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Statistical Review and Evaluation BLA STN 125363

BLA/Supplement Number: BLA STN 125363

Product Name: MenHibrix[®]
Meningococcal Groups C and Y and Haemophilus b
Tetanus Toxoid Conjugate (Hib-MenCY-TT) Vaccine

Indication(s): Active immunization to prevent invasive meningococcal
disease caused by *Neisseria meningitidis* serogroups A, C,
Y and W-135.

Applicant: GlaxoSmithKline Biologicals

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1. Executive Summary

Biologics License Application (BLA) STN 125363 was submitted on August 12th, 2009 by GlaxoSmithKline (GSK) Biologicals for licensing the MenHibrix® (Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y and tetanus toxoid conjugate vaccine: in short, Hib-MenCY-TT) vaccine. The applicant seeks licensure of MenHibrix® for active immunization of infants and toddlers aged 6 weeks through 15 months for the prevention of invasive diseases caused by Haemophilus influenzae type b (Hib) virus and Neisseria meningitidis serogroups C (MenC) and Y (MenY) bacteria. Hib-MenCY-TT vaccine is to be administered as a 4-dose series (0.5-mL per dose) by intramuscular injections at 2, 4, 6, and 12 through 15 months of age. The first dose may be given as early as 6 weeks of age.

1.1 Brief Overview of Clinical Studies

This BLA submission contains results from eleven studies. Six of them investigated effects of the primary vaccine doses (primary vaccination phase), and the remaining five studies assessed effects of the fourth dose (booster) vaccination phase. Two studies also evaluated antibody persistence. The studies were conducted in Germany and Belgium, Australia, Mexico, and the United States. Please note that, in each study, MenHibrix vaccine was co-administered with Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, DTaP), or 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) during the infant period and with MMRII and varicella (Varivax) vaccines during the toddler period.

The main clinical trial was study Hib-MenCY-TT-009/010, which was the pivotal Phase III study evaluating safety and immunogenicity of 1-4 doses, and lot-to-lot consistency. The first phase (Hib-MenCY-TT-009) of the study was planned to cover the three-dose vaccination course (using the 2-4-6 month administration schedule) but was extended to include evaluation of antibody persistence up to the time when the fourth dose of the vaccine would be administered. In the subsequent (extension) phase (Hib-MenCY-TT-010) of the study, an additional dose of Hib-MenCY-TT vaccine was administered to subjects 12-15 months of age who had previously received three doses in the first phase (Hib-MenCY-TT-009) of the study.

Other studies included in the BLA supplied supportive evidence for the MenHibrix vaccine. Studies Hib-MenCY-TT-005 and Hib-MenCY-TT-007 provided evaluations of the immunogenicity and safety of the Hib-MenCY-TT vaccine administered on the 2, 4, and 6 month schedule. Data from studies Hib-MenCY-TT-006 and 008 were used for evaluations of the immunogenicity and safety of the Hib-MenCY-TT vaccine given at age 12 to 15 months to subjects who underwent the primary vaccination.

The pivotal Phase III study Hib-MenCY-TT-011/012 provided additional safety data mainly for the 4-dose vaccination regimen. Immunogenicity data were not collected in this study.

1.2 Conclusions, Major Statistical Findings, and Recommendations

GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid conjugate vaccine, MenHibrix® (Hib-MenCY-TT). Clinical development of this vaccine was conducted under US IND (b)(4). The proposed indication is for active immunization of infants at 2, 4, and 6 months of age (3 primary doses) and at 12 to 15 months of age (fourth dose), for the prevention of invasive diseases caused by Neisseria meningitidis serogroups C and Y and Haemophilus influenzae type b. The current GSK application was to provide data to support the applicant's claim: when administered over a 4-dose schedule, Hib-MenCY-TT candidate vaccine is "immunogenic, and its reactogenicity and safety profile is clinically acceptable, and compares favorably to that of licensed ActHib or PedvaxHib vaccine."

The statistical evaluation of the submission was based predominantly on two pivotal studies (Hib-MenCY-TT-009/010 (immunogenicity and safety) and Hib-MenCY-TT-011/012 (safety pivotal study)) and one supplemental study.

Based on the Hib-MenCY-TT-009/010 immunogenicity data, the study results did not meet the pre-specified criteria for study success. The first co-primary objective (the lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT vaccine) was not met. The estimated values of geometric mean titers (GMTs) for three lots were comparable for the C serogroup, but not for the Y serogroup. Statistical analyses showed differences in GMTs, especially for lots A and B, for the Y serogroup. There could be a few reasons why the hypotheses related to lot-to-lot consistency were not met: for instance, the small number of subjects included in these analyses, manufacturing inconsistencies, and/or variability between assay runs used for measuring titers.

As per the applicant's assumptions pre-specified in the study protocol, the objectives of study Hib-MenCY-TT-009/010 should be assessed in a hierarchical manner according to the order presented in the protocol. Due to this presumption and the fact that the first co-primary objective (the lot-to-lot consistency) was not met, based purely on statistical principles and without consideration of other subject-matter disciplines, the pre-specified criteria for study success were not entirely fulfilled.

Disregarding the hierarchical assumption, other pre-defined co-primary hypotheses were also tested and it was found that criteria related to these hypotheses were met. However, it is worth noting that testing of these hypotheses was based on immunogenicity datasets with about 30% missing data. This large amount of missing data could introduce biases into the study results.

The overall profile of safety data, generated from pivotal studies Hib-MenCY-TT-009/010 and Hib-MenCY-TT-011/012, showed that there were no sizable differences

between safety data for Hib-MenCY-TT and Hib (Hib or PedvaxHib) vaccines co-administered with the routine infant vaccines. The statistical analyses were performed for each study separately and then for the pooled data from different studies. However, issues regarding comparability of studies (required for poolability) may exist because different protocols and different populations were used in different studies. An overview of the vaccine safety, derived from two studies (Hib-MenCY-TT-009/010 and Hib-MenCY-TT-011/012), is provided in Section 4 of this statistical review. In summary, for the primary vaccination schedule at 2, 4, and 6 months of age, serious adverse event (SAE) rates ranged from 4.4% to 4.5%, while SAE rates were about 2.1% after the fourth dose. These rates were mostly similar among the treatment groups. Please note that there were 16 deaths (10 in the Hib-MenCY group and six in the Hib group) reported in the pooled studies Hib-MenCY-TT-009 and -011 from Day 0 after Dose 1 through the day preceding Dose 4, and one death after the fourth dose. However, fatal events were assessed by the study investigators as not related to vaccination.

Please refer to the clinical review for more safety details and an assessment of clinical significance of some of the observed differences.

Recommendations:

A regulatory decision based on this submission depends on the evaluation of the clinical significance of the following findings:

- The statistical analysis of data related to immune responses to Hib-MenCY-TT vaccine showed that the pre-specified criteria were met
- No interference in seroresponse was observed when Hib-MenCY-TT was administered concomitantly with the routine infant vaccines: e.g., Infanrix, Pediarix, and MMRV
- There were no notable differences between safety data for Hib-MenCY-TT and Hib (Hib or PedvaxHib) vaccines co-administered with the routine infant vaccines.

However, there appeared to be a potential interference between Hib-MenCY-TT and PCV.

It is worth noting that the three investigated lots only met the pre-defined criteria, established for the lot-to-lot consistency, in the case of PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C lot comparisons narrowly missed the lower equivalence margin of 0.5.

It is up to the review team to determine whether the product is approvable and if so what language should be considered in the label to point out the following issues:

- the possible interference between Hib-MenCY-TT and PCV
- differences in AEs rates among countries
- missing immunogenicity data.

2. Introduction

2.1 Overview

Hib-MenCY-TT (MenHibrix®) vaccine is a sterile, lyophilized powder which is reconstituted at the time of use with the accompanying saline diluent. The vaccine contains *Neisseria meningitidis*, serogroups C and Y, and *Haemophilus b* capsular polysaccharide antigens.

In the past, it was shown that specific levels of PRP (Polyribosylribitol phosphate) antibodies, in short anti-PRP, were correlated with protection against invasive disease due to *H. influenzae* type b. An efficacy study with unconjugated *Haemophilus b* polysaccharide vaccine indicated that anti-PRP concentrations ≥ 1.0 mcg/mL predict protection through at least 1-year period. This cut-off antibody level has been used in subsequent studies to evaluate the effectiveness of vaccines containing *H. influenzae* type b, including MenHibrix®.

Specific levels of bactericidal antibodies to *N. meningitidis* serogroups C (MenC) and Y (MenY), measured by serum bactericidal assay using human complement (hSBA), have been associated with protection against invasive meningococcal disease. MenHibrix® induces production of meningococcal bactericidal antibodies specific to the capsular polysaccharides of serogroups C and Y. It has been common practice to assume the hSBA MenY and hSBA MenC titer threshold $\geq 1:8$ as a protection level against invasive meningococcal disease. However, it is known that a protection level against invasive meningococcal disease depends on the assay characteristics (e.g., LLOQ).

The immunogenicity of the final Hib-MenCY-TT formulation was evaluated based on the immunogenicity data collected during the following clinical trials:

- **Hib-MenCY-TT-009/010; Phase 009** was a partially double-blinded, randomized, multinational study conducted in Australia, Mexico, and the US. The study evaluated the safety and immunogenicity of a 3-dose primary vaccination course with Hib-MenCY-TT vaccine co-administered with Pediarix (Pevnar co-administration was strongly encouraged) to healthy infants at 2, 4, and 6 months of age as compared to the immune response to and safety of vaccination with ActHIB administered concomitantly with Pediarix (Pevnar co-administration was strongly encouraged). Assessment of lot-to-lot consistency for three manufacturing lots of Hib-MenCY-TT vaccine was the first primary objective.

Hib-MenCY-TT-009/010; Phase 010 was a single-blinded, controlled extension of Hib-MenCY-TT-009. The study evaluated the safety and immunogenicity of the fourth dose of Hib-MenCY-TT vaccine as compared to the fourth dose of PedvaxHIB (co-administration with M-M-RII, Varivax, and Pevnar was strongly encouraged), at 12 to 15 months of age. A subset of children was additionally evaluated for the non-inferiority of immune responses to the co-administered M-

M-RII and Varivax vaccines. Note: Co-administration with M-M-RII and Varivax was mandatory in this cohort. The analysis of the immunogenicity induced by the co-administered vaccines M-M-RII and Varivax was performed on the dataset pooled from studies Hib-MenCY-TT-008 and Hib-MenCY-TT-010.

- **Hib-MenCY-TT-005 (Primary vaccination) and Hib-MenCY-TT-006 (Booster vaccine phase);** These were Phase II, single-blinded, randomized, controlled, multicenter primary and booster vaccination studies to evaluate the immunogenicity, reactogenicity, and safety of Hib-MenCY-TT as compared to ActHIB, each co-administered with Pediarix and Prevnar, in healthy infants at 2, 4, and 6 months of age and in healthy toddlers at 12 to 15 months of age (booster dose, co-administered with Prevnar).
- **Hib-MenCY-TT-007 (Primary vaccination phase) and Hib-MenCY-TT-008 (Booster vaccine phase);** These were Phase II, open-label, randomized, controlled, multicenter primary and booster vaccination studies of GSK Biologicals' Hib-MenCY-TT conjugated vaccine versus Hib and MenC conjugate licensed vaccines 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 proposed licensure of Hib-MenCY-TT is based on:

- Demonstration of lot-to-lot consistency
- Demonstration of vaccine efficacy (immunogenicity) as compared to ActHIB or PedvaxHIB vaccine
- Demonstration of vaccine safety as compared to ActHIB or PedvaxHIB vaccine.

2.2 Data Sources

This review is based on, but not limited to, the clinical study reports (CSRs) for the pivotal study (Hib-MenCY-TT-009/010) and two supportive studies. The statistical reviewer performed various statistical analyses on submitted SAS transport datasets to verify the results. The CSRs and SAS datasets as well as other related materials were provided by the applicant at the time of the sBLA submission (STN 125363, 08/12/2009) and were primarily located in Module 5 of the eCTD submission package ("m5-clinical-study-reports"). For each clinical study, the key datasets are: DEMOG, ADVERSE, IMMUN, POP, PROTDEV, and LABDATA, but other datasets were also used if necessary.

2.3 Material Reviewed

The statistical review of BLA submission STN125363 is based on the following materials provided by applicant:

- I. STN 125363/0; Module 1 Volume 1; administrative information, labeling.
- II. STN 125363/0; Module 5 Volumes 1-32; clinical study reports, Reports of Post-marketing Experience
- III. STN 125363/0; Module 2; Clinical Overview, Summary of Clinical Safety, Summary of Clinical Effectiveness
- IV. STN 125363/0.1 (August 26, 2009): Safety Information Amendment (response to CBER request of June 19, 2009)
- V. STN 125363/0.2 (January 8, 2010); the response to CBER request of October 21, 2009
- VI. STN 125363/0.12 (April 20, 2011); the applicant responses to the June 11 CR letter.

3. Statistical Evaluation of Immunogenicity Data

3.1 Study Hib-MenCY-TT-009/010

Title of the study: “A phase III, randomized, multi-national study, double-blinded for the immunogenicity and consistency evaluation of 3 Hib-MenCY-TT vaccine lots and single-blinded and controlled for the evaluation of safety and immunogenicity of GSK Biologicals' Haemophilus influenzae type b and Neisseria meningitides 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.”

Study Period: February 22, 2006 - August 27, 2007 (Hib-MenCY-TT-009)
December 29, 2006 – August 5, 2008 (Hib-MenCY-TT-010)

Note: This study was conducted under two different protocols: Hib-MenCY-TT- 009 (Primary Vaccination Phase) and Hib-MenCY-TT-010, BST: 009 (Fourth Dose Vaccination Phase). This report concurrently evaluates results of both phases, including the extended safety follow-up period that ended 6 months after the fourth dose vaccination.

3.1.1 Brief Overview of the Study

Study design

The 009 phase of the clinical trial was planned as a Phase III, randomized, consisting of four parallel groups, multinational study that was double-blinded for evaluation of the immunogenicity and consistency of 3 Hib-MenCY-TT vaccine lots, but single-blinded and controlled for the evaluation of safety and immunogenicity of Hib-MenCY-TT as compared to corresponding effects of ActHib vaccine. Target enrollment in this phase was 4,400 subjects. Subjects were randomized to 3 lot groups receiving the Hib-MenCY-

TT vaccine and to the Hib group which received ActHib vaccine. In the 010 phase of the study (the Fourth Dose Phase), three Hib-MenCY-TT lot groups were pooled into a single Hib-MenCY group in which the fourth dose of Hib-MenCY-TT, derived from a single lot, was administered. The comparator vaccine in this Fourth Dose Phase was PedvaxHIB.

The general objectives of the study were:

1. To demonstrate the consistency of 3 manufacturing lots of Hib-MenCY-TT.
2. To evaluate the safety and immunogenicity of Hib- MenCY-TT vaccine as compared to ActHib vaccine, each administered to healthy infants at 2, 4, and 6 months of age and co-administered with Pediarix or Infanrix.
3. To evaluate the safety and immunogenicity of a booster dose of Hib-MenCY-TT vaccine administered at age 12 to 15 months as compared to PedvaxHIB.
4. To evaluate the immunogenicity of Pediarix vaccine co-administered either with Hib-MenCY-TT or with ActHIB, following 3 primary doses.

The study subjects participated in one of three cohorts:

1. Cohort 1 (US Safety and Immunogenicity):
Cohort 1 was composed of subjects enrolled at sites located within the US. Both safety and immunogenicity data were evaluated for this cohort. Protocol-planned enrollment was 1080 subjects.
2. Cohort 2 (Safety only):
Cohort 2 was composed of subjects enrolled at both US and non-US sites. Only safety data were evaluated for this cohort. Protocol-planned enrollment was 3120 subjects.
3. Cohort 3 (non-US Safety and Immunogenicity):
Cohort 3 was composed of the first 200 subjects enrolled at one site in Mexico. Both safety and immunogenicity data were evaluated for this cohort. The immunogenicity data were summarized descriptively.

The randomization procedure was performed with a balanced allocation of subjects at a ratio 1:1:1:1 to the four treatment groups with cohort stratification. Assignment to a cohort was connected with the study site, i.e., investigators could enroll all subjects at a given study center into either Cohort 1 or Cohort 2. The exception was the single center in Mexico which enrolled its first 200 subjects into Cohort 3. However, during the enrollment to the study, some study centers originally assigned to Cohort 2 were re-assigned to Cohort 1. This was done, according to the applicant's explanation, because the projected enrollment for Cohort 2 (i.e., no serum sampling required as a study procedure) was completed faster than expected.

Treatment Groups

I. Primary Phase (009):

Hib-MenCY group: vaccinated with Hib-MenCY-TT vaccine, co-administered with commercially available combined DTaP-HepB-IPV vaccine used under the trade name Pediarix in the US and Mexico and Infanrix penta in Australia; Hib-MenCY group encompassed pooled groups: Hib-MenCY Lot A, Hib-MenCY Lot B, and Hib-MenCY Lot C.

Hib group: vaccinated with ActHIB vaccine, co-administered with commercially available combined DTaP-HepB-IPV vaccine used under the trade name Pediarix in the US and Mexico and Infanrix penta in Australia.

II. Fourth Dose Phase (010):

Hib-MenCY group: vaccinated with Hib-MenCY-TT vaccine, co-administered with M-M-R® II, Varivax and Prevnar (primed with Hib-MenCY-TT + Pediarix (+ Prevnar))

Hib group: vaccinated with PedvaxHIB, co-administered with M-M-R ® II, Varivax and Prevnar (primed with ActHIB + Pediarix (+ Prevnar)).

General information on the primary and fourth dose phase study design including: sample size, vaccine(s) administered and timing of dosing is presented in Table 3.1.1.1.

Table 3.1.1.1: Summary of the general study design of studies 009 and 010

Study Hib-MenCY-TT	Total # of Subjects	Cohort	Vaccine Group	Vaccination Schedule	Concomitant Vaccines
009	US - 1084	1 (Immunogenicity and Safety)	Hib-MenCY-TT Lot 1 Hib-MenCY-TT Lot 2 Hib-MenCY-TT Lot 3 ActHib	2, 4, 6 months	Pediarix other (PCV7, Synagis, Influenza)
	US - 1953 non-US - 1200	2 Safety	Hib-MenCY-TT Lot 1 Hib-MenCY-TT Lot 2 Hib-MenCY-TT Lot 3 ActHib		
	Mexico - 200	3 (Immunogenicity and Safety)	Hib-MenCY-TT Lot 1 Hib-MenCY-TT Lot 2 Hib-MenCY-TT Lot 3 ActHib		
010	US - 1084	1 (Immunogenicity and Safety)	Hib-MenCY-TT (Hib-MenCY-TT primed) PedvaxHib (ActHib primed)	12-15 months	MMR, Varivax other (Prevnar)
	US - 1920 non-US - 1200	2 (safety only)	Hib-MenCY-TT (Hib-MenCY-TT primed) PedvaxHib (ActHib primed)		
	Mexico - 200	3 (Safety and Immunogenicity)			

Source: Reviewer's table

Primary Vaccination Schedule

Infants would be vaccinated with Hib-MenCY-TT or ActHIB vaccine, each co-administered with Pediarix/Infanrix penta at age 2, 4, and 6 months. Prevnar, Synagis, influenza, and rotavirus vaccines were permitted to be given concomitantly with the study vaccines.

Fourth Dose Vaccination Schedule

Cohort 1 (safety and immunogenicity): Infants would be vaccinated with Hib-MenCY-TT or PedvaxHIB vaccine, each co-administered with MMRII and Varivax at age 12 to 15 months of age. Subjects who received Hib-MenCY-TT vaccine in the primary series would receive the fourth dose of Hib- MenCY-TT vaccine. Subjects who received ActHIB in the primary series would receive PedvaxHIB as the fourth dose. Prevnar, hepatitis A vaccine, and influenza vaccine were permitted to be given concomitantly with the study vaccines.

Cohort 2 and Cohort 3: Infants would be vaccinated with Hib-MenCY-TT or PedvaxHIB vaccine, depending on the primary vaccine received, at age 12 to 15 months. Prevnar, measles, mumps, rubella, varicella, hepatitis A vaccine, and influenza vaccine were permitted to be given concomitantly with the study vaccines.

Blood Samples

Blood samples would be collected only from infants/toddlers in Cohorts 1 and 3.

For Phase 009, blood samples would be drawn at Visit 4 (at age 7 months) after primary vaccinations. The applicant claims that sub-randomization was performed in order to allocate sera samples for assays. Table 3.1.1.2 (Clinical Report, page 111, Table 7) shows summary of blood sampling time-points and assay markers for the assessment of immunology variables.

Table 3.1.1.2: Summary of blood sampling time-points and assay markers of immunology variables

Group	Blood sampling time point			Marker	N of enrolled subjects
	Timing	Month	Visit #		
Cohort 1 and 2	Post-vacc III	5	4	Anti-PRP, hSBA-MenC, hSBA-MenY anti-PSC, anti-PSY	1080 (US) 200 (non-US)
70% of subjects	Post-vacc III	5	4	Anti-D, anti-T, anti-PT, anti-FHA anti-PRN, anti-polio type 1, 2 and 3 anti-HBs	756 (US) 140 (non-US)

Source: Table 7 on Page 111 in the applicant's CSR for Hib-MenCY-TT-009

Cohort 1=subjects at all US sites

Cohort 3= the first 200 subjects enrolled at the single center in Mexico identified for descriptive immunogenicity analysis.

Post-vaccination III = one month after the third vaccine dose

N = protocol-projected number

Non-US = single site in Mexico

For Phase 010, blood samples from Cohorts 1 and 3 would be drawn prior to the fourth dose vaccination at Visit 5 (12-15 months of age) and at Visit 6 (13.5-16.5 months of age in Cohort 1, and 13-16 months of age in Cohort 3). The following assay runs would be performed:

- For Cohort 1: PRP, hSBA-MenC, hSBA-MenY, measles, mumps, rubella, varicella, Influenza: H1N1, H3N2, B (where applicable), anti-PSC, anti-PSY.
- For Cohort 3: PRP, hSBA-MenC, hSBA-MenY, anti-PSC, anti-PSY

However, anti-PSC and anti-PSY would be tested only for those subjects in Cohorts 1 and 3 for whom sufficient sera were available.

Duration of the study

Durations of the primary vaccination and the fourth dose vaccination phases would be 10 to 13 months and 6 months post last-vaccination, respectively.

Primary objectives and related hypotheses

In the protocol, there were eight pre-specified co-primary objectives. The co-primary objectives, in order provided within the study protocol, were:

- 1) To demonstrate lot-to-lot consistency, in terms of immunogenicity to PRP (as measured by ELISA) and to MenC and MenY (as measured by hSBA), of 3 manufacturing lots of Hib-MenCY-TT vaccine.
- 2) To demonstrate that, following the fourth dose, the immune response to PRP in the group that received 3 primary vaccine doses of Hib-MenCY-TT vaccine and the fourth dose of Hib-MenCY-TT vaccine co-administered with MMRII 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 MMRII and Varivax.
- 3) To evaluate immunogenicity following four doses of Hib-MenCY-TT vaccine co-administered with Pediarix at 2, 4, and 6 months of age and with MMRII and Varivax at 12 to 15 months of age in terms of immune response measured by hSBA 6 weeks post-fourth dose.
- 4) To evaluate the “specific” effect (geometric mean of the individual post-fourth dose/pre-fourth dose titers ratio) of the fourth dose of Hib-MenCY-TT vaccine co-administered with MMRII and Varivax at 12 to 15 months of age in terms of the response to the fourth dose vaccine as measured by hSBA.
- 5) To demonstrate the non-inferiority of Hib-MenCY-TT vaccine as compared to ActHIB, each co-administered with Pediarix, following 3 primary doses in terms of immunogenicity to PRP measured by ELISA.
- 6) To demonstrate the non-inferiority of MMRII when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to MMR II co-administered with a dose of PedvaxHIB, each co-administered with Varivax.
- 7) To demonstrate the non-inferiority of Varivax co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to Varivax co-administered with a dose of PedvaxHIB, each co-administered with MMRII in terms of immunogenicity to varicella as measured by fluorescent antibody to membrane antigen (FAMA).
- 8) To demonstrate that the incidence of fever greater than 39.5C (103.1F), within the 4-day period following any vaccination in the 3-dose Hib-MenCY-TT series, is non-inferior to fever incidence in the group receiving ActHIB.

The above listed co-primary objectives were tested using the following criteria:

- (1) To establish lot-to-lot consistency, the criterion was to demonstrate that for each pair of lots and for immune response to each antigen (anti-PRP, hSBA-MenC, hSBA-MenY), the two-sided 95%CI of 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 the 4th vaccination, the criterion was to demonstrate that the lower limit of 95% CI for the difference [pooled Hib-MenCY-TT – ActHIB®] of percentages of subjects with anti-PRP concentration ≥ 1.0 mcg/mL is $\geq -10\%$.
- (3) To evaluate immunogenicity 6 weeks after the 4th vaccination with respect to hSBA Men C and Men Y titers $\geq 1:8$, the criterion was to determine that the lower limits of the exact 95% CI for percentages of subjects with hSBA titers $\geq 1:8$ are $\geq 90\%$ for MenC and MenY.
- (4) To evaluate the specific effect of the 4th dose of Hib-MenCY-TT in terms of immune response measured by hSBA-MenC and hSBA-MenY, the criterion was that the lower limits of the 95% CIs for the geometric mean of the individual ratio of titers post-dose 4/pre-dose 4 is greater than or equal to 2.
- (5) To demonstrate the non-inferiority of Hib-MenCY-TT vaccine as compared to ActHIB, each co-administered with Pediarix, following 3 primary doses in terms of immunogenicity to PRP as measured by ELISA, the criterion was to demonstrate that the lower limit of the 95% CI for the difference [pooled Hib-MenCY-TT – ActHIB®] in percentage of subjects with anti-PRP concentrations ≥ 1.0 mcg/mL is $\geq -10\%$.
- (6) To demonstrate the non-inferiority of MMR®II when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to MMRII co-administered with the fourth dose of PedvaxHIB, each co-administered with Varivax, the criterion was to determine that the lower limits of 95% CIs for the group difference [Hib-MenCY-TT – PedvaxHIB®] in percentage of subjects with
 - a. anti-measles concentration ≥ 150 mIU/mL
 - b. anti-mumps titer ≥ 28 ED₅₀,
 - c. anti-rubella concentration ≥ 10 mIU/mL,
 are greater than or equal to -5.
- (7) To demonstrate the non-inferiority of Varivax® when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to Varivax co-administered with a fourth dose of PedvaxHIB, each co-administered with MMRII, in terms of the immunogenicity to varicella, the criterion was to show that lower limit of the 95% CI for the difference [Hib-MenCYTT vaccine fourth dose group minus PedvaxHIB fourth dose group] in the percentage of subjects with seroconversion for varicella antibody (anti-varicella antibody titer $\geq 1:5$ dilution) in initially seronegative subjects (anti-varicella antibody titer $< 1:5$ dilution) is $\geq -10.0\%$.

It was assumed that for both the primary and the fourth dose phases of the study, the co-primary hypotheses would be tested in a hierarchical manner according to the order presented in the protocol (and the above). This means, a co-primary hypothesis could

only be considered if the statistical criteria for all previous co-primary objectives were met.

It is worth noting that there were ten secondary objectives defined in the protocols. A general outline of the primary and secondary objectives, with their endpoints, is presented in the Phase 009 Body Report, page 119.

For detailed definitions of primary and secondary endpoints, please refer to the clinical reviewer's memo.

The most important from the point of view of this review the lot-to-lot consistency hypothesis was formulated as follows:

for each PRP, and C, Y serogroup,

$H_0: \phi_{ij} \leq 0.5$, or $\phi_{ij} \geq 2$ for some combinations of $i \neq j$

$H_a: 0.5 < \phi_{ij} < 2$, for all combinations of $i \neq j$

where $\phi_{ij} = \mu_i/\mu_j$, and μ_i and μ_j are the means of GMC or GMTs values for one month post-Dose 3 and for the i^{th} and j^{th} lots, respectively.

Sample size

Under the applicant's assumptions and full enrollment of 4400 subjects, the applicant claims that the overall power to meet the multiple primary objectives would be 75.0%.

Study populations used for evaluations

For evaluations of study results, the applicant created several cohorts listed as follows:

(1) Primary Total Vaccinated Cohorts

Primary Total Vaccinated Cohort - includes all vaccinated subjects.

Primary Total Vaccinated Cohort for Analysis of Safety - includes all subjects with documented administration of at least one vaccine

Primary Total Vaccinated Cohort for Analysis of Immunogenicity - includes vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

(2) Primary According-To-Protocol (ATP) Cohort for Safety

Primary ATP Cohort for Safety - includes all eligible subjects.

(3) Primary ATP Cohort for Immunogenicity

Primary ATP Cohort for Immunogenicity - includes all evaluable subjects (i.e., those who met all eligibility criteria, complied with the procedures defined in the protocol and did not meet elimination criteria during the study) from the Primary ATP Cohort for Safety for whom assay results were available for antibodies against at least one study vaccine antigen for the blood sample taken during the primary vaccination (after the third vaccine dose).

(4) Fourth Dose ATP Cohort for Safety

Fourth Dose ATP Cohort for Safety - includes all eligible subjects who received 3 vaccine doses in the primary vaccination course and the fourth vaccine dose and who have not received a vaccine that was not specified in or forbidden by the protocol.

(5) Fourth Dose ATP Cohort for Immunogenicity

Fourth Dose ATP Cohort for Immunogenicity - includes all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) from the Fourth Dose ATP Cohort for Safety for whom assay results were available for antibodies against at least one study vaccine antigen for the blood sample taken 42 days after administration of the fourth dose vaccine. The time interval between Visit 5 and Visit 6 for inclusion in the Fourth Dose ATP Cohort for Immunogenicity was defined as 35 to 56 days.

(6) Enlarged Fourth Dose ATP Cohort for immunogenicity

Enlarged Fourth Dose ATP Cohort for Immunogenicity - includes all evaluable subjects from the Fourth Dose ATP Cohort for Safety for whom assay results were available for antibodies against at least one study vaccine antigen found in blood samples taken 42 days after administration of the fourth dose vaccine, but for whom the interval between Visit 5 and Visit 6 was 35 to 77 days. Thus, the Enlarged Fourth Dose ATP cohort for Immunogenicity consisted of subjects from the Fourth Dose ATP Cohort for Immunogenicity plus the subjects for whom the interval between Visits 5 and 6 was 57-77 days.

3.1.2 Evaluation of Study Immunogenicity Results

A. Primary Vaccination Phase (3 doses)

Disposition of Subjects

In total, 4441 subjects were enrolled and vaccinated in 91 study centers (one center in Mexico, four centers in Australia and 86 centers in the United States (US). However, all

261 subjects who were enrolled and vaccinated at US Center #24660 were eliminated from all analyses due to the repeated GCP violations and significant protocol non-compliance in spite of the applicant's "intense monitoring and remediation efforts." The applicant claimed that "certain key data points, such as vaccine accountability, could not be fully reconciled at the site."

Thus, 4180 subjects enrolled and vaccinated in 90 study centers (86 centers in the U.S., 1 center in Mexico, and 4 centers in Australia; the number of subjects per center ranged from 1 to 800) were eligible for inclusion in the Primary Total Vaccinated Cohort (3136 Hib-MenCY-TT subjects and 1044 Hib subjects).

The disposition of subjects for both phases of the study is summarized in Table 3.1.2.1.

Table 3.1.2.1: Disposition of subjects at the end of the Primary Vaccination Phase and the Fourth Dose Vaccination Phase by treatment group

	Study Phases			
	Primary Vaccination Phase		Fourth Dose Phase	
	Hib-MenCY	ActHIB	HiB-MenCY	PedvaxHIB
Enrolled - 4441				
Vaccinated (Eligible)	3136	1018	2769	923
Discontinued	248	83	87	24
Lost to Follow-up	60	14	53	12
Withdrew consent	93	40	10	1
Other Reason	95	29	24	11

Source: Reviewer's analysis based on the CSRs Hib-Men009 and 010

Primary Vaccination Phase:

Hib-MenCY (HibMenCY-TT Lot A, Lot B or Lot C pooled)= HibMenCY + Pediarix (+ Prevnar if available)

ActHIB = ActHIB + Pediarix (+ Prevnar if available)

Fourth Dose Phase:

Hib-MenCY = Hib-MenCY-TT + MMRII + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

PedvaxHib = PedvaxHIB + MMRII + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

It can be concluded from Table 3.1.2.1 that the major reason for the premature withdrawals was withdrawal of consent (3% - 4% of subjects in the Primary Vaccination Phase). In total, 331 subjects were withdrawn from the primary phase of the study. Seven and four subjects withdrew as the result of serious adverse events and non-serious adverse events, respectively. Protocol violations resulted in early withdrawal of 33 subjects.

As shown in Table 3.1.2.1, 3692 eligible subjects (2769 + 923) were included in the Fourth Dose Total Vaccinated Cohort and were vaccinated in 89 centers.

Protocol Deviations

Per the applicant's report, during the primary and the fourth dose vaccination phases, 345 and 590 protocol deviations were reported, respectively.

REVIEWER'S COMMENTS:

For the immunogenicity analysis, the applicant reported that from 991 subjects in Cohort 1 who were eligible for inclusions in the Primary Total Vaccinated Cohort, 296 subjects (29.9%) were not eligible for inclusion in the Primary ATP Immunogenicity Cohort. The main reason for eliminations was lack of essential serological data (for 200 subjects, serological data were missing).

The applicant claimed that the numbers of evaluable Hib-MenCY-TT recipients were 163 for Lot A, 182 for Lot B, and 177 for Lot C (in total, 522 subjects for the lot-to-lot consistency evaluation). However, based on the serology data submitted by the applicant, there were 542 evaluable subjects for the lot-to-lot consistency evaluation.

For the Fourth Dose Phase, 521 subjects from Cohort 1 (US population) were included in the Fourth Dose ATP Immunogenicity Cohort.

The applicant reported that all subjects (261 and 189 subjects from the Primary Vaccination and the Fourth Vaccination Phases, respectively) who were enrolled at Center #24660 were eliminated from all analyses due to GCP violations and the protocol non-compliance. To ensure that these incidents did not impact the study integrity, a statistical analysis testing for possible influence of this center on the immunogenicity and safety results was performed by the applicant. This analysis revealed that outcomes from this center did not have a meaningful influence on the final clinical study outcomes.

Immunogenicity results

Post-dose three and pre- and post-fourth dose immunogenicity analyses were performed on immunogenicity ATP data from Cohort 1. Disposition of subjects enrolled and eligible for the primary and fourth dose ATP analyses is presented in Table 3.1.2.2.

Table 3.1.2.2: Numbers of subjects enrolled into study and eligible for statistical analyses for the primary and fourth dose phases

	Study Phases			
	Primary Vaccination Phase		Fourth Dose Phase	
	#of Subjects	# of Missing Subjects	#of Subjects	# of Missing Subjects
Enrolled	1084		885	
Subjects at Center with GCP non-compliance		93		69
Primary Total Vaccinated Cohort	991		816	
Protocol violation		20		126
Primary ATP Safety Cohort	971		690	
Protocol violation		123		75
Essential serological data missing		153		94
ATP Immunogenicity Cohort	695		521	

Source: Reviewer's analysis based on the CSRs Hib-Men009 and 010

It can be seen from the above table that for both vaccination phases approximately 36% of subjects were not eligible for inclusion into the Primary ATP Cohort for Immunogenicity Analyses.

Please note that the Fourth Dose ATP Immunogenicity Cohort (521 subjects) was not a subset of the Primary ATP Immunogenicity Cohort (695 subjects) because 29% of subjects of the Fourth Dose ATP Immunogenicity Cohort were not included in the Primary ATP Immunogenicity Cohort.

The primary analysis of antibody persistence was performed on all eligible Cohort 1 subjects from the Fourth Dose ATP Cohort for Safety who had immunogenicity results at the pre-fourth dose time-point for at least one antigen. The primary analysis of immune response to the fourth dose was performed for subjects belonging to the Fourth Dose ATP Cohort for Immunogenicity and Cohort 1, namely, for all evaluable subjects from the Fourth Dose ATP Cohort for Safety for whom assay results, based on the blood samples taken 42 days after the administration of the fourth dose of vaccine, were available for antibodies against at least one study vaccine antigen.

Non-inferiority of co-administration with MMRII® and Varivax® was tested on data pooled from Hib-MenCY-TT-010 and the non-U.S. study Hib-MenCY-TT-008 conducted in Australia under the same IND.

I. Primary immunogenicity hypotheses

Primary Objective #1 - Lot-to-lot consistency (Primary Vaccination)

The primary immunogenicity hypotheses, Objective #1, are related to clinical lot-to-lot consistency. The criteria for lot-to-lot consistency were: for each pair of lots and for the anti-PRP, hSBA-MenC and hSBAMenY antibody responses, the two-sided 95% CI of the GMCs/GMTs ratio between lots for the corresponding antibody should be within the [0.5, 2.0] interval. A summary of the hypothesis testing is presented in Table 3.1.2.3.

Table 3.1.2.3: Lot-to-lot consistency results for anti-PRP, hSBA-MenC, and hSBA-MenY GMC/Ts one month post-Dose 3 based on the unadjusted statistical analyses

Antibody	Lot A			Lot B			Lot C		
	N	GMC/T	95% CI	N	GMC/T	95% CI	N	GMC/T	95% CI
Anti-PRP	168	10.33	(9.01, 11.85)	187	11.59	(9.89, 13.58)	183	12.01	(9.99, 14.43)
hSBA-MenC	164	925.27	(772.4, 1108.4)	174	1147.57	(958.4, 1364.5)	172	912.81	(738.9, 1127.5)
hSBA-MenY	156	180.12	(138.1, 234.9)	174	291.01	(237.0, 357.3)	170	256.05	(202.5, 323.8)
Antibody	Ratio of GMCs or GMTs (95% CI)								
	Lot A vs. Lot B			Lot A vs. Lot C			Lot B vs. Lot C		
Anti-PRP	0.89 (0.72, 1.10)			0.86 (0.68, 1.09)			0.97 (0.76, 1.23)		
hSBA-MenC	0.81 (0.63, 1.04)			1.01 (0.77, 1.34)			1.25 (0.95, 1.65)		
hSBA-MenY	0.62 (0.44, 0.86)			0.70 (0.49, 1.00)			1.14 (0.83, 1.55)		

Source: Reviewer's analysis

Based on Table 3.1.2.3, the three investigated lots only met the pre-defined criteria for lot-to-lot consistency for the PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C comparisons narrowly missed the lower equivalence margin of 0.5, i.e., the lower limits were 0.44 and 0.49, respectively.

REVIEWER'S COMMENTS:

1. For the lot-to-lot consistency testing, the reviewer performed exploratory analyses using regression models with adjustment for "Center." In all cases, "Center" was not a significant covariate in the models for hSBA-MenC and hSBA-MenY GMTs. However, these analyses showed that the lots were statistically different, especially lot A compared to lot B.
2. Please note that only about 70% of the subjects from the Primary Total Vaccinated Cohort were included in testing lot-to-lot consistency. The main reasons for exclusions were: non-compliance with vaccination schedule, non-compliance with blood sampling schedule, and essential serological data missing.

3. In order to carry out, in the hierarchical manner, further evaluations of the subsequent study objectives, the applicant conducted additional post-hoc supplementary analyses to support lot-to-lot consistency of Hib-MenCY-TT vaccine and to justify pooling of the immunogenicity data from three lots. One of the applicant's post-hoc analyses included the pre-specified Cohort 1 as well as 181 subjects from Cohort 3 (Mexico) who qualified for the Primary ATP Cohort for Immunogenicity. Of the subjects from Mexico, 91 subjects were randomized to either Lot A or Lot B. Incorporation into analysis of these subjects "improved" one of the CI limits for GMTs and then the pre-specified criterion was met. The applicant concluded that "this observation suggests that inadequate sample size contributed to the finding in the primary analysis." However, the applicant's statement is not quite meaningful because the subjects of Hispanic origin had GMCs and GMTs higher than subjects from Cohort 1. The US and Mexico populations do not appear to be comparable with respect to immune system reactions to the MenHibrix vaccination.

Primary Objectives #2, 3, and 4 - Hypotheses related to the fourth dose vaccination

Primary Objective #2:

The non-inferiority immunogenicity hypothesis, objective #2, was to demonstrate that the post-fourth dose immune response to Hib polysaccharide (PRP) in the group that received 3 primary vaccine doses of Hib-MenCY-TT vaccine and the fourth dose of Hib-MenCY-TT vaccine co-administered with MMR2 and Varivax was 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 MMR2 and Varivax. The comparisons were based on the percentages of subjects with the anti-PRP concentrations ≥ 1.0 $\mu\text{g/mL}$. To support the non-inferiority hypotheses, the applicant should demonstrate that the lower limit of the two-sided 95% CI for the difference between Hib-MenCY and PedvaxHib groups of the percentages of subjects with the anti-PRP concentrations greater than or equal to 1.0 mcg/mL after the fourth dose vaccination was greater than or equal to -10%. A summary of the results is given in Table 3.1.2.4.

Table 3.1.2.4: Difference between study groups in anti-PRP concentration greater than or equal to 1.0 mcg/mL 42 days after the fourth dose vaccination (Fourth Dose According-To-Protocol Cohort for Immunogenicity, US population)

Antibody	Hib-MenCY (N=370)		PedvaxHib (N=132)		Estimated difference in rate (%)
	Estimated Endpoint (%)	95% CI	Estimated Endpoint (%)	95% CI	
anti-PRP	99.19	(97.64, 99.83)	99.24	95.85, 99.98)	-0.05 (-1.79, 1.69)

Source: Reviewer's analysis

It may be concluded from Table 3.1.2.4, that the statistical criterion for the primary co-immunogenicity hypothesis for objective #2 was met. However, please note that over 37% (502/ 816) of immunogenicity data was missing. Excessive missing data may introduce biases into the statistical results. Additionally, the original randomization scheme may not be preserved in the ATP US immunogenicity data.

Primary Objective #3

The immunogenicity objective #3 was to evaluate immunogenicity after the fourth dose of Hib-MenCY-TT vaccine in terms of immune response measured by hSBA-MenC and hSBA-MenY. The immune response was assessed by the percentages of subjects with hSBA-MenC and hBA-MenY titers greater or equal to 1:8. To support the immunogenicity MenC and MenY hypotheses, the applicant should demonstrate that the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA-MenC and hSBA-MenY titers $\geq 1:8$ is $\geq 90\%$. A summary of the pertinent statistical analyses are presented in Table 3.1.2.5.

Table 3.1.2.5: Percentage of subjects with hSBA-MenC and hSBA-MenY titers greater than or equal to 1:8 after the fourth dose vaccination (Fourth Dose According-To-Protocol Cohort for Immunogenicity)

Antibody	N	Estimated Endpoint (%)	95% CI	
			LL	UL
MenC	330	98.51	96.55	99.51
MenY	346	98.84	97.07	99.68

Source: Reviewer's analysis

It may be concluded from Table 3.1.2.5, that the criteria for the co-primary immunogenicity hypothesis for objective #3 were met. The lower limits of the 95% CIs for the percentages of subjects with hSBA-MenC and hSBA-MenY titers $\geq 1:8$ after the fourth dose were 96.55% and 97.07%, respectively, i.e., above the pre-specified LL of $\geq 90.0\%$. However, please note that over 35% of immunogenicity data was missing.

Primary Objective #4

Objective #4 was to evaluate, using the Fourth Dose ATP Cohort for Immunogenicity data, a “specific” effect of the fourth dose of Hib-MenCY-TT vaccine co-administered with MMRII and Varivax at 12 to 15 months of age, namely, geometric mean ratios of the individual post-fourth dose to pre-fourth dose hSBA titers (geometric mean fold rise). A summary of the statistical analyses performed on the Fourth Dose ATP Cohort for Immunogenicity is presented in Table 3.1.2.6.

Table 3.1.2.6: Geometric mean fold rise (GMFR) of hSBA titers (based on post-fourth dose to pre-fourth dose hSBA titers)

Antibody	GMT - pre-fourth dose		GMT post fourth dose		Estimated GMFR
	Estimated GMT	95% CI	Estimated GMT	95% CI	
MenC (N=288)	181.71	(155, 213)	2186.46	(1866, 2562)	12.03 (10.45, 13.85)
MenY (N= 300)	121.29	(102, 144)	1434.05	(1235, 1665)	11.82 (10.15, 13.77)

Source: Reviewer's analysis

It may be concluded from Table 3.1.2.6 that the criteria for co-primary immunogenicity hypothesis for objective #4 were met. For the Hib-MenCY group, the lower limits of the 95% CIs for the GMFR of hSBA titers (from pre-fourth dose to 42-day post-fourth dose) were 10.45 for hSBA-MenC and 10.15 for hSBA-MenY, i.e., above the pre-specified LL of ≥ 2 . However, please note that more than 30% of immunogenicity data was missing.

[REVIEWER'S COMMENT related to Objectives #3 and #4](#)

Study Hib-MenCY-TT-009/010 was carried out based on two different protocols: Hib-MenCY-TT-009 and 010. However, the final protocol for study Hib-MenCY-TT-009/010 was created and submitted on April 7th, 2009, i.e., after the end of the study (August 5th 2008). Hypotheses on which objectives #3 and #4 are based were added/defined at the time of the final protocol submission. These objectives are related to the immune response after the fourth dose of Hib-MenCY-TT vaccine co-administered with *MMRII* and *Varivax*. This means that data used for testing hypotheses #3 and #4 were really generated by study Hib-MenCY-TT-010. Because some subjects could be dropped out or excluded during the transition period from phase (study) 009 to phase (study) 010 and the data were un-blinded after the primary phase (study) 009, the applicant evaluated robustness of results of the primary endpoint analyses (related to the Fourth Dose Phase). In CSR 010, results of the LOCF (Last Observation Carried Forward) methods were discussed. The last observed value for a subject was imputed if a value for that subject for the fourth dose analysis was not available, i.e., when the subject either dropped out from the study between the primary and fourth dose vaccination phases or the subject participated in the fourth dose phase but did not have immunogenicity data available. If a subject was in the Primary ATP Cohort for Immunogenicity (Cohort 1) but did not participate in the fourth dose study (including subjects withdrawn during the ESFU of the primary study), then that subject was included in the Fourth Dose ATP Cohort for Immunogenicity for the LOCF analysis. If a subject did not have a post-fourth dose result but did have a pre-fourth dose result, then the pre-fourth dose result was imputed onto the fourth dose timepoint. If a subject did not have a pre- or post-fourth dose result but did have a post-dose 3 result, then the post-dose 3 result for that subject was imputed onto the post-fourth dose timepoint. The conclusions from testing hypotheses #3 and #4 on the Fourth Dose ATP Cohort for Immunogenicity with all subjects for whom the last observation carried forward (LOCF) strategy was used did not change the main results, i.e., the criteria were met.

Because pre-dose 4 and post dose 3 immunogenicity results tend to be lower than the post-dose 4 results, it appears that the above defined LOCF approach for the hSBA-MenC and hSBA-MenY post-dose 4 objectives constitutes the worst case scenario for robustness evaluation of the primary analyses results. Therefore, although the LOCF method of imputation is generally biased and discouraged by CBER, in this particular situation, it is likely acceptable for imputing values for the missing observations.

Additionally, the applicant showed that exclusion from analysis of subjects from the non-compliant center did not impact the results.

The potential influence of assay runs was evaluated by the applicant and the reviewer (using the revised definition of assay run introduced by the applicant). It is worth noting that the clinical study was not designed to specifically measure the effect of the assay run, and it is not possible to separate this effect from several other factors (such as, e.g., order of arrival of the sample, season, place of sample in the plate). Hence, the impact of the assay run was evaluated by checking whether the results obtained for primary and secondary endpoints using models including the assay run information were consistent with the ones that were already presented in the Clinical Study Reports and obtained by models not taking into account the assay run. It appears that, for the primary and secondary endpoints related to MenC and MenY, accounting for the assay run does not have a negative impact on the conclusions of the analyses.

Primary Objective #5 – Non-inferiority of Hib-MenCY-TT for the Primary Vaccination Phase

Objective #5 was to demonstrate non-inferiority of Hib-MenCY-TT vaccine as compared to ActHIB (each co-administered with Pediarix) following 3 primary vaccination doses. The comparison was to be performed in terms of immunogenicity to the PRP antigen component as measured by the percentage of subjects with anti-PRP concentration ≥ 1.0 $\mu\text{g/mL}$. A summary of results of the statistical analysis is given in Table 3.1.2.7.

Table 3.1.2.7: Difference between groups in percentage of subjects with anti-PRP equal to or above the cut-off value of 1.0 mcg/mL (Primary According-To-Protocol Cohort for Immunogenicity)

Antibody	Hib-MenCY Group (N=538)		ActHib Group (N=178)		Estimated difference in rate (%)
	Estimated Endpoint (%)	95% CI	Estimated Endpoint (%)	95% CI	
anti-PRP	96.47	(95, 98)	91.01	(86, 95)	5.46 (0.99, 9.94)

Source: Reviewer's analysis

Based on Table 3.1.2.7, the criterion related to the co-primary non-inferiority hypothesis for objective #5 was met. The pre-specified criterion was accomplished because the lower limit of the 95% CI for the between-groups difference in percentage of subjects

with anti-PRP concentration $\geq 1.0 \mu\text{g/mL}$ after the third dose was 0.99%, i.e., greater than the pre-specified LL $\geq -10\%$.

Primary Objectives #6 and #7– Additional Non-inferiority Hypotheses related to the Fourth Dose Vaccination Phase

Objective #6 was to demonstrate the non-inferiority of M-M-RII when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to M-M-RII co-administered with PedvaxHIB. Additionally, each subject was vaccinated with Varivax.

The pre-specified criterion for non-inferiority was that, 42 days after the fourth dose vaccination and for each induced by M-M-RII vaccine antibodies (measles, mumps and rubella), the corresponding LL of the 95% CI for the difference between groups (Hib-MenCY-TT minus PedvaxHIB groups) in the percentage of subjects with seroconversion (i.e., for instance, with measles antibody concentration $\geq 150 \text{ mIU/mL}$) in initially seronegative subjects (i.e., for instance, with measles antibody concentration $< 150 \text{ mIU/mL}$) should be $\geq -5.0\%$.

Objective #7 was to demonstrate non-inferiority of Varivax co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to Varivax co-administered with PedvaxHIB, each co-administered with MMRII. The comparison was to be performed in terms of immunogenicity to varicella as measured by the fluorescent antibody to membrane antigen method.

Testing of these hypotheses, according to the study protocol, was to be based on pooled immunogenicity data: subjects from Hib-MenCY-TT-008 (Hib-MenCY and Hib groups, 3 centers in Australia) and the subjects from the Fourth Dose ATP Cohort for Immunogenicity of study Hib-MenCY-TT-010. In the Annex Clinical Study Report for Study, the applicant presented analyses of poolability of these two datasets and the non-inferiority of MMRII and Varivax when co-administered with the fourth dose of Hib-MenCY-TT compared to MMRII and Varivax co-administered with a dose of PedvaxHIB in terms of anti-measles, anti-mumps, anti-rubella, and anti-varicella seroconversions 42 days after administration of the vaccines. The pre-specified criteria for pooling of the measles, mumps, rubella, and varicella co-vaccination data from study Hib-MenCY-TT-010 and study Hib-MenCY-TT-008 were as follows: the point estimate of the difference between the Hib and the Hib-MenCY group, in terms of anti-measles seroconversion, anti-mumps seroconversion, anti-rubella seroresponse, and anti-varicella seroconversion was to be above the pre-defined non-inferiority limits (-5% for anti-measles seroconversion, anti-mumps seroconversion, anti-rubella seroresponse and -10% for anti-varicella seroconversion). These analyses were performed within each of the individual studies. The analyses demonstrating poolability of data from studies Hib-MenCY-TT-010 and -008 are presented in Tables 3.1.2.9.A and B.

Table 3.1.2.9.A: Difference between the Hib-MenCY and Hib (PedvaxHib) groups in terms of percentage of subjects with antibody concentration or titer greater than or equal to the pre-specified value at 42 days post-fourth dose vaccination for only initially seronegative subjects (Fourth Dose According-To-Protocol Cohort for Immunogenicity Fourth Dose, study Hib-MenCY-TT-010)

								Estimation of Difference (Hib-MenCY minus Hib)	
		Hib-MenCY			Hib				
Antibody	Cut-off	N	n	%	N	n	%	%	95% CI
Anti-measles	150 mIU/ml	351	346	98.6	115	111	96.5	2.05	(-0.73, 7.27)
Anti-mumps	28 ED ₅₀	269	265	98.5	81	81	100	-1.49	(-3.76, 3.07)
Anti-rubella	10 IU/mL	350	350	100	114	113	99.1	0.88	(-0.22, 4.81)
Anti-varicella	1:5	319	319	100	104	104	100	0.00	(-1.19, 3.57)

Source: Table 8s on 32 in the applicant's CSR for Hib-Men-TT-009 study

Hib-MenCY = Hib-MenCY-TT + MMR2 + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHIB + MMR2 + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

Initially seronegative subjects: anti-measles concentration <150 mIU/mL, anti-mumps titer < 28 ED₅₀, anti-rubella concentration < 4 IU/mL and anti-varicella titer < 1:5.

Table 3.1.2.9.B: Difference between Hib-MenCY and Hib (PedvaxHib) groups in terms of percentage of subjects with antibody concentration or titer greater than or equal to the pre-specified value at 42 days post-fourth dose vaccination for only initially seronegative subjects (Booster According-To- Protocol Cohort for Immunogenicity, study Hib-MenCY-TT-008)

								Estimation of Difference (Hib-MenCY minus Hib)	
		Hib_MenCY			Hib				
Antibody	Cut-off	N	n	%	N	n	%	%	95% CI
Anti-measles	150 mIU/ml	501	469	93.6	171	163	95.3	-1.71	(-5.16, 2.92)
Anti-mumps	28 ED ₅₀	332	330	99.4	110	110	100	-0.60	(-2.17, 2.78)
Anti-rubella	10 IU/ml	500	498	99.6	171	171	100	-0.40	(-1.45, 1.8)
Anti-varicella	1:5	404	403	99.8	119	119	100	-0.25	(-1.39, 2.89)

Source: Table 4 on page 14 in the applicant's Annex Clinical Study Report for Study Hib-MenCY-TT-008 and 010

Hib-MenCY = Hib-MenCY-TT + MMR2 + Varivax primed with Hib-MenCY-TT + Infanrix penta + Prevnar

Hib = PedvaxHIB + MMR2 + Varivax primed with ActHIB + Infanrix penta + Prevnar

Initially seronegative subjects: anti-measles concentration <150 mIU/mL, anti-mumps titer < 28 ED₅₀, anti-rubella concentration < 4 IU/mL and anti-varicella titer < 1:5.

According to Tables 3.1.2.9.A and B, the applicant's pre-specified criteria for pooling measles, mumps, rubella, and varicella co-vaccination data from study Hib-MenCY-TT-010 and study Hib-MenCY-TT-008 were met.

Please note that, due to the definition of "seronegative subject," analyses for Hib-MenCY-TT-010 and -008 were based on datasets limited to subjects with the following initial pre-fourth dose antibody concentrations or titers: < 150 mIU/mL for measles,

< 28ED₅₀ for mumps, < 4IU/mL for rubella, < 1:5 for varicella. Approximately one-third of participants in both treatment groups in study Hib-MenCY-TT-010 had the pre-fourth vaccination anti-mumps titers > 28ED₅₀.

The results of testing the pre-specified non-inferiority hypotheses based on the pooled data from studies Hib-MenCY-TT-010 and Hib-MenCY-TT-008 are presented in Table 3.1.2.10.

Table 3.1.2.10: Summary of results of testing non-inferiority hypotheses based on data pooled from studies Hib-MenCY-TT-010 and Hib-MenCY-TT-008

Antibody	Threshold	Hib-MenCY						Estimation of Difference (%) (Hib-MenCY minus Hib)	
		N	n	%	N	n	%	%	95% CI
Anti-Measles	≥ 150 mIU/ML	852	815	95.7	286	274	95.8	-0.15	(-2.56, 3.06)
Anti-Mumps	≥ 28 ED ₅₀	536	532	99.3	176	176	100	-0.75	(-1.9, 1.40)
Anti-Rubella	≥ 10 IU/ML	850	848	99.8	285	284	99.6	0.12	(-0.57, 1.73)
Anti-Varicella	≥ 5 1/DIL	723	722	99.9	223	223	100	-0.14	(-0.78, 1.56)

Source: Table 6 on page 16 in the applicant's Annex Clinical Study Report for Study Hib-MenCY-TT-008 and 010

Hib-MenCY = Hib-MenCY-TT + MMR2 + Varivax primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHib + MMR2 + Varivax + primed with ActHIB + Pediarix + Prevnar

N = number of subjects with anti-measles concentration < 150 mIU/mL, anti-mumps titer < 28 ED₅₀, anti-rubella concentration < 4 IU/mL and anti-varicella titer < 1:5 before administration of the fourth dose

n/% = number/percentage of subjects with concentration or titer within the specified range

Initially seronegative subjects: anti-measles concentration < 150 mIU/mL, anti-mumps titer < 28 ED₅₀, anti-rubella concentration < 4 IU/mL and anti-varicella titer < 1:5.

REVIEWER'S COMMENTS:

As shown in Table 3.1.2.10, the criteria related to the co-primary non-inferiority hypotheses for objectives #6 and #7 were met because lower limits of the 95% CIs were higher than the pre-specified non-inferiority margins -5% for anti-measles concentrations, anti-mumps titers, and anti-rubella concentrations, and higher than the pre-specified non-inferiority margin -10% for anti-varicella titers.

Please note that the applicant only showed that responses to MMR2 and Varivax vaccines observed in studies 008 and 009/010 were deemed acceptable for pooling data for these analyses. However, it does not mean that datasets (study populations) from these two different studies carried out in different countries are poolable. (Study 008 was carried out in Australia while study Hib-MenCY-TT -009/010 was carried out in the USA, Australia, and Mexico.) Statistical similarity of these two datasets was not shown. For example, the applicant did not show how comparable (with respect to the immunogenicity responses to treatment vaccinations) datasets were after the primary vaccination phase.

Please refer to the clinical review for more information on the results related to the immunogenicity data evaluation from study Hib-MenCY-TT-009/010.

REVIEWER'S COMMENTS:

Due to concerns regarding the quality of the meningococcal serum bactericidal assays (SBA) used to assess the efficacy of the Group Y component of the vaccine, the statistical reviewer investigated the influence of the cutoff value on some statistical results.

Two primary objectives in this study utilized a titer cutoff of 1:8 in assessing the clinical endpoints. To investigate potential influence of the cutoff value on the results, these two objectives were re-evaluated by the reviewer using cutoff values 1:16 and 1:32.

The first case:

The study primary immunogenicity objective #3 was to evaluate immunogenicity after the fourth dose of Hib-MenCY-TT vaccine in terms of immune response measured by hSBA-MenC and hSBA-MenY titers. Immune response was assessed by the percentages of subjects with hSBA-MenC and hBA-MenY titers greater or equal to 1:8. The evaluation criterion was that the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA-MenC and hSBA-MenY titers $\geq 1:8$ should be $\geq 90\%$. Table 3.1.2.11 presents the reviewer's results for the estimations of endpoints and CI limits for three cutoff values.

Table 3.1.2.11: Percentage of subjects with hSBA-MenC and hSBA-MenY antibody titers greater than or equal to 1:8, 1:16, and 1:32 after the fourth dose vaccination (According-To-Protocol (ATP) fourth dose cohort for immunogenicity)

Antibody	N	$\geq 1:8$			$\geq 1:16$			$\geq 1:32$		
		n	Estimated Endpoint (%)	95% CI	n	Estimated Endpoint (%)	95% CI	n	Estimated Endpoint (%)	95% CI
MenC	335	330	98.5	(97, 99)	330	98.5	(97, 99)	327	97.6	(95, 99)
MenY	346	342	98.8	(97, 99)	342	98.8	(97, 99)	342	98.8	(97, 99)

Source: Reviewer's analysis

The second case:

One of the secondary objectives was to evaluate immunogenicity after the primary doses (3 doses) of Hib-MenCY-TT vaccine in terms of immune response measured by hSBA-MenC and hSBA-MenY titers. Immune response was assessed by the percentages of subjects with hSBA-MenC and hBA-MenY titers greater or equal to 1:8. The evaluation criteria were that the lower limits of the two-sided 95% CIs for the percentage of subjects with hSBA-MenC and hSBA-MenY titers $\geq 1:8$ should be $\geq 90\%$ and $\geq 85\%$, respectively. Table 3.1.2.12 presents the reviewer's results for the estimations of endpoints and CI limits for three cutoff values.

Table 3.1.2.12: Percentage of subjects with hSBA-MenC and hSBA-MenY antibody titers greater than or equal to 1:8, 1:16, and 1:32 after one month post-dose 3 (Primary ATP cohort for immunogenicity (Cohort 1))

Antibody	N	≥ 1:8			≥ 1:16			≥ 1:32		
		n	Estimated Endpoint (%)	95% CI	n	Estimated Endpoint (%)	95% CI	n	Estimated Endpoint (%)	95% CI
MenC	510	504	98.8	(97, 99)	503	98.6	(97, 99)	500	98.04	(96, 99)
MenY	500	480	96	(94, 98)	473	94.6	(92, 96)	446	89.2	(86, 92)

Source: Reviewer's analysis

It can be concluded from Tables 3.1.2.11 and 3.1.2.12 that changing cutoff values to 1:16 and 1:32 has very little influence on the results as compared to the cutoff value 1:8. Only a slight decline in percent responders is observed for the MenY component.

Immunogenicity Comments

- (1) Please note that
 - a. Post-dose 4 GMTs for hSBA-MenC and hSBA-MenY are rather high, 2040 and 1390, respectively.
 - b. For the fourth dose of Hib-MenCY-TT vaccine, a single lot (DMEHA024A which was not used in the primary stage of the study) was utilized
 - c. The three investigated lots (in the primary study) met the pre-defined criteria for establishing lot-to-lot consistency only for the PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C comparisons did not quite satisfy the lower equivalence margin of 0.5: the lower limits were 0.44 and 0.49, respectively.
- (2) The immunogenicity analyses were carried out on datasets with over 35% of the immunogenicity data missing

3.2 Summary of the Statistical Findings for Immunogenicity Data

The clinical database supporting licensure of the candidate vaccine Hib-MenCY-TT comprises data from 13 completed clinical studies. Information on the immune response to vaccination with this vaccine (primary course or fourth dose) and on response persistence was obtained in 11 (of the 13) studies. In these studies, in total 4,166 subjects received the licensure formulation of the vaccine according to the 2, 4, and 6 month schedule, and a total of 3,630 subjects received Hib-MenCY-TT according to a four-dose schedule.

Study **Hib-MenCY-TT-009/010** was the pivotal, Phase III study, investigating safety, immunogenicity, and lot-to-lot consistency, performed in support of the Hib-MenCY-TT

BLA. In total, 4441 subjects were enrolled and vaccinated in 91 study centers. However, all 261 subjects who were enrolled and vaccinated in US Center #24660 were eliminated from all analyses due to the GCP violations. Thus, 4180 subjects (3136 Hib-MenCY-TT subjects and 1044 Hib subjects) enrolled and vaccinated were eligible for inclusion in the Primary Total Vaccinated Cohort. For the immunogenicity analyses, the applicant reported that from 991 subjects in Cohort 1, who were eligible for inclusion in the Primary Total Vaccinated Cohort, 296 subjects (29.9%) were not eligible for inclusion in the Primary ATP Immunogenicity Cohort. The main reason for eliminations was lack of essential serological data (200 subjects did not have serological data).

The first co-primary objective was to demonstrate lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT vaccine (co-administered with Pediarix) in terms of immunogenicity with respect to the PRP, MenC, and MenY antigen components as measured by GMCs/GMTs of antibodies post dose 3. The three investigated lots met the pre-defined criteria to establish lot-to-lot consistency for the PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C comparisons narrowly missed the lower equivalence margin of 0.5: the lower limits were 0.44 and 0.49, respectively. Please note that about 70% of the subjects from the Primary Total Vaccinated Cohort were included in testing of the lot-to-lot consistency. The main reasons for exclusions were non-compliance with vaccination schedule, non-compliance with blood sampling schedule, and missing essential serological data.

There could be a few reasons why the hypotheses related to the lot-to-lot consistency were not fully met: for example, a small number of subjects included in these analyses, a manufacturing inconsistency, or variability between assay runs used for measuring titers. The statistical reviewer could not check the influence of assay runs on the statistical results because identification numbers of assay runs were not included in the SAS datasets.

Please note that the applicant assumed that, for both (the primary and the fourth dose) phases of the study, co-primary objectives should be assessed in a hierarchical manner according to the order presented in the protocol. This hierarchical structure means a co-primary objective could only be considered to be met if the statistical criteria for all previous co-primary objectives were met. In this study, the first co-primary hypotheses were not fully met.

Based on the immunogenicity data from study **Hib-MenCY-TT-005/006**, testing of the pre-defined hypotheses yielded the following results:

- The pre-specified criterion related to the non-inferiority of the Hib component response to Hib-MenCY-TT as compared to that of ActHIB at the post-dose 3 and post-dose 4 time-points was met.
- The pre-specified criterion related to the non-inferiority of the immune responses to the pertussis components of Pediarix when Pediarix was co-administered with Hib-MenCY-TT as compared to co-administration with ActHIB was met.
- The pre-specified criterion related to the non-inferiority of the immune responses to the seven pneumococcal polysaccharides contained within Prevnar when

Pprevnar was co-administered with Hib-MenCY-TT as compared when it was co-administered with ActHIB was met. (This result is especially important because, per agreement with CBER at the time that GSK had difficulties to source Pprevnar for all subjects in the phase III study, evaluation of the immunogenicity to co-administered Pprevnar was not repeated in the phase III study.)

Based on the immunogenicity data from study **Hib-MenCY-TT-007/008**, testing of the pre-defined hypotheses yielded the following results:

- The criterion related to the non-inferiority of the Hib component response to Hib-MenCY-TT as compared to that of ActHIB at the post-dose 3 was met.
- The criteria related to the non-inferiority of the immune responses to M-M-RII and Varivax when they were co-administered with Hib-MenCY-TT vaccine as compared when they were co-administered with PedvaxHIB were met but the analyses utilized a datasets received by pooling data from studies Hib-MenCY-TT-008 and Hib-MenCY-TT-010 (note: all pre-specified criteria for poolability were also met).

It is worth noting that there were notable differences between geometric mean titers (GMTs) for the MenY (after 3 and 4 doses) serogroup among studies MenCY-TT-005/006, Hib-MenCY-TT-007/008, and Hib-MenCY-TT-009/010. The hSBA-MenY GMTs after the third dose for studies MenCY-TT-005/006, Hib-MenCY-TT-007/008, and Hib-MenCY-TT-009/010 were 139.8, 86.4, and 236.6, respectively. After the fourth dose, the range of GMTs was from 246.6 to 1389.5. Potential causes of this disparity of results are unclear. The same issues were encountered, for MenC. Additionally, for study Hib-MenCY-TT-009/010, it is unknown why GMTs for MenC and Y were so high after the fourth dose of Hib-MenCY-TT.

Please refer to the clinical review for more information on the immunogenicity data evaluation across different studies included in this BLA submission.

In summary: Data included in this BLA submission appear to support the conclusion that the candidate vaccine Hib-MenCY-TT, given as the four dose regimen at ages 2, 4, 6, and 12-15 months of age induces a robust immune response that persist 1 year post-fourth dose vaccination. Immune memory to the three vaccine components is also induced. However, the conclusions are based on datasets with over 30% missing immunogenicity data.

3.3 Seroresponses to Hib-MenCY by Gender and Race

In response to CBER's request included in the CR letter, the applicant submitted an Efficacy Information Amendment that contains statistical analyses results showing the influence of the factors Race and Gender on the immune responses (GMTs/GMCs) after the 3rd and the 4th doses of Hib-MenCY-TT vaccine. In the Efficacy Information Amendment, the following statistical analysis results were included:

- Estimations of the percentages of subjects above thresholds and GMC/Ts for Anti-PRP, hSBA-MenC, and hSBA-MenY after dose 3 by

- gender (Table 11 and Table 12),
- race (Table 13 and Table 14)
- center (Table 15 and Table 16).
- Estimations of the percentages of subjects above thresholds and GMC/Ts for Anti-PRP, hSBA-MenC, and hSBA-MenY after dose 4 by
 - gender (Table 17 and Table 18)
 - race (Table 19 and Table 20)
 - center (Table 21 and Table 22).

The statistical analyses related to evaluation of the influence of the factors Race and Gender on the immune responses (GMTs/GMCs) after the 3rd and the 4th doses of Hib-MenCY-TT vaccine were post hoc in nature, and many of the subgroups consisted of rather small numbers of subjects (n <10 subjects). Therefore, differences, if any, observed between sub-groups may not be reliable. Based on the above mentioned tables, given in the Efficacy Information Amendment, there is no indication that factors Race and Gender have influence on the immune responses to Hib-MenCY-TT vaccine. When the sample sizes in the racial subgroups were small (e.g., Asia, Hawaii), results for such small subgroups were not taken into consideration.

4. Statistical Evaluation of Safety Data

4.1 Overview of safety data assessment

In the Summary of Clinical Safety, the applicant presented reports on eleven Phase II and Phase III clinical studies related to the Hib-MenCY-TT vaccine. Analyses of the safety data were performed on the Total Vaccinated Cohort (TVC), which was defined as all subjects to whom at least one dose of a study vaccine was administered. Study vaccines were: Hib-MenCY-TT vaccine (licensure formulation only), and monovalent Hib vaccine (ActHIB or PedvaxHIB).

The applicant stated that in the six primary phase studies (Hib-MenCY-TT-001, Hib-MenCY-TT-003, Hib-MenCY-TT-005, Hib-MenCY-TT-007, Hib-MenCY-TT-009 and Hib-MenCY-TT-011) 7521 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. In five studies (Hib-MenCY-TT-004, Hib-MenCY-TT-006, Hib-MenCY-TT-008, Hib-MenCY-TT-010 and Hib-MenCYTT-012) of the fourth dose phase, 7023 subjects received a dose of the Hib-MenCY-TT vaccine. Of these 7023 subjects, 6686 subjects received the fourth dose of the Hib-MenCY-TT vaccine at approximately 12 to 15 months of age. This means, the safety profile of four doses of Hib-MenCY-TT vaccine was evaluated only for 6686 infants/toddlers.

For safety assessment, based on pivotal studies Hib-MenCY-TT-009/010 and Hib-MenCY-TT-011/012, the applicant presented only descriptive analyses (sometimes adjusting for the factor “country”). Using descriptive statistics, the applicant asserted that there were no meaningful differences between HibMenCY-TT and Hib vaccines as

regards safety. The statistical analyses were performed for each study separately and then for the pooled data from different studies. Please note that studies appeared to be dissimilar with respect to populations (studies were conducted in Australia, Mexico, and the USA) and protocols. The demographic profiles with respect to mean age, gender, and racial distributions for both groups were comparable within each separate (particular) study but were not always comparable for different studies. The study protocols were also different, e.g., solicited AEs were not captured and diary cards were not used in studies Hib-MenCY-TT-011 and -012. But, solicited AEs were collected in the Hib-MenCY-TT-009 and -010. The exclusion criteria for study Hib-MenCY-TT-011 stated that subjects who had previously received a dose of Prevnar, i.e., subjects from Mexico, should be excluded from the enrollment. Such exclusion criterion was not applied in study Hib-MenCY-TT-009.

Differences in study design and study assessments make it difficult to determine whether the safety profiles for all 11 studies under review were comparable or not.

A detailed assessment of the vaccine safety was performed by the reviewer only for the pivotal safety studies.

4.2 Evaluation of Hib-MenCY-TT-009/010 safety data

The applicant performed statistical analyses initially on safety data for phases 009 and 010 separately and then on the combined data that covered the entire Hib-MenCY-TT-009/010 study.

The following safety endpoints were considered by the applicant:

- unsolicited symptoms reported within the 31-day follow-up period (Day 0 - Day 30) after any vaccination
- serious adverse events (SAEs), new onsets of chronic diseases (NOCD; e.g., onsets of autoimmune disorders, asthma, type I diabetes and allergies), rashes, and adverse events (AEs) resulting in Emergency Room (ER) visits from Day 0 (counting from administration of Dose 1) through six months after Dose 4
- SAEs, NOCD, rashes and AEs resulting in ER visits from Day 31 after Dose 3 until the day before Dose 4 and from Day 31 after Dose 4 through six months after Dose 4.

Safety datasets

For the Hib-MenCY-TT-009 phase, an analysis of safety was performed on the Primary Total Vaccinated Cohort. This cohort included all subjects from Cohort 1 (all US sites), Cohort 2 (sites in US, Mexico, and Australia) and Cohort 3 (the first 200 subjects enrolled at a single site in Mexico). In total, 4180 subjects were eligible for inclusion into this cohort. Out of these 4180 subjects, 3966 (94.8%) received all three doses of the three-dose study vaccination course, and 3136 and 1044 received at least one dose of Hib-MenCY-TT vaccine or ActHib vaccine, respectively.

The applicant reported that, in the pooled Hib-MenCY lot groups, compliance for reporting of reactogenicity for local injection site and for general symptoms after each of the three doses was 95.4% and 95.3%, respectively, and for both local and general symptoms in the ActHib group was 94.7%.

For Hib-MenCY-TT-010 phase, the analysis of safety was performed on the Fourth Dose Total Vaccinated Cohort. This cohort consisted of 3692 (88% of the Primary Total Vaccinated Cohort) subjects. The overall compliance for reactogenicity reporting was 91.4% for general symptoms and 91.3% for local symptoms in the Hib-MenCY group, and 90.2 % for general and local symptoms in the control PedvaxHib group.

The ATP Safety Cohorts for the primary and the fourth dose phases were defined and consisted of 4096 and 3293 subjects, respectively. However, ATP Safety Cohorts were not used for the main safety analyses.

Primary vaccination phase

Statistical analyses of safety data – non-inferiority hypotheses

One of the co-primary objectives was to demonstrate the non-inferiority of Hib-MenCY-TT vaccine as compared to ActHib (each co-administered with Pediarix) in terms of the percentages of subjects who experienced fever $> 39.5^{\circ}\text{C}$ within the 4-day follow-up period after any dose. In order to demonstrate non-inferiority, the lower limit of the 95% CI for the group difference of fever incidences should be $\geq -2.4\%$. Based on the applicant's results, Table 4.2.1 shows the statistical results for the group differences between the ActHib group and the Hib-MenCY group (pooled Hib-MenCY-TT lot groups) in terms of the percentage of subjects with fever $>39.5^{\circ}\text{C}$ ($>103.1^{\circ}\text{F}$) within the 4 days follow-up period (Day 0 to Day 3) after any vaccination.

Table 4.2.1: Percentages and differences between ActHib and Hib-MenCY groups in the incidence of fever greater than 39.5°C during the 4-day (Days 0-3) follow-up period (Primary Total Vaccinated Cohort)

Timing	Hib			Hib-MenCY			Estimation of Difference (%) Hib minus Hib-MenCY	
	N	n	%	N	n	%	%	95% CI
Dose 1	1008	4	0.4	3056	11	0.4	0.04	(-0.34, 0.67)
Dose 2	951	6	0.6	2900	15	0.5	0.11	(-0.37, 0.88)
Dose 3	905	6	0.7	2736	20	0.7	0.07	(-0.61, 0.74)
Overall/dose	2864	16	0.6	8692	46	0.5	0.03	(-0.25, 0.40)
Overall/subject	1015	16	1.6	3089	46	1.5	0.09	(-0.7, 1.12)

Source: Table 48 on I92 in the applicant's CSR for Hib-Men-TT-009 study

Hib-MenCY = Hib-MenCY-TT (Lot A, Lot B or Lot C) + Pediarix (+ Prevnar if available)

Hib = ActHIB + Pediarix (+ Prevnar if available)

N = Number of subjects with at least one documented dose, n/% = number/percentage of subjects reporting a symptom

It can be concluded from Table 4.2.1 that, regarding Fever, the differences between two groups were minute. The lower limit of the 95% CI for the group difference (Hib minus Hib-MenCY) of the percentages of subjects with fever (measured by any method) greater than 39.5°C during the 4 days post-vaccination period (overall per subject) was -0.70%. This lower limit of the 95% CI was greater than the pre-specified limit of -2.4%. This means, the safety criterion related to body temperature was met.

REVIEWER'S COMMENTS:

The dataset on which safety statistical analyses were performed was created by pooling datasets from three countries: US, Mexico, and Australia. These countries are different with respect to primary health care and demographic factors. Therefore, all safety statistical analyses should be adjusted for the factor "country." Additionally, for the Three- dose vaccination period, at least one concomitant medication was used by 72.1% and 75.2% of Hib-MenCY and ActHib recipients, respectively, during 4 days after each vaccination. Please note that the use of an antipyretic medication is correlated with occurrences of fever events. Therefore, the applicant's distributions of fever events by study group may not supply unbiased results.

A summary of the medication use during 4 days after any vaccination is presented in Table 4.2.2 (the applicant's Table 81, Clinical Study Report, page 283).

Table 4.2.2: Incidence of concomitant use of medication during 4 days after vaccination; stratified by study group

Concomitant Medication	Hib-MenCY				Hib			
	N	n	%	95% CI	N	n	%	95% CI
DOSE 1								
Any	3136	1720	54.8	(53.1, 56.6)	1044	614	58.8	(55.8, 61.8)
Any antibiotic	3136	55	1.8	(1.3, 3.3)	1044	25	2.4	(1.6, 3.5)
Any antipyretic	3136	1528	48.7	(47, 50.5)	1044	555	53.2	(50.1, 56.2)
Prophylactic antipyretic	3136	475	15.1	(13.9, 16.4)	1044	146	14.0	(11.9, 16.2)
DOSE 2								
Any	3021	1619	53.6	(51.8, 55.4)	998	554	55.5	(52.4, 58.6)
Any antibiotic	3021	91	3.0	(2.4, 3.7)	998	24	2.4	(1.5, 3.6)
Any antipyretic	3021	1390	46.0	(44.2, 47.8)	998	483	48.4	(45.3, 51.5)
Prophylactic antipyretic	3021	306	10.1	(9.1, 11.3)	998	100	10.0	(8.2, 12.1)
DOSE 3								
Any	2964	1379	46.5	(44.7, 48.3)	983	502	51.1	(47.9, 54.2)
Any antibiotic	2964	136	4.6	(3.9, 5.4)	983	48	4.9	(3.6, 6.4)
Any antipyretic	2964	1102	37.2	(35.4, 38.9)	983	399	40.6	(37.5, 43.7)
Prophylactic antipyretic	2964	266	9.0	(8, 10.1)	983	79	8.0	(6.4, 9.9)
OVERALL/Dose**								
Any	9121	4718	51.7	(50.7, 52.8)	3025	1670	55.2	(53.4, 57.0)
Any antibiotic	9121	282	3.1	(2.7, 3.5)	3025	97	3.2	(2.6, 3.9)
Any antipyretic	9121	4020	44.1	(43.1, 45.1)	3025	1437	47.5	(45.7, 49.3)
Prophylactic antipyretic	9121	1047	11.5	(10.8, 12.2)	3025	325	10.7	(9.7, 11.9)
OVERALL/Subject*								
Any	3136	2261	72.1	(70.5, 73.7)	1044	785	75.2	(72.5, 77.8)
Any antibiotic	3136	250	8.0	(7, 9)	1044	82	7.9	(6.3, 9.7)
Any antipyretic	3136	2045	65.2	(63.5, 66.9)	1044	719	68.9	(66, 71.7)
Prophylactic antipyretic	3136	666	21.2	(19.8, 22.7)	1044	216	20.7	(18.3, 23.3)

Source: Table 81 on 283 in the applicant's CSR for Hib-Men-TT-009 study

For each dose and overall/subject*: N= number of subjects with at least one administered dose n/= number/percentage of subjects who took the specified concomitant medication at least once during the mentioned period

For overall/dose:** N= number of administered doses; n/= number/percentage of doses after which the specified concomitant medication was taken by subjects at least once during the mentioned period

Table 4.2.2 demonstrates that the concomitant use of medication after vaccinations in both groups was comparable.

The distribution of any concomitant use of medication by country is shown in Table 4.2.3.

Table 4.2.3: Percentage of individuals with concomitant use of any medication during four days after vaccinations by country and treatment group

Country	Hib-MenCY	ActHib
US	82.80%	85.70%
Australia	75.10%	83.40%
Mexico	32.80%	32.50%

Source: Reviewer's analysis

Table 4.2.3 demonstrates that the rates of concomitant use of any medication were comparable in the U.S. and Australia, but much lower in Mexico. This was probably connected with the different levels of primary health care utilization.

In summary: The applicant's presentation of results for the safety non-inferiority hypothesis might not provide unbiased results because factors like "country" and "medication used" have influence on the occurrence of events, and they were not taken into account in the applicant's analysis.

Descriptive evaluation of adverse event occurrences

In the Clinical Report, the applicant presented rates of "at least one adverse event occurrence" (either solicited or unsolicited) during the 4 days follow-up after each dose. The reviewer's Table 4.2.4, which was prepared based on the applicant's analyses, presents a summary of the common solicited and unsolicited adverse events that occurred during the 4-day post-vaccination periods.

Table 4.2.4: Occurrence rates and nature of adverse event symptoms (solicited and unsolicited) during the 4-day (Days 0-3) follow-up period after each dose

Dose	Group	Any symptom (95% CI)	General symptoms (95% CI)	Local symptoms (95% CI)
Dose 1	Hib-MenCY (N=3136)	90.3% (89%, 91%)	84.1% (83%, 85%)	70.4% (69%, 72%)
	ActHib (N= 1044)	90.5% (89%, 92%)	86.6% (84%, 89%)	74.0% (71%, 77%)
Dose 2	Hib-MenCY (N=3021)	88.3% (87%, 89%)	81.8% (80%, 83%)	71.5% (70%, 73%)
	ActHib (N= 998)	88.7% (87%, 91%)	83.6% (81%, 86%)	73.7% (71%, 77%)
Dose 3	Hib-MenCY (N=2964)	81.1% (80%, 83%)	72.1% (71%, 74%)	66.3% (65%, 68%)
	ActHib (N= 983)	83.3% (81%, 86%)	73.8% (71%, 77%)	69.4% (66%, 72%)
Overall	Hib-MenCY (N=3136)	96.4% (95%, 97%)	94.3% (93%, 95%)	87.8% (87%, 89%)
	ActHib (N= 1044)	95.2% (94%, 96%)	93.8% (92%, 95%)	87.0% (85%, 89%)

Source: Reviewer's table based on Table 49 on 193 in the applicant's CSR for Hib-Men-TT-009 study

Table 4.2.4 demonstrates that, in overall, about 95.0% of subjects, in both treatment groups, reported adverse event symptoms during the 4 days follow-up after each dose.

Overall rates of reported symptoms in both (Hib-MenCY and ActHib) groups differed by 7% and were approximately 94% and 87%, for general (systemic) and local (injection site) symptoms, respectively. Rates of adverse events did not increase with subsequent doses of either vaccination regimen.

The observed incidence of any unsolicited adverse event occurring within the 31-day (Days 0-30) post-vaccination period over the three-dose vaccination course was 58.0% in the Hib-MenCY pooled group and 57.7% in the Hib group. The most frequently reported unsolicited symptom in both vaccination groups was an upper respiratory tract infection, which was reported in 16.7% of Hib-MenCY recipients and in 16.6% of Hib recipients. Other unsolicited symptoms reported in more than 5% of subjects in both vaccination groups were: otitis media, vomiting, diarrhea, pyrexia, and cough. The percentages of subjects who experienced at least one of these unsolicited adverse events were similar in both vaccination groups.

Adverse events for extended follow-up period

Cases of observed SAEs, new onsets of chronic diseases (e.g., type I diabetes, allergies, asthma, and autoimmune disorders – NOCD), rashes (hives, idiopathic thrombocytopenic purpura, and petechiae), and conditions prompting ER visits or physician office visits were reported during the entire phase period that began on Day 0/Dose 1 and ended at Month 6 following the last primary dose or until administration of the fourth dose, whichever came first. At each contact during the 3-dose vaccination course and during the initiation visit of the booster phase at Month 10-13 or via telephone prior to the booster visit (6 months following Dose 3), parents/guardians were questioned specifically about occurrences of any events that may have taken place since the last study contact. A summary of the registered events is given in Table 4.2.5.

Table 4.2.5: Summary of selected adverse events from Day 0 after Dose 1 until Month 6 following Dose 3 or until administration of Dose 4, whichever came first (Primary Total Vaccinated Cohort)

Adverse Event	Hib-MenCY		ActHib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3136		N=1044	
At least one symptom	1552	0.495	515	0.493
SAE	126	0.040	50	0.048
New onset chronic disease	163	0.052	52	0.050
Rash	470	0.150	154	0.148
Emergency room visit	217	0.069	72	0.069
Physician office visit	1336	0.426	433	0.415

Source: Reviewer's table based on Table 60 on 224 in the applicant's CSR for Hib-Men-TT-009 study

Table 4.2.5 demonstrates that the rates of observed different SAEs were comparable in both groups.

REVIEWER'S COMMENTS:

In the Hib-MenCY-TT-009 phase, the overall incidence rates of SAEs, NOCD, rash, and AEs resulting in ER visits were similar in the Hib-MenCY and ActHib groups, regardless of the observation period considered. However, the safety descriptive analyses were done at the patient level without taking into account the structure of the datasets (e.g., longitudinal data, drop out over time, and populations from different countries).

A total of 261 serious adverse events were reported for 172 subjects during the course of the study with a fatal outcome in four cases (2 in US and 2 in Mexico; one case was baby shaken syndrome and one SIDS). Two serious adverse events were determined by the investigator to be vaccine related (a 7-week old female was hospitalized due to an axillary/oral temperature of 39.4°C; a 6-week old male was hospitalized due to a rectal temperature of 39.6°C).

Most adverse events were hospitalizations for infectious type events and nearly all had resolved with the exception of cases of tuberous sclerosis and infantile spasms (one subject), HIV infection (one subject), and complex febrile convulsion (one subject in the Hib group), that happened in the US, and a case of haemangioma (left eye) in one subject in Australia.

In 11 subjects, adverse events led to premature discontinuation/withdrawal from the study: seven withdrawals due to serious adverse events (all Hib-MenCY recipients) and four withdrawals due to non-serious adverse events (three Hib-MenCY recipients and one Hib recipient).

The Fourth Dose Phase

Statistical analyses of safety data – non-inferiority hypotheses

One of the co-secondary objectives was to demonstrate non-inferiority of Hib-MenCY-TT vaccine in terms of the incidence of fever $> 39.5^{\circ}\text{C}/103.1^{\circ}\text{C}$ within the 4-day follow-up period after administration of the fourth dose of Hib-MenCY-TT as compared to *PedvaxHIB*, each co-administered with *MMRII* and *Varivax*. The pre-specified statistical criterion for non-inferiority was that the LL of the 95% CI for the group difference (Hib group minus Hib-MenCY group) should be $\geq -1.6\%$. Table 4.2.6 presents the results of testing this non-inferiority hypothesis (the applicant's Table 54, Clinical Report, page 223).

Table 4.2.6: Difference between the Hib and Hib-MenCY groups in percentage of subjects reporting fever greater than 39.5°C during the 4-day post-vaccination period

Adverse Event	Hib			Hib-MenCY			Difference
	N	n	%	N	n	%	% (95%CI)
Temperature >39.5	831	5	0.6	2527	18	0.7	-0.11 (-0.66, 0.72)

Source: Table 54 on 224 in the applicant's CSR for Hib-Men-TT-010 study

Hib-MenCY = Hib-MenCY-TT + MMRII + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHIB + MMRII + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

It may be concluded from Table 4.2.6 that the statistical criterion for the non-inferiority safety hypothesis corresponding to the endpoint “temperature” was met.

REVIEWER’S COMMENTS:

The dataset, on which testing the hypothesis regarding temperature was performed, was created by pooling data from three countries. Countries under consideration, especially US and Mexico, are different with respect to primary health care and demographic factors. Therefore, all safety statistical analyses should be adjusted for the factor “country.” Additionally, at least one concomitant medication was used by 38% and 43% of Hib-MenCY and PedvaxHib recipients, respectively, during 4 days after the fourth dose vaccination. Please note that the use of antipyretic medication is correlated with occurrences of fever events. Therefore, the applicant’s distributions of fever events by study group may not provide unbiased results.

Please note that the non-inferiority analyses were performed on a subset of the Fourth dose Total Vaccinated Cohort that consisted of 3358 subjects, i.e., 80% of the Primary Total Vaccinated Cohort. Many (20%) randomized subjects from the original Hib-MenCY-TT study were not included in this analysis. Because of the large amount of subjects excluded in this study, it is unlikely that the randomization scheme was preserved in the analyzed datasets. That is, it is unknown whether subjects who were excluded were different from subjects who were analyzed, potentially yielding groups that were no longer comparable with respect to known and unknown prognostic factors. This situation could introduce biases into the study results.

General information on solicited or unsolicited adverse events during 4 days follow-up

Per the applicant’s tables provided within the submission (Clinical Report –Hib-MenCY-TT-010, pages 224-225), at least one adverse event (solicited or unsolicited) was reported within the 4-day post-vaccination follow-up period (Days 0-3 post-vaccination) for 79.5% and 83% of subjects in the Hib-MenCY and PedvaxHib groups, respectively. At least one grade 3 adverse event (solicited or unsolicited) was reported in 9.1% and 12.9% of subjects in the Hib-MenCY and PedvaxHib groups, respectively. Grade 3 local (injection site) symptoms were reported in 5.3% of subjects in the Hib-MenCY group and in 9.5% of subjects in the PedvaxHib group. Grade 3 general (systemic) symptoms rates

were comparable between both groups, ranging from 4.8% (Hib-MenCY group) to 5.5% (PedvaxHib group).

Adverse events for extended follow-up period

Cases of observed SAEs, new onsets of chronic disease (NOCD; e.g. onsets of type I diabetes, allergies, asthma, and autoimmune disorders), rash (e.g., hives, idiopathic thrombocytopenic purpura and petechiae), ER visits and uncommon illnesses causing physician office visits occurring between the fourth dose vaccination and the end of the extended safety follow-up (6 months post-vaccination) are summarized in Table 4.2.7.

Table 4.2.7: Summary of selected adverse events during 6 months of follow-up after the fourth dose vaccination (Fourth Dose Total Vaccinated Cohort)

Adverse Event	Hib-MenCY		PedvaxHib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=2769		N=923	
At least one symptom	860	0.311	274	0.297
SAE	47	0.017	18	0.02
New onset chronic disease	85	0.031	33	0.036
Rash	265	0.096	94	0.102
Emergency room visit	137	0.049	54	0.059
Physician office visit	668	0.241	205	0.222

Source: Table 62 on 250 in the applicant's CSR for Hib-Men-TT-010 study

Hib-MenCY = Hib-MenCY-TT + MMRII + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

PedvaxHib = PedvaxHIB + MMRII + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

At least one symptom = at least one symptom experienced

N = number of subjects with the administered dose

Table 4.2.7 indicates that there was no difference between the Hib-MenCY and PedvaxHib groups in the overall incidence rate of adverse events during 6 months of follow-up after the fourth dose vaccination.

Serious adverse events

During the 6 months follow-up after the fourth dose, 84 serious adverse events were reported for 65 subjects (47 subjects in the Hib-MenCY group and 18 subjects in the PedvaxHib group). One death unrelated to vaccination was reported in the Hib-MenCY group. A toddler 13 months old died due to multiple injuries sustained in a motor vehicle accident. Among the other 83 serious adverse events reported in 65 subjects, one event (idiopathic thrombocytopenic purpura) was considered related to vaccination. The onset of this event was 14 days after the fourth dose vaccination. The event required hospitalization (and thus was reported as a SAE), was rated as intensity grade 3, and was resolved 53 days later.

The observed incidence rates of serious adverse events during 6 months follow-up after the fourth dose were similar in both treatment groups (1.7% in the Hib-MenCY group and 2.0% in the PedvaxHib group).

Withdrawals due to adverse events/serious adverse events

Premature discontinuation/withdrawal from the study was reported for 1 subject (a 13-month old female 29 days after the fourth dose vaccination) in the Hib-MenCY group. It was due to the death of the subject caused by a severe trauma suffered in a motor vehicle accident.

4.3 Evaluation of Hib-MenCY-TT-011/012 safety data

Title of the study: “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”

Note: This study consisted of two phases: the primary vaccination phase (105987, Hib-MenCY-TT-011) and the booster phase (105988, Hib-MenCY-TT-012 BST:011).

Study Period for Hib-MenCY-TT-011: Initiation: September 15, 2006

Completion: March 28, 2008

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

Completion: November 12, 2008

Study Hib-MenCY-TT-011

General Information

Study Hib-MenCY-TT-011 was a Phase III, single-blind, randomized (3:1), controlled, multinational study conducted in Mexico and the US. The study evaluated safety of the Hib-MenCY-TT vaccine as compared to ActHib, both co-administered with Pediarix and Prevnar (if available), in healthy infants at 2, 4, and 6 months of age. Administration of RotaTeq, Synagis, and licensed influenza vaccine was permitted during the study based on a given country's recommendations. Safety follow-up was conducted from Day 0 after Dose 1 until the day preceding administration of Dose 4.

The study had 2 active phases and 2 extended follow-up phases. The active phases were: the primary vaccination phase from Day 0 through 1 month after the 3rd vaccination and the 4th dose vaccination phase from administration of the 4th dose to Day 31 post-

vaccination. The extended follow-up phases were: the extended safety follow-up (ESFU) phase for the primary vaccination from the end of the active primary vaccination phase (one month post-dose 3) to the 4th dose and the 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.

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

Objective

The primary objective was to evaluate the safety profile of Hib-MenCY-TT vaccine as compared to ActHib, with respect to the occurrences of SAEs, NOCD (New Onset Chronic Disease), rash, and AEs resulting in ER visits that took place in two time periods, namely, from Day 0 after Dose 1 until Day 30 after Dose 3 and from Day 0 after Dose 1 until the day preceding administration of Dose 4.

Results

The Total Vaccination Cohort encompassed 4,391 subjects (3,278 in the Hib-MenCY group and 1,113 in the Hib group). The mean age at the time of the first vaccination was 58.7 days (ranging from 42 to 96 days). Main results of the Hib-MenCY-TT-011 study are presented in two tables. Table 4.3.1 presents percentages of subjects reporting SAEs, NOCD, rash and AEs resulting in ER visits from Day 0 (counting from administration of Dose 1) through Day 30 after Dose 3, while Table 4.3.2 shows percentages of subjects reporting SAEs, NOCD, rash, and AEs resulting in ER visits from Day 0 after Dose 1 through the day preceding Dose 4.

Table 4.3.1: Summary of selected adverse events from Day 0 after Dose 1 through Day 30 after Dose 3 (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011))

Adverse Event	Hib-MenCY		Hib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3278		N=1113	
At least one symptom	422	0.129	149	0.134
SAE	109	0.033	33	0.031
NOCD	50	0.015	18	0.016
Rash	243	0.074	81	0.058
AE resulting in ER visit	114	0.035	44	0.04

Source: Supplement 33 on 165 in the applicant's CSR for Hib-Men-TT-011 study

Table 4.3.2: Summary of selected adverse events from Day 0 after Dose 1 through the day preceding Dose 4 (Total Vaccination Cohort)

ADVERSE EVENT	Hib-MenCY		Hib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3278		N=1113	
At least one symptom	654	0.200	232	0.208
SAE	157	0.048	48	0.043
NOCD	66	0.016	25	0.022
Rash	386	0.107	134	0.120
AE resulting in ER visit	198	0.060	69	0.062

Source: Table 19 on 79 in the applicant's CSR for Hib-Men-TT-011 study

Hib-MenCY = Hib-MenCY + Pediarix (+ Pevnar if available)

Hib = ActHIB + Pediarix (+ Pevnar if available)

REVIEWER'S COMMENTS:

As can be concluded from Tables 4.3.1 and 4.3.2, in study Hib-MenCY-TT-011, the overall incidence rates of SAEs, NOCD, rash, and AEs resulting in ER visits were similar for both Hib-MenCY and ActHib groups and for both observation periods. However, the safety descriptive analyses were performed at the patient level without taking into account the structure (longitudinal data, drop out over time, and populations from different countries) of the datasets.

It appears that the results of safety descriptive analyses for study Hib-MenCY-TT009 data are not consistent with results for study Hib-MenCY-011, because subjects from study Hib-MenCY-011 experienced considerably fewer adverse events than subjects from study Hib-MenCY-009.

Please note that there were twelve deaths [seven deaths in the Hib-MenCY group (including three deaths due to Sudden Infant Death Syndrome (SIDS)) and five deaths in the Hib group (including 2 cases of SIDS)) reported in study Hib-MenCY-TT-011 from Day 0 after Dose 1 through the day preceding Dose 4. The applicant claimed that all fatal events were assessed by the investigators as not related to vaccination. Please note that the probability of death (and SIDS) occurrence in study Hib-MenCY-TT011 was higher than in phase Hib-MenCY-009, which had a similar number of subjects enrolled (approximately 4000).

Study Hib-MenCY-TT-012

General Information

Study Hib-MenCY-TT-012 was a Phase III, single-blind, controlled, multinational study conducted in Mexico and the US. The study evaluated safety of the fourth dose of Hib-MenCY-TT vaccine as compared to PedvaxHib, both co-administered with MM-

RII, Varivax, and Prevnar, when given at 12 to 15 months of age to healthy toddlers who were primed in study Hib-MenCY-TT-011. Administration of a licensed influenza vaccine and/or hepatitis A vaccine was permitted based on a given country's recommendations.

Safety follow-up was conducted from Day 0 until 6 months after Dose 4.

Objective

One of the objectives of the study was to evaluate the safety profile of Hib-MenCY-TT vaccine as compared to PedvaxHib with respect to the occurrences of SAEs, NOCD, rash, and AEs resulting in ER visits in two time periods, namely, within the 31-day (Days 0-30) post-vaccination period after Dose 4, and from Day 0 until 6 months after Dose 4.

Results

The Total Vaccination Cohort encompassed 4,020 subjects (3,010 subjects in the Hib-MenCY group and 1,010 subjects in the Hib group). The mean age at the time of vaccination was 12.1 months (ranging from 11 to 17 months).

The percentages of subjects who reported SAEs, NOCD, rash, and AEs resulting in ER visits in study Hib-MenCY-TT-012 within the 31-day (Days 0-30) post-vaccination period after Dose 4 and within 6 months follow-up after Dose 4 are presented in Table 4.3.3 and Table 4.3.4, respectively.

Table 4.3.3: Summary of selected adverse events reported within the 31-day (Days 0-30) post-vaccination period after Dose 4 by treatment group

ADVERSE EVENT	Hib-MenCY		Hib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3010		N=1010	
At least one symptom	164	0.054	59	0.058
SAE	12	0.004	1	0.001
NOCD	12	0.004	6	0.006
Rash	123	0.041	41	0.041
AE resulting in ER visit	29	0.010	16	0.016

Source: Supplement 42 on 195 in the applicant's CSR for Hib-Men-TT-011 study

Table 4.3.4: Summary of selected adverse events reported during the 6 months follow-up after the fourth dose (Fourth Dose Total Vaccinated Cohort)

ADVERSE EVENT	Hib-MenCY		Hib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3010		N=1010	
At least one symptom	395	0.131	137	0.136
SAE	72	0.024	18	0.018
NOCD	50	0.017	18	0.018
Rash	227	0.075	82	0.081
AE resulting in ER visit	129	0.043	48	0.048

Source: Table 23 on 104 in the applicant's CSR for Hib-Men-TT-012 study

Hib-MenCY = Hib-MenCY-TT + MMRII + Varivax (+ Prevnar) primed with Hib-MenCY-TT + Pediarix (+ Prevnar)

Hib = PedvaxHIB + MMRII + Varivax (+ Prevnar) primed with ActHIB + Pediarix (+ Prevnar)

REVIEWER'S COMMENTS:

As can be concluded from Tables 4.3.3 and 4.3.4, the percentages of subjects who experienced SAEs, NOCD, rash, and AEs resulting in ER visits in the periods 31 days after the 4th dose (Days 0-30) and 6 months after Dose 4 were almost similar in the Hib-MenCY and the Hib groups. However, a slight statistical imbalance can be noticed (Table 4.3.3) for the overall rate of SAEs reported during the 31-day follow-up period (0.4% in Hib-MenCY vs. 0.1% in Hib, $p=0.0499$). One subject (number 6927 in the Hib-MenCY group), reported two SAEs that were assessed by the PI as vaccine-related (pyrexia on Day 0 and neutropenia on Day 3). Both events resolved after 5 days and were mild to moderate in intensity. No deaths were reported during the Hib-MenCY-TT-012 study.

Please note that the distribution of adverse events per country was different: the observed rates of reported adverse events in the US were much higher than in Mexico (see Table 4.3.5). This difference in reported AEs may have been connected with the different levels of primary health care utilization in the US and Mexico.

Table 4.3.5: Percentages of subjects with selected adverse events during 6 months of follow-up after the booster dose, for US and Mexico subjects (Booster Total Vaccinated cohort, Hib-MenCYTT-012 BST:011)

United States	HibMenCY (N = 864)				Hib (N = 304)			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one AE	264	31	27.9	34.2	94	30.9	25.8	36.4
SAE	23	2.7	1.7	4	4	1.3	0.4	3.3
NOCD	50	5.8	4.3	7.6	18	5.9	3.5	9.2
Rash	153	17.7	15.2	20.4	55	18.1	13.9	22.9
ER visit	116	13.4	11.2	15.9	45	14.8	11	19.3

Mexico	HibMenCY (N = 2146)				Hib (N = 706)			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one AE	127	5.9	5	7	43	6.1	4.4	8.1
SAE	49	2.3	1.7	3	14	2	1.1	3.3
NOCD	0	0	0	0.2	0	0	0	0.5
Rash	74	3.4	2.7	4.3	27	3.8	2.5	5.5
ER visit	13	0.6	0.3	1	3	0.4	0.1	1.2

Source: Tables in the applicant's CSR for Hib-Men-TT-012 study, page 193

As can be seen in Table 4.3.5, the reported rates of AEs differed considerably between the US and Mexico. Therefore, the percentages of subjects with NOCD, rash, and AEs resulting in ER visits during 6 months of follow-up after the booster shown in Table 4.3.4 may supply misleading information because there are noticeable differences between different countries, e.g., the US and Mexico.

4.4 Evaluation of the pooled safety data from Hib-MenCY-TT-009/10 and Hib-MenCY-TT-011/012

The Hib-MenCY-TT-011/12 multinational study was carried out as an “extension” of study Hib-MenCY-TT 009/010, with the goal to evaluate frequency of occurring of serious adverse events and medically significant adverse events such as emergency room visits, rash (e.g. idiopathic thrombocytopenia purpura, petechiae), new onsets of chronic diseases (NOCD) (e.g., autoimmune disorders, asthma, type I diabetes), and allergic reactions. The applicant pooled datasets for subjects from Hib-MenCY-TT-009/10 and Hib-MenCY-TT-011/12 and:

1. Evaluated occurrences of SAEs, NOCD, rash, and emergency room (ER) visits following Hib-MenCY-TT vaccine, as compared to a monovalent Hib vaccine (PedvaxHIB or ActHIB), for the following time-intervals: Day 0 to one month after post-dose 3 and Day 0 to pre-dose 4.

2. Evaluated occurrences of SAEs and medically significant adverse events following Hib-MenCY-TT vaccine, as compared to a monovalent Hib vaccine (PedvaxHIB or ActHIB), within 30 days and within 6 months after the 4th dose.

The inclusion and exclusion criteria for the Hib-MenCY-TT-011/012 study were the same as for the Hib-MenCY-TT-009/010 study. The study designs, study vaccines, timing of vaccination, concomitant vaccines, and study populations were similar for studies Hib-MenCY-TT-011 and -009. The applicant performed an acceptability test for the poolability of both data using the Breslow and Day test.

The pooled population from studies Hib-MenCY-TT-011 and -009 that was used for safety statistical analysis included 8,571 subjects (6,414 subjects in the Hib-MenCY group and 2,157 subjects in the Hib group). The mean age at the time of the first vaccination was 61.1 days (range: from 37 to 116 days).

A comparison of percentages of subjects for whom SAEs, NOCD, rash, and AEs resulting in ER visits from Day 0 (baseline) through Day 30 after Dose 3 and from Day 0 after Dose 1 through the day preceding administration of Dose 4 (Extended Safety Follow-up) that were reported in the pooled studies Hib-MenCY-TT-011 and -009 is presented in Table 4.4.1.

Table 4.4.1: Summary of percentages of subjects experiencing selected adverse events by study groups based on pooled data from studies Hib-MenCY-TT-011 and -009 (Primary Total Vaccinated Cohort, Studies Hib-MenCYTT-009 and -011)

AE category	Time period	HibMenCY N = 6414			Hib N = 2157			Relative Risk (HibMenCY/Hib)	
		n	%	95% CI	N	%	95% CI	RR	95% CI
at least one AE	0 - 30	975	15.2	(14.3, 16.1)	334	15.5	(14, 17.01)	0.98	(0.9, 1.08)
	0 - ESFU	1409	22	(21, 23)	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, 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	(0.83, 1.21)
Rash	0 - 30	621	9.7	(9, 10.4)	209	9.7	(8.5, 11)	1	(0.89, 1.12)
	0 - ESFU	856	13.3	(12.5, 14.2)	288	13.4	(11.9, 14.9)	1	(0.91, 1.1)
ER visit	0 - 30	259	4	(3.6, 5.2)	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	(0.87, 1.14)

Source: Reviewer's table based on tables (e.g., page 99) in the applicant's CSR for Hib-Men-TT-011 study

Based on Table 4.4.1 for the pooled studies Hib-MenCY-TT-009 and -011, no statistical imbalances were detected between the Hib-MenCY group and the Hib group in terms of the percentages of overall incidence of SAEs, NOCD, rash, and AEs resulting in ER visits reported from baseline after Dose 1 through Day 30 after Dose 3 or up to the day preceding administration of Dose 4.

There were 16 deaths (10 in the Hib-MenCY group and 6 in the Hib group) reported in the pooled studies Hib-MenCY-TT-009 and -011 from Day 0 after Dose 1 through the day preceding Dose 4. All fatal events were assessed by the study investigators as not related to vaccination.

It is worth noting that in the statistical analyses, most of the time, the applicant did not take into account missing data and influence on the results of some covariates such as “country” that may reduce the magnitude of possible biases and improve the precision of the results.

Pooled datasets from studies Hib-MenCY-TT-012 and -010 used in safety analyses included 7,712 subjects (5,779 subjects in the Hib-MenCY group and 1,933 subjects in the Hib group). The mean age at the time of Dose 4 was 12.1 months (range: from 11 to 17 months).

The percentages of subjects who experienced SAEs, NOCD, rash, or AEs resulting in ER visits in the pooled studies Hib-MenCY-TT-012 and -010 within the 31-day (Days 0-30) post-vaccination period after Dose 4 and from Day 0 after Dose 4 through the end of the study are presented in Table 4.4.2.

Table 4.4.2: Summary of percentages of subjects experiencing selected adverse events based on pooled data from studies Hib-MenCY-TT-012 and -010

AE category	Time period	Hib-MenCY N = 5779			Hib N = 1933			Relative Risk (HibMenCY/Hib)	
		n	%	95% CI	N	%	95% CI	RR	95% CI
≥ 1 AE	0 – 30	419	7.3	(6.6, 7.9)	146	7.6	(6.4, 8.8)	0.96	(0.84, 1.1)
	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, 1.6)	1.11	(0.85, 1.46)
NOCD	0 – 30	44	0.8	(0.6, 1)	17	0.9	(0.5, 1.4)	0.87	(0.58, 1.33)
	0 – ESFU	135	2.3	(2, 2.8)	51	2.6	(2, 3.5)	0.89	(0.71, 1.13)
Rash	0 – 30	309	5.3	(4.8, 6)	98	5.1	(4.1, 6.1)	1.05	(0.9, 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	(1.4, 2.7)	0.68	(0.51, 0.91)
	0 – ESFU	266	4.6	(4.1, 5.2)	102	5.3	(4.3, 6.4)	0.88	(0.75, 1.04)

Source: Reviewer’s table based on tables (e.g., page 126) in the applicant’s CSR for Hib-Men-TT-012 study

It can be concluded from Table 4.4.2 that, for the pooled studies Hib-MenCY-TT-010 and -012, there were overall small differences between Hib-MenCY and Hib groups but there were noticeable differences in percentages of incidences of SAEs, NOCD, rash, and AEs resulting in ER visits between periods 31- days (Days 0-30) post-vaccination after Dose 4 and within 6 months after the 4th dose.

There was one death reported in the pooled studies Hib-MenCY-TT-010 and -012 after the 4th dose. The event was assessed by the study investigator as not related to the vaccination.

REVIEWER'S COMMENTS:

The applicant submitted large safety datasets. Most of the time, the applicant presented summaries of adverse event occurrences stratified by some factors such as Dose, Country, or period of follow-up per subject. However, for study Hib-MenCY-TT-009, the applicant presented statistical analysis results based on a longitudinal statistical analysis approach. It appears that for the endpoint Fever, factors like Dose and Country may reduce the magnitude of possible biases and improve the treatment effect estimation.

4.5 Integrated summary of safety (ISS) analysis

The applicant performed an integrated summary of safety (ISS) analysis across the 3-dose and the 4th dose studies for Hib-MenCY-TT vaccine. A total of 9,148 subjects have received at least one dose of the licensure formulation of Hib-MenCY-TT vaccine (7,858 subjects during the Hib-MenCY-TT vaccine clinical development and approximately 1,290 subjects in the ongoing study MenACWYTT- 057).

The overall profile of solicited local and general symptoms reported within the 4-days post-vaccination period over the 4-dose schedule appears to be acceptable. All statistical imbalances detected in incidences of solicited local and general symptoms were attributable to lower frequency of the events in the Hib-MenCY group as compared to the Hib control group. The percentage of subjects reporting injection site reactions and irritability were lower in the Hib-MenCY group as compared to the Hib group, while the rates of other solicited symptoms were similar for the Hib-MenCY and Hib groups.

The rates of SAEs reported within the 31-days post-vaccination period and for events reported during the entire course of studies were similar between the Hib-MenCY group and the Hib control group over the 4-dose schedule. The rates of subjects' withdrawal from study participation due to AEs or SAEs were similar between groups. The rates of unsolicited AEs within the 31-days post-vaccination period and specific categories of AEs (NOCD, rash, and AEs resulting in ER visits) during the 6-month ESFU period were similar between the Hib-MenCY group and the licensed Hib control group.

A detailed evaluation of the applicant's meta-analysis of safety data is included in Dr. Patricia J. Rohan's review. Please also refer to her review for more information on the ISS document.

4.6 Subgroup safety analysis

Because the study subjects were infants and toddlers, there is no need for subgroup analysis by age. Subgroup safety analyses by Dose, Lot, and Country for various safety endpoints were provided in the respective subsections of this review or in the applicant's CSR.

5. Summary and Conclusions

5.1 Summary of Statistical Results

The objective of this applicant's submission is to provide evidence of immunogenicity and safety of Hib-MenCY-TT vaccine administered at 2, 4, and 6 months of age (3 primary doses) and at 12 to 15 months of age (the fourth dose), for the prevention of invasive diseases caused by *Neisseria meningitidis* serogroups C and Y, and *Haemophilus influenzae* type b. Six Phase III studies investigated effects of the primary vaccine doses (primary vaccination phase) and five other studies assessed effects of the fourth dose (booster). Two studies also evaluated antibody persistence. The studies were conducted in Germany and Belgium, Australia, Mexico, and the United States.

The statistical evaluation of the submission was based predominantly on two pivotal studies (Hib-MenCY-TT-009/010 (immunogenicity and safety) and Hib-MenCY-TT-011/012 (safety pivotal study)) and one supplemental study.

Based on the Hib-MenCY-TT-009/010 immunogenicity data, results indicate that not all pre-specified criteria for study success were met. The first co-primary objective (lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT vaccine) was not met. The estimated values of geometric mean titers (GMTs) for three lots were comparable for the C serogroup, but not for the Y serogroup. Statistical analyses showed differences in GMTs, especially for lots A and B, for the Y serogroup. There could be a few reasons why the hypotheses related to lot-to-lot consistency were not met: for instance, the small number of subjects included in these analyses, manufacturing inconsistencies, and/or variability between assay runs used for measuring titers.

As per the applicant's pre-specified assumptions in the study protocol, the objectives of study Hib-MenCY-TT-009/010 should be assessed in a hierarchical manner according to the order presented in the protocol. Due to this presumption and the fact that the first co-primary objective (lot-to-lot consistency) was not met, based purely on statistical principles and without consideration of other subject-matter disciplines, the pre-specified criteria for study success were not entirely fulfilled.

Disregarding the hierarchical assumption, other pre-defined co-primary hypotheses were tested and it was found that criteria related to these hypotheses were met. However, it is worth noting that testing of these hypotheses was based on immunogenicity datasets with

at least 30% missing data. This large amount of missing data could introduce biases into the study results.

The overall profile of safety data, generated from pivotal studies Hib-MenCY-TT-009/010 and Hib-MenCY-TT-011/012, showed that there were no noteworthy differences between safety data for Hib-MenCY-TT and Hib (Hib or PedvaxHib) vaccines co-administered with the routine infant vaccines. For the primary vaccination schedule at 2, 4, and 6 months of age, serious adverse event (SAE) rates ranged from 4.4% to 4.5%, while SAE rates were about 2.1% after the fourth dose. There were 16 deaths (10 in the Hib-MenCY group and 6 in the Hib group) reported in the pooled studies Hib-MenCY-TT-009 and -011 from Day 0 after Dose 1 through the day preceding Dose 4, and one death after the fourth dose. However, all fatal events were assessed by the study investigators as not related to vaccination.

5.2 Conclusions and Recommendations

A regulatory decision based on this submission depends on the evaluation of the clinical significance of the following findings:

- The statistical analysis of data related to immune responses to Hib-MenCY-TT vaccine showed that the pre-specified criteria were met
- No interference in seroresponse was observed when Hib-MenCY-TT was administered concomitantly with routine infant vaccines: e.g., Infanrix, Pediarix, and MMRV
- There were no notable differences between safety data for Hib-MenCY-TT and Hib (Hib or PedvaxHib) vaccines co-administered with the routine infant vaccines.

However, there appeared to be a potential interference between Hib-MenCY-TT and PCV.

It is worth noting that the three investigated lots only met the pre-defined criteria established for lot-to-lot consistency for the PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C lot comparisons narrowly missed the lower equivalence margin of 0.5.

It is up to the review team to determine whether the product is approvable and if so what language should be considered in the label to point out the following issues:

- the possible interference between Hib-MenCY-TT and PCV
- differences in AE rates among countries
- missing immunogenicity data.

6. Distribution List

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