hib-MenCY-TT-005				
Grade 3 solicited and unsolicited AEs Days 0-3 Co-primary objective	Non-inferiority vs. ActHib LL of 95% CI >-10%	Any symptoms	7.22	
		General symptoms	4.10	
		Local symptoms	3.14	
Hib-MenCY-TT-009				
Fever >39.5°C (>103.1°F) Secondary objective	Non-inferiority vs. ActHib LL 95% CI for difference ≥ -2.4%	Dose 1	-0.34	
		Dose 2	-0.37	
		Dose 3	-0.61	
		Overall/dose	-0.25	
		Overall/subject	-0.70	
Hib-MenCY-TT-10				
Fever >39.5°C (>103.1°F) Co-secondary objective	Non-inferiority vs. PedVaxHib (Both co-administered with MMRII and Varivax) LL 95% CI ≥ -1.6%	Fever> 39.5°C (>103.1° F)	-0.66	
STN 1253633/0, Section 2.7.4, Tables 39, 40, 41				

5. Additional Solicited Symptoms of Interest Related to Concomitant Vaccine Administration (MMRII and Varivax)

The following solicited symptoms were evaluated as they are considered of interest for the concomitantly administered vaccines:

- Signs of meningitis
- Febrile convulsions
- Parotid/salivary gland swelling
- Fever >38°C measured by any method over the 42-day follow-up period
- Measles/rubella/varicella-like rash

The Hib-MenCY cohort exhibited no increase over the Hib cohort in rates of solicited symptoms specific to co-administered *M-M-R/II* and *Varivax* in studies Hib-MenCY-TT-008 (all study subjects) and -010 (US Safety and Immunogenicity Cohort only) after the fourth dose.

Adverse events associated with office visits were evaluated in studies Hib-MenCY-TT-005, -006, -007, -008, -009 and -010 (see Table 10 below). The data were reported in the respective clinical study reports but not evaluated in the ISS analysis. No consistent trend or statistical imbalance was reported in these studies.

Hib-MenCY-TT-005	HibMenCY N = 287				ActHIB N = 319								
	N	%	LL	UL	N	%	LL	UL					
Physician's office visit	181	63.1	57.2	68.7	190	59.6	54	65					
Physician's office visit not related to common illnesses	51	17.8	13.5	22.7	46	14.4	10.8	18.8					
Hib-MenCY-TT-006	HibMenCY N = 236				ActHIB_ActHIB N = 130				ActHIB_HibMenCY N = 132				
	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL	
Physician's office visit	75	31.8	25.9	38.1	31	23.8	16.8	32.1	43	32.6	24.7	41.3	
Physician's office visit not related to common illnesses	13	5.5	3.0	9.2	8	6.2	2.7	11.8	13	9.8	5.3	16.3	
Hib-MenCY-TT-007	HibMenCY N = 661				Meningitec + ActHIB N = 221				ActHib N = 221				
	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL	
Physician's office visit	291	44.0	40.2	47.9	90	40.7	34.2	47.5	88	39.8	33.3	46.6	
Hib-MenCY-TT-008 (booster)	Hib-MenCY (primed w/ Hib-MenCY) N = 625				Hib-MenCY (primed w/ Meningitec + ActHIB) N = 206				PedvaxHIB (primed w/ ActHIB) N = 204				
	N	%	LL	UL	N	%	LL	UL	N	%	LL	UL	
Physician's office visit	220	35.2	31.5	39.1	64	31.1	24.8	37.9	63	30.9	24.6	37.7	
Hib-MenCY-TT-009	Hib-MenCY N = 3136				Hib N = 1044				Relative Risk (Hib-MenCY / Hib)			P- Value	P-value Interact
	N	%	LL	UL	N	%	LL	UL	RR	95% CI			
Physician's office visit	1336	42.6	40.9	44.4	433	41.5	38.5	44.5	1.03	0.92	1.15	0.654 3	0.9831
Hib-MenCY-TT-010	Hib-MenCY N = 2769				Hib N = 923				Relative Risk (Hib-MenCY / Hib)			P- Value	P-value Interact
	N	%	LL	UL	N	%	LL	UL	RR	95% CI			
Physician's office visit	668	24.1	22.5	25.8	205	22.2	19.6	25.0	1.08	0.92	1.27	0.343 5	0.0850
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term) n/% = number/percentage of subjects reporting a given symptom at least once *Common illnesses: well-child care, vaccination, injury, or common acute illnesses (e.g., upper respiratory tract infection, otitis media, pharyngitis, gastroenteritis)													
STN 1253633/0, Section 5.3.5.1.3, Clinical Study Reports 005, 006, 007, 008,009, 010; Tables 46, 39, 29, 41, 60, 62, respectively													

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)

N = number of subjects with at least one administered dose

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

95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

*Common illnesses: well-child care, vaccination, injury, or common acute illnesses (e.g., upper respiratory tract infection, otitis media, pharyngitis, gastroenteritis)

STN 1253633/0, Section 5.3.5.1.3, Clinical Study Reports 005, 006, 007, 008, 009, 010; Tables 46, 39, 29, 41, 60, 62, respectively

Serious Adverse Events

1. Primary vaccination studies (Hib-MenCY-TT-005, -007, -009, -011)

No statistically significant imbalances between vaccine cohorts was observed in the reported rates of overall and specific reported SAEs in the primary vaccination studies.

There was one statistical imbalance detected by the Breslow and Day test, an increase in viral infection SAEs in the Hib-MenCY group vs. Hib group in Hib-MenCY-TT-009, but the rates are lower for the Hib-MenCY groups vs. the respective Hib groups in studies MenCY-TT-005, -007, and -011.

2. Fourth dose studies (Hib-MenCY-TT-006, -008, -010 and -012)

No statistically significant imbalances between vaccine cohorts was observed in the reported rates of overall and specific reported SAEs in studies of a fourth vaccine dose.

There were no statistical imbalances detected by the Breslow and Day test across studies.

3. SAEs of interest

- ITP

One case occurred 14 days after the fourth vaccine dose in the Hib-MenCY group in a 12-month old male in study Hib-MenCY-010, and one case of ITP occurred in a 14-month old male in the Hib-MenCY group 58 days after the fourth dose of the vaccine.

- Henoch-Schonlein Purpura

One case occurred in the Hib-MenCY group in an 18-month old male, 171 days after the fourth dose of the vaccine.

Deaths

A total of 25 deaths have been reported involving 18 individuals in the Hib-MenCY group including 1 in the earlier formulation, Hib-MenCY-TT (5/5/5), group and 7 individuals in the Hib group and are summarized in Table 10 below.

Nineteen deaths [12 deaths in the Hib-MenCY group (including 1 death in the Hib-MenCY-TT (5/5/5) group), and 7 deaths in the Hib group] were reported during the entire course of the completed primary vaccination phase studies. The onset of the fatal events occurred within the 31-day post-vaccination period for 10 cases.

Two deaths [both in the Hib-MenCY-TT group] have been reported in the completed 4th dose vaccination studies.

Four deaths, all in Hib-MenCY vaccinees, were reported thru February 16, 2009, in the ongoing study, MenACWY-TT-057.

Table 11: Summary of deaths reported in clinical studies with the Hib-MenCY-TT vaccine (TVC)

Study	N total	Deaths	Hib-MenCY		Hib	
			N	Deaths	N	Deaths
Completed primary vaccination phase studies						
Hib-MenCY-TT-001	407	1*	82	1*	82	0
Hib-MenCY-TT-003	388	0	78	0	-	-
Hib-MenCY-TT-005	756	1	287	1	319	0
Hib-MenCY-TT-007	1103	1	661	0	221	1
Hib-MenCY-TT-009	4180	4	3136	3	1044	1
Hib-MenCY-TT-011	4391	12	3278	7	1113	5
Completed fourth dose phase studies						
Hib-MenCY-TT-004	222	0	47	0	-	-
Hib-MenCY-TT-006‡	498	1	236	1	130	0
Hib-MenCY-TT-008†	1035	0	625	0	204	0
Hib-MenCY-TT-010	3692	1	2769	1	923	0
Hib-MenCY-TT-012	4020	0	3010	0	1010	0
Ongoing study (data lock point: 16 February 2009)						
MenACWY-TT-057 (primary phase) §	~1548	4	~1290	4	~258	0
Note: No deaths reported in ongoing studies Hib-MenCY-TT-002, -013 and -014 Note: The fatal SAE in the Hib group listed in Hib-MenCY-TT-007 began during the ESFU of that study, but the subject died during ESFU in Hib-MenCY-TT-008 after receiving the fourth dose of study vaccine as planned N = number of subjects in the TVC * The death was reported in the Hib-MenCY-TT (5/5/5) group ‡ For study Hib-MenCY-TT-006: 132 subjects in the <i>ActHIB</i> _Hib-MenCY group received a single dose of the Hib-MenCY-TT vaccine at approximately 12-15 months of age after priming with <i>ActHIB</i> † Study Hib-MenCY-TT-008: 206 subjects were assigned to the LicMenC group in the primary phase, and of these, 205 subjects received a single dose of the Hib-MenCY-TT vaccine 12-15 months after priming with <i>ActHIB</i> and <i>Meningitec</i> § SAE data from ongoing studies are considered to be preliminary.						
STN 1253633/0. Section 1.16. PVP. Table 16						

Table 12: Serious adverse events leading to death during the completed primary vaccination phase studies (Hib-MenCY-TT-001, -003, -005, -007, -009, and -011, all groups)

Group	Subj. No. / Country	Case Id	Age at onset (Week)	Sex	Preferred term	MA type	Dose	Day of onset	Duration	Outcome
Study Hib-MenCY-TT-001										
	5/5/2005	001-357 / Australia	B0303285A	23	F	Sudden infant death syndrome	ER	1	88	- Fatal
Study Hib-MenCY-TT-005										
	Hib-MenCY	005-100297 / US	A0544121A	22	F	Sudden infant death syndrome	ER	2	30	1 Fatal
Study Hib-MenCY-TT-007										
	Hib	007-577 / Australia	B0435502A	49	M	Hypertrophic cardiomyopathy	HO	3	160	179 Fatal
Study Hib-MenCY-TT-009										
	Hib-MenCY	009-11906 / Mexico	B0452039A	28	M	Gastroenteritis	HO	3	29	2 Fatal
	Hib-MenCY	009-1187 / US	B0470445A	34	M	Child maltreatment syndrome	HO	3	30	49 Fatal
	Hib-MenCY	009-7472 / US	B0439262A	16	F	Sudden infant death syndrome	MD	1	43	1 Fatal
	Hib	009-11559 / Mexico	B0467393A	37	F	Aspiration bronchial	ER	3	89	1 Fatal
Study Hib-MenCY-TT-011										
	Hib-MenCY	011-4021 / Mexico	B0451077A	7	F	Sudden infant death syndrome	ER	1	10	1 Fatal
	Hib-MenCY	011-28 / Mexico	B0445944A	12	F	Hypovolaemic shock	HO	1	14	8 Fatal
	Hib-MenCY	011-636 / Mexico	B0460907A	21	M	Bronchiolitis	ER	2	16	11 Fatal
					Dehydration	ER	2	24	3 Fatal	
					Gastroenteritis	ER	2	24	3 Fatal	
	Hib-MenCY	011-4302 / Mexico	B0460908A	13	F	Pneumonia	MD	1	26	2 Fatal
	Hib-MenCY	011-1403 / Mexico	B0468848A	11	F	Sudden infant death syndrome	ER	1	37	1 Fatal
	Hib-MenCY	011-7729 / US	B0451815A	14	M	Sudden infant death syndrome	MD	1	38	1 Fatal
	Hib-MenCY	011-1359 Mexico	B0475988B	44	M	Pneumonia	HO	3	77	9 Fatal
	Hib	011-1325 Mexico	B0466435B	19	M	Pneumonia	HO	2	13	30 Fatal
					Cardiac failure congestive	HO	2	42	1 Fatal	
	Hib	011-4241 Mexico	B0463326A	18	M	Bronchopneumonia	HO	2	16	8 Fatal
							Pharyngitis	HO	2	16
	Hib	011-3786 Mexico	B0451071A	10	M	Sudden infant death syndrome	ER	1	22	1 Fatal
	Hib	011-3381 Mexico	B0453412A	10	M	Pneumonia	MD	1	24	28 Fatal
	Hib	011-3420 Mexico	B0455715A	11	F	Sudden infant death syndrome	MD	1	25	1 Fatal

Sex = Male (M) or Female (F)
Dose = Last dose administered prior to the start of the SAE
Day of onset = Number of days since last vaccine dose
MA type (Medical Attention type) = HO: hospitalization; ER: emergency room visit; MD: medical doctor visit; MC = missing confirmed

STN 1253633/0, Section 1.16, PVP, Table 17

**Table 13: Serious adverse events leading to death during the entire course of the fourth dose studies
(Studies Hib-MenCY-TT-004, -006, -008, -010, and -012, all groups)**

Group	Subj. No. / Country	Case Id	Age at onset (Week)	Sex	Preferred term	MA type	Dose	Day of onset	Duration	Outcome
Study Hib-MenCY-TT-006										
Hib-MenCY	006-100113 / US	B0420193A	72	M	Sudden death	ER	4	140	1	Fatal
Study Hib-MenCY-TT-010										
Hib-MenCY	010-4890 / US	B0468818A	57	F	Multiple injuries	MC	4	29	1	Fatal
Sex = Male (M) or Female (F) Dose = Last dose administered prior to the start of the SAE										
Day of onset = Number of days since last vaccine dose										
MA type (Medical Attention type) = HO: hospitalization; ER: emergency room visit; MD: medical doctor visit, MC: missing confirmed										
STN 1253633/0, Section 2.4.7, Summary of Clinical Safety Table 50										

**Table 14: Serious adverse events in unblinded subjects who died up to 16-FEB-2009 data lock point in ongoing study
(Study MenACWY-TT-057, uncleaned database)**

Group	Subj. No. / Country	Case Id	Age at onset (Week)	Sex	Preferred term	MA type	Dose	Day of onset	Duration	Outcome
Study Hib-MenCY-TT-057 primary phase vaccination study (US subjects randomization 5:1 to Hib-MenCY or Hib)										
Hib-MenCY	1912 / US	R0000398A	11	M	Bronchiolitis	HO	1	24	19	Recovered / resolved
		R0000398C	12		Dyspnoea	HO	1	31	10	Recovered / resolved
		R0000398D	14		Apnoea	HO	1	42	5	Recovered / resolved
		R0000398E	12		Respiratory arrest	HO	1	27	3	Recovered / resolved
		R0000398F	17		Convulsion	HO	1	65	---	Not recovered / Not resolved
		R0000398G	21		Sudden infant death syndrome	ER	1	89	1	Fatal
Hib-MenCY	2603 / US	R0000425A	13	F	Sudden infant death syndrome	ER	1	33	1	Fatal
Hib-MenCY	2709 / US	R0000387A	16	M	Dehydration	HO	1	43	57	Fatal
			16		Haemolytic uraemic syndrome	HO	1	43	57	Fatal
			16		Septic shock	HO	1	43	57	Fatal
Hib-MenCY	3913 / US	R0000785A*	36	F	Leukaemia	HO	3	57	101	Fatal
NOTE: The SAE data from ongoing studies are considered to be preliminary until final reconciliation is completed after study conclusion.										
Sex = Male (M) or Female (F) Dose = Last dose administered prior to the start of the SAE Day of onset = Number of days since last vaccine dose										
MA type (Medical Attention type) = HO: hospitalization; ER: emergency room visit; MD: medical doctor visit, MC: missing confirmed										
* = SAE available in GSK SAE database but not in clinical database. SAEs reported in clinical studies are recorded both in the clinical study database and in the GSK SAE database.										
Since these preliminary safety data have not undergone a final reconciliation, some SAEs are available only in the GSK SAE database at this time.										
STN 1253633/0, Section 2.4.7, Summary of Clinical Safety Table 51										

Deaths in Infants

Table 15 displays PTs reported in infants who died, whereas Table 11, above, displays deaths reported in children of all ages in the indicated clinical studies. The infant cohort is a subset of all children enrolled in the clinical studies since older children were also enrolled

Table 15: Frequency of PTs reported in Infants who died during primary Vaccination Studies (Studies Hib-MenCY-TT-001, -003, -005, -007, -009, and -011)

Preferred Term	Number of Death Cases by Vaccine Cohort		
	Total	Hib-MenCY N = 4113	Hib N = 1635
Any	23*	11	7
Aspiration bronchial	1	1	0
Bronchiolitis	1	1	0
Bronchopneumonia	1	0	1
Cardiac failure congestive	1	0	1
Childhood maltreatment syndrome	1	1	0
Dehydration	1	1	0
Gastroenteritis	2	2	0
Hypertrophic cardiomyopathy	1	0	1
Hypovolaemic shock	1	1	0
Pharyngitis	1	0	1
Pneumonia	4	2	2
Sudden Infant Death Syndrome	8*	6	2

*Includes one subject who received the non-license formulation Hib-MenCY-TT (5/5/5)
NOTE: More than one PT may have been reported for a subject

STN 1253633/0. Section 1.16. PVP. Table 17

Sudden Infant Death Syndrome

The most commonly reported cause of death in the submitted studies was Sudden Infant Death Syndrome (SIDS). This syndrome is defined as sudden death in an infant less than 12 months age and not explained by review of clinical history, investigation of the death scene and autopsy.

A total of 8 cases of SIDS were reported (6 cases in Hib-MenCY recipients and 2 cases in Hib recipients) including 5 females and 3 males; two additional cases of SIDS have occurred in the ongoing study, MenACWY-TT-057. In the Hib-MenCY cohort, 4 cases are from the US, 3 cases from Mexico and 1 case from Australia; in the Hib cohort 2 cases are from Mexico.

SIDS was reported following Dose 1 in seven cases and Dose 2 in one case and occurred 10-89 days postvaccination (median 38 days).

Table 16: Sudden Infant Death Cases occurring during completed primary vaccination studies (Studies Hib-MenCY-TT-001, -003, -005, -007, -009, and -011)

Group	Subj. No. / Country	Case Id	Age at onset (Wk)	Sex	MA type	Dose	Day of onset	Duration	
Study Hib-MenCY-TT-001									
	5/5/2005	001-357 / Australia	B0303285A	23	F	ER	1	88	-
Study Hib-MenCY-TT-005									
	Hib-MenCY	005-100297 / US	A0544121A	22	F	ER	2	30	1
Study Hib-MenCY-TT-007 - No SIDS cases									
Study Hib-MenCY-TT-009									
	Hib-MenCY	009-7472 / US	B0439262A	16	F	MD	1	43	1
Study Hib-MenCY-TT-011									
	Hib-MenCY	011-4021 / Mexico	B0451077A	7	F	ER	1	10	1
	Hib-MenCY	011-1403 / Mexico	B0468848A	11	F	ER	1	37	1
	Hib-MenCY	011-7729 / US	B0451815A	14	M	MD	1	38	1
	Hib	011-3786 Mexico	B0451071A	10	M	ER	1	22	1
	Hib	011-3420 Mexico	B0455715A	11	F	MD	1	25	1
Sex = Male (M) or Female (F)									
Day of onset = Number of days since last vaccine dose									
MA type (Medical Attention type) = HO: hospitalization; ER: emergency room visit; MD: medical doctor visit									
STN 1253633/0, Section 1.16, PVP, Table 17									

Pharmacovigilance Plan:

Focused Postmarketing safety surveillance

1. Serious expected adverse events

At the request of the FDA, GSK proposes to provide monthly periodic reports, consisting of all US serious, expected adverse event reports, for one year following US licensure of HibMenCY-TT vaccine. This will be in addition to expedited reporting of serious unexpected events and filing quarterly periodic safety reports per regulation.

2. Purpura

In the *Menitorix* (*Haemophilus influenzae* type b and *Neisseria meningitidis* group C conjugate) vaccine UK Risk Management Plan, purpura is considered to be a class effect for meningococcal conjugate vaccines. In addition, the FDA requested that GSK monitor cases of purpura during the Hib-MenCY-TT clinical trials. As part of this PVP, purpura is considered to be an important potential risk per applicable guidances.

GSK Biologicals will follow up reports of purpura with a targeted questionnaire to obtain a more standardized and detailed description of the cases in order to facilitate detection of any patterns or potential risk factors. This questionnaire is presented in Appendix 1, Section 1.16 Risk Management Plans. All spontaneous reports of purpura will be discussed in each US Periodic Report/PSUR.

RiskMAP

The sponsor asserts that no specific risks have been identified, and therefore no RiskMAP is required.

Postmarketing Experience with Related Product (Hiberix)

Menitorix [Haemophilus type b and Neisseria meningitidis group C conjugate vaccine]

Routine pharmacovigilance:

a. Safety signal of anaphylactic reaction / anaphylactoid reaction

30-MAR-08 Pharmacovigilance Review: Proposed inclusion in the Core Safety Information (CSI) for Menitorix

b. Safety signal of febrile convulsion

12-OCT-07 Pharmacovigilance Review: Proposed inclusion in the CSI for Menitorix

Proposed Labeling for Hib-MenCY with Respect to Postmarketing Experience

Based upon postmarketing surveillance through 31-MAY-08 and subsequent data analysis, the sponsor proposes to include the following spontaneously reported adverse events in the Postmarketing Experience section of the HibMenCY US package insert:

- | | |
|---|---|
| • Rash | • Urticaria |
| • Convulsion (with or without fever) | • Allergic reactions (anaphylactic/anaphylactoid reactions) |
| • Hypotonic-hyporesponsive episode | • Angioedema |
| • Syncope or vasovagal responses to injection | • Extensive swelling of vaccinated limb |
| • Somnolence | • Injection site induration |
| • Apnea | |

Postmarketing Studies (planned)

1. Study Hib-MenCY-TT-016

Immunogenicity, safety and reactogenicity of GSK Biologicals' Hib-MenCY-TT vaccine compared to Sanofi-Pasteur's DTPa- IPV/Hib vaccine in healthy infants and toddlers, evaluating the safety and immunogenicity of Havrix and Rotarix concomitantly administered with Hib-MenCY-TT vaccine. When available, a draft protocol will be provided to CBER for review and agreement. GSK expects to initiate this study in 2010, once licensure of Hib-MenCY-TT vaccine has been granted with the study report submitted to CBER in 2013.

2. Possible post-authorization safety study which is not further described in this submission.

REVIEW COMMENTS:

1. This reviewer finds no actual or potential safety issues that would require a PMR.
2. Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical and product reviews.
3. Epidemiologic comments on reported cases of deaths including SIDS
 - a. The reported rates of all cause death and sudden infant death syndrome following vaccination with HibMnCY-TT as described in this review appear to be comparable to recent background rates in the US (Heron, National Vital Statistics Reports, Deaths: Final Data for 2006 as shown in Tables A and B, below), noting that some of the study data are submitted from non-US study sites and data on background rates for these non-US populations are not readily available.

Table A: 2006 U.S. infant mortality rates per 1,000 live births

All infants	6.69
Neonatal (0-27 days)	4.45
Post-neonatal (28 days – 1 yr)	2.24
Males	7.32
Females	6.03
White*	5.56
Black*	13.29
*based upon race of mother	

- b. Cause of death is available only for infants overall, and not for post-neonatal infants, the age group enrolled in the Hib-MenCY-TT studies. It appears that many of the listed causes would have either resulted in death prior to recruitment or likely precluded enrollment.

Table B: The 10 leading causes of U.S. infant death in 2006*

Rank	Cause of Death (ICD-10, 2004)	N	% of total deaths	Rate*
---	All causes	28,527	100.0	668.8
1	Congenital malformation, deformations, and chromosomal abnormalities	5,819	20.4	136.4
2	Disorders related to short gestation and low birth weight, no elsewhere classified	4,841	17.0	113.5
3	Sudden infant death syndrome	2,323	8.1	54.5
4	Newborn affected by maternal complications of pregnancy	1,683	5.9	39.5
5	Accidents Unintentional injuries)	1,147	4.0	26.9
6	Newborn affected by complications of placenta, cord and membranes	1,140	4.0	26.7
7	Respiratory distress of newborn	825	2.9	19.3
8	Bacterial sepsis of newborn	807	2.8	18.9
9	Neonatal hemorrhage	618	2.2	14.5
10	Disease of the circulatory system	543	1.9	12.7
---	All other causes	8,781	30.8	205.9

*Rates are infant deaths per 100,000 live births

Heron (2009), National Vital Statistics Reports, Deaths: Final Data for 2006

- c. SIDS—sudden infant death syndrome is more recently considered under the broader term, SUID – sudden unexplained death with includes two additional terms: ASSB—accidental suffocation and strangulation in bed; and death due to unknown causes. This would be expected to impact current reporting rates and comparison of to historical rates of SIDS.
 - d. It should be noted that nearly 3 times as many subjects were exposed to Hib-MenCY as compared to Hib

vaccine in the primary vaccination studies and 4th dose studies, so that the proportion of subjects with SIDS in the vaccine cohorts appears to be a reflection of the differential enrollment into the two vaccine cohorts.

- e. There does not appear to be any particular temporal clustering of SIDS cases, taking into account the safety observation periods and sizes of the studies. While SIDS occurs most commonly in infants 2-4 months of age, the multiple dose vaccination schedule and postvaccination safety observation periods might be expected to identify relatively more SIDS cases in older infants. However, 7 of the 8 SIDS cases occurred after Dose 1 administered at 2 months of age, representing the higher incidence SIDS in younger infants.