



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION
BLA

FDA NUMBER: BLA STN 125363

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

SPONSOR: GlaxoSmithKline Biologicals

SUBJECT: Evaluation of the Immunogenicity, Safety, Reactogenicity, and Lot
Consistency of MenHibrix[®]

INDICATION: Immunization of infants and toddlers 6 weeks through 15 months
of age for the prevention of diseases caused by Haemophilus
influenzae type b and Neisseria meningitidis serogroups C and Y.

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1. Executive Summary

Note

This BLA review was written in support of a CR letter to the applicant and should not be treated as the final statistical review. Future applicant's response to the CR letter may influence the final review conclusions. Therefore, the statistical reviewer reserves the right to revise conclusions and update this review.

1.1 Brief Overview of Clinical Studies

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-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.

This BLA submission reports 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 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 a 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 a 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 supply 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 Issues, and Recommendations

GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid conjugate vaccine. Clinical development of this vaccine, which was originally designated Hib-MenCY-TT, 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.

Results, based on the immunogenicity Hib-MenCY-TT-009/010 data, did not support the pre-specified criteria for the 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 inconsistency, and/or variability between assay runs used for measuring titers. The statistical reviewer needs more information on assay runs, i.e., identification numbers of assay runs, which were not included in the submitted SAS datasets, despite Agency request during the pre-BLA meeting.

As per applicant 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 (the lot-to-lot consistency) was not met, the pre-specified criteria for the study success were not fulfilled, based purely on statistical principles and without consideration of other subject-matter disciplines.

However, despite not meeting the first co-primary lot-to-lot hypothesis, other pre-defined co-primary hypotheses were checked and met the statistical significance criteria. Please note that testing of these hypotheses was based on immunogenicity datasets with 30%

missing data. This large amount of missing data could introduce biases into the study results.

For safety assessment of the 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”) and showed that there were no meaningful differences between HibMenCY-TT and Hib vaccines with regard to safety. The statistical analyses were performed for each study separately and then for the pooled data from different studies. However, issues regarding comparability of studies may exist due to the use of different protocols and different study populations.

A major concern with the applicant’s safety assessment is that no clear, unbiased evaluation of the comprehensive safety profile of four doses of the Hib-MenCY-TT (MenHibrix) vaccine for infants and toddlers was presented. The statistical analyses taking into account the longitudinal structure of safety data, missing data, and influence of some covariates like “country” and “medication used” may reduce the magnitude of possible biases and improve the precision of the results. Therefore, this type of statistical analyses should be applied to infants’ safety data.

Based on the review of the submitted materials, the statistical reviewer recommends sending a CR letter that would include the proposed statistical comments included in Section 5.2 of this statistical review.

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.

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

The applicant supplied various important SAS datasets at the time of the BLA submission (08/12/2009).

2.3 Material Reviewed

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

- I. STN 125363/0; Module 1 Volume 1; administrative information, labeling.
- II. STN 125363/0; Module 5 Volumes 1-32; clinical study reports.

3. STATISTICAL EVALUATION OF IMMUNOGENICITY DATA

3.0 List of Studies

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 the 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 Prevnar 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, multicentre 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.

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 meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib- MenCY-TT) compared to monovalent Hib vaccine in healthy infants at 2, 4, 6, and 12 to 15 months of age.”

Note: This study was conducted in two phases: the primary vaccination phase (Hib-MenCY-TT- 009) and the fourth dose vaccination phase (Hib-MenCY-TT-010, BST: 009). 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 study design is presented in Table 3.1.1.1:

Table 3.1.1.1: General study design

Study Hib-MenCY-TT	Total # of Subjects	Cohort	Vaccine Group	Vaccination Schedule	Concomitant Vaccines
009	US - 1084	1 (Safety and Immuno)	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 only)	Hib-MenCY-TT Lot 1 Hib-MenCY-TT Lot 2 Hib-MenCY-TT Lot 3 ActHib		
	Mexico - 200	3 (Safety and Immuno)	Hib-MenCY-TT Lot 1 Hib-MenCY-TT Lot 2 Hib-MenCY-TT Lot 3 ActHib		
010	US - 1084	1 (Safety and Immuno)	Hip-MenCY-TT (Hip-MenCY-TT primed) PedvaxHib (ActHib primed)	12-15 months	MMR, Varivax other (Prevnam)
	US - 1920 non-US - 1200	2 (Safety only)	Hip-MenCY-TT (Hip-MenCY-TT primed) PedvaxHib (ActHib primed)		
	Mexico - 200	3 (Safety and Immuno)	Hip-MenCY-TT (Hip-MenCY-TT primed) PedvaxHib (ActHib primed)		

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 M-M-R II 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: Blood sampling time-points and assay markers by immunology variables

Group	Blood sampling timepoint			Marker	N of enrolled subjects
	Timing	Month	Visit no.		
Both Cohort 1 and 3	Post-vacc III	5	4	Anti-PRP, hSBA-MenC, hSBA-MenY, anti-PSC, anti-PSY,	1080 (US) 200 (non-US)*
70.0% of subjects	Post-vacc III	5	4	Anti-D, anti-T, anti-PT, anti-FHA, anti-PRN, anti-poliovirus types 1, 2 and 3, anti-HBs	756 (US) 140 (non-US)*

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

There were eight pre-specified co-primary objectives.

It was assumed that for both the primary and the fourth dose phases of the study, the co-primary objectives would be assessed in a hierarchical manner according to the order presented in the protocol. A co-primary objective could only be considered if the statistical criteria for all previous co-primary objectives were met.

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 M-M-R II and Varivax is non-inferior to the corresponding immune response in the group that received 3 primary vaccine doses of ActHIB and a booster dose of PedvaxHIB co-administered with M-M-R II 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 M-M-R II 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 M-M-R II 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 M-M-R II when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to M-M-R 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-MenCYTT vaccine as compared to Varivax co-administered with a dose of PedvaxHIB, each co-administered with M-M-R II 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.

Additionally, there were ten secondary objectives defined in the protocols. A general outline of the primary and secondary objectives, with their endpoints, is presented in Tables 3.1.1.3 and 3.1.1.4. Objectives were to be assessed in a hierarchical manner according to the order presented in the tables.

Table 3.1.1.3: Priority ranking of the co-primary objectives (Phase 009 Body Report, page 119 (Table 9))

Ranking	Objective	Timing	Endpoint	Criteria on 95% CI limit
1	Lot-to-lot consistency	Post priming	Anti-PRP GMC, hSBA-MenC, hSBA-MenY GMT	95% CI for the group ratio within [0.5, 2.0]
2	Non inferiority	Post-dose 4	Anti-PRP ≥ 1.0 $\mu\text{g/mL}$	LL of the 95% CI for the group difference $\geq -10\%$
3	Immunogenicity	Post-dose 4	Seroprotection rate for: hSBA-MenC, hSBA-MenY $\geq 1:8$	MenC: LL $\geq 90.0\%$ MenY: LL $\geq 90.0\%$
4	Immunogenicity	Post-dose 4	Effect of fourth Hib-MenCY dose: Individual post-dose 4/pre-dose 4 titer ratio	GMT MenC: LL ≥ 2 GMT MenY: LL ≥ 2
5	Non inferiority	Post priming	Anti-PRP ≥ 1.0 $\mu\text{g/mL}$	LL of the 95% CI for the group difference $\geq -10.0\%$
6	Non inferiority	Post-dose 4	Measles seroconversion, Mumps seroconversion: percentage of subjects with ≥ 28 ED ₅₀ , in subjects with initial anti-mumps antibody < 28 ED ₅₀ , Rubella seroresponse	LL of the 95% CI for the group difference $\geq -5.0\%$
7	Non inferiority	Post-dose 4	Varicella seroconversion	LL of the 95% CI for the group difference $\geq -10.0\%$

Anti-PRP: Anti-polyribosylribitol phosphate

hSBA: Serum bactericidal activity measured with human complement as exogenous source

LL: Lower limit, 95% CI; 95% confidence interval

Table 3.1.1.4: Secondary objectives and their endpoints and criteria

Ranking	Objective	Timing	Endpoint	Criteria on 95% CI limit
Primary vaccination study (3-dose)				
	Immunogenicity	Post priming	Seroprotection rate for: hSBA-MenC $\geq 1:8$	MenC: LL $\geq 90.0\%$
	Immunogenicity	Post priming	Seroprotection rate for: hSBA-MenY $\geq 1:8$	MenY: LL $\geq 85.0\%$
	Non inferiority	Post priming	Seroprotection rate for: Anti-D, Anti-T, Anti-Polio 1, Anti-Polio 2, Anti-Polio 3	LL of the 95% CI for the group difference $\geq -10.0\%$
	Non inferiority	Post priming	Anti-PT, Anti-FHA, Anti-PRN GMCs	LL of the 95% CI for the group GMC ratio ≥ 0.67
	Non inferiority	Across the 3 primary doses (Day 0-3)	Fever $\geq 39.5^\circ\text{C}$	LL of the 95% CI for the group difference $\geq -2.4\%$
Fourth dose study				
	Immunogenicity	Pre fourth dose	hSBA-MenC, titer $\geq 1:8$	MenC: LL of the 95% CI $\geq 70\%$
	Non inferiority	Post fourth dose	Measles seroresponse, Mumps seroresponse	LL of the 95% CI for the group difference $\geq -5.0\%$
	Non inferiority	Post fourth dose	Varicella seroresponse	LL of the 95% CI for the group difference $\geq -10.0\%$
	Non inferiority	During fourth dose (Day 0-3)	Fever $\geq 39.5^\circ\text{C}$	LL of the 95% CI for the group difference $\geq -1.6\%$

Post priming = one month following Dose 3 of the 3-dose primary vaccination regimen

Anti-D= Anti-diphtheria antibody

Anti-T= Anti-tetanus antibody

Anti-Polio 1= Anti-Poliiovirus type 1 antibody

Anti-Polio 2= Anti-Poliiovirus type 2 antibody

Anti-Polio 3=Anti-Poliiovirus 3 antibody

Anti-PT= Anti-pertussis toxoid antibody

Anti-FHA= Anti-filamentous hemagglutinin antibody

Anti-PRN= Anti-pertactin antibody;

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

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. 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 (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: Dispositions of subjects at the ends of the Primary and the Fourth Dose Vaccination Phases

	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

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 + M-M-R II + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

PedvaxHib = PedvaxHIB + M-M-R II + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

In total, 331 subjects were withdrawn from the primary phase of the study. Seven and four subjects were withdrawn 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: Disposition of Cohort 1 subjects for the immunogenicity 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	
Total missing data in ATP Immunogenicity Cohort		389 (35%)		364 (41%)

Approximately, 35% (389/1084) of subjects were not eligible for inclusion into the Primary ATP Cohort for Immunogenicity Analyses. The applicant stated in the clinical report that “if the percentage of enrolled subjects with serological results excluded from this ATP cohort was >5%, a second analysis based on the Total Vaccinated Cohort was to be performed.” Therefore, to support some statistical results, additional analyses were performed by the applicant for the primary and the fourth phase endpoints.

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.

The non-inferiority of co-administration with M-M-R II® 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 the clinical lot-to-lot consistency. To support the hypotheses, the applicant should demonstrate that vaccines drawn from three different vaccine lots -- Lot A, Lot B, and Lot C -- elicit equivalent immune responses. For pair-wise comparisons of lots, the ratios of post-vaccination anti-PRP GMCs, and the hSBA-MenC and hSBA-MenY GMTs should be entirely within the interval (0.5, 2). A summary of the results for lot-to-lot consistency endpoints 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)		

REVIEWER'S COMMENTS:

1. The three investigated lots met the pre-defined criteria to establish the lot-to-lot consistency for the PRP and C serogroups. For serogroup Y, the A vs. B and A vs. C comparisons narrowly missed ruling out the lower equivalence margin of 0.5: the lower limits were 0.44 and 0.49, respectively.
2. 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.
3. Please note that only 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 essential serological data missing.
4. 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 the 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 M-M-R II 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 M-M-R II 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 (ATP US population)

Antibody	Hib-MenCY Group (N=370)		PedvaxHib Group (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)

REVIEWER'S COMMENTS:

It may be concluded from Table 3.1.2.4, that 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: The percentage of subjects with hSBA-MenC and hSBA-MenY titers greater than or equal to 1:8 after the fourth dose vaccination (Fourth Dose ATP Cohort for Immunogenicity, Cohort 1)

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

REVIEWER'S COMMENTS:

It may be concluded from Table 3.1.2.5, that the co-primary immunogenicity hypotheses 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 M-M-R II 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- ratios of the individual 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)

REVIEWER'S COMMENTS:

It may be concluded from Table 3.1.2.6 that the co-primary immunogenicity hypothesis for objective #4 was 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.

ADDITIONAL REVIEWER'S COMMENT related to Objectives #3 and #4

The protocol for study Hib-MenCY-TT009/010 was finalized on March 19th, 2009, after the end of the study and the hypotheses on which objectives #3 and #4 are based were added/defined at the time.

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

Objective #5 was to demonstrate the 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 $\geq 1.0 \mu\text{g/mL}$. 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 ATP Cohort for immunogenicity, Cohort 1)

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)

REVIEWER'S COMMENTS:

Based on Table 3.1.2.7, 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., above 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-R II when co-administered with the fourth dose of Hib-MenCY-TT vaccine as compared to M-M-R II co-administered with PedvaxHIB. Additionally, each subject was vaccinated with Varivax.

The pre-specified criterion for the non-inferiority was that, 42 days after the fourth dose vaccination and for each induced by M-M-R II 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 the 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 M-M-R II. The comparison was to be performed in terms of the immunogenicity to varicella as measured by the ---b(4)-----

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 pool-ability of these two datasets and the non-inferiority of M-M-R-II and Varivax when co-administered with the fourth dose of Hib-MenCY-TT compared to M-M-R-II 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) in each of the individual studies. The analyses demonstrating pool-ability of data from studies Hib-MenCY-TT-010 and -008 are presented (based on the results presented in the Clinical Report) in Tables 3.1.2.9.A and B.

Table 3.1.2.9.A: Differences between the Hib-MenCY and Hib (PedvaxHib) groups in the percentages of subjects with anti-measles, anti-mumps, anti-rubella and anti-varicella antibody concentrations or titers greater than or equal to the pre-specified value at 42 days post the fourth dose vaccination for initially seronegative subjects (Fourth Dose ATP Cohort for Immunogenicity, study Hib-MenCY-TT-010)

								Difference in percentage (Hib-MenCY minus Hib)		
		Hib-MenCY			Hib				95% CI	
Antibody	Cut-off	N	n	%	N	n	%	%	LL	UL
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

Hib-MenCY = Hib-MenCY-TT + M-M-R II + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHIB + M-M-R II + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

N = number of subjects with available results

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

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

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

Table 3.1.2.9.B: Differences between the Hib-MenCY and Hib groups in percentages of subjects with anti-measles, anti-mumps, anti-rubella and anti-varicella antibody concentrations or titers greater than or equal to the pre-specified value 42 days after the fourth dose vaccination for initially seronegative subjects (Booster ATP Cohort for Immunogenicity, study Hib-MenCY-TT-008)

								Difference in percentage (Hib-MenCY minus Hib)		
		Hib-MenCY			Hib			95% CI		
antibody	cut-off	N	n	%	N	n	%	%	LL	UL
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

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

Hib = PedvaxHIB + M-M-RII + Varivax primed with ActHIB + Infanrix penta + Prevnar

N = number of subjects with available results

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

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

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 pre-specified by the applicant 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: Results of testing the non-inferiority hypotheses based on data pooled from studies Hib-MenCY-TT-010 and Hib-MenCY-TT-008

								Difference in percentage (Hib-MenCY minus Hib)		
		Hib-MenCY			Hib			95% CI		
Antibody	Type	N	n	%	N	n	%	%	LL	UL
Anti-Measles	≥ 150 mIU/mL	852	815	95.7	286	274	95.8	-0.15	-2.56	3.06
Anti-Mumps	≥ 28 ED ₅₀	601	595	99.0	191	191	100	-1.00	-2.16	0.98
Anti-Rubella	≥ 10 IU/mL	850	848	99.8	285	284	99.6	0.12	-0.57	1.73
Anti-Varicella	≥ 1:5	723	722	99.9	223	223	100	-0.14	-0.78	1.56

Hib-MenCY = Hib-MenCY-TT + M-M-RII + Varivax primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHib + M-M-RII + 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
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
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 non-inferiority hypotheses were met because lower limits of the 95% CI 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 from study 008 and phase 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 pool-able. Study 008 and Hib-MenCY-TT -009/010 009 were carried out in Australia, and countries USA, Australia, Mexico, respectively. 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.

3.1.3 Summary of the Statistical Findings for Immunogenicity Data

Study Hib-MenCY-TT-009/010 was the pivotal, Phase III study, investigating safety, immunogenicity, and lot-to-lot consistency, that was 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 into the Primary Total Vaccinated Cohort. For the immunogenicity analyses, the applicant reported that from 991 subjects in Cohort 1 who were eligible for inclusion into the Primary Total Vaccinated Cohort, 296 subjects (29.9%) were not eligible for inclusion into 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 the lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT vaccine (co-administered with Pediarix) in terms of the 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 the 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.

Despite not meeting the first co-primary lot-to-lot hypotheses, other pre-defined co-primary hypotheses were tested and their results were statistically significant. However, in addition to disregarding the rules of hierarchical testing, the co-primary hypotheses were tested on immunogenicity datasets with 30% missing data. Excessively missing data could introduce biases into the study results. It is possible that the original randomization scheme was not preserved in the statistical analyses. Additionally, some of the immunogenicity hypotheses were defined after locking the study data. This timing is inappropriate and could introduce biases into the results.

4. Statistical Evaluations of Safety Data

4.1 Overview of safety data assessment

In the Summary of Clinical Safety, the applicant presented reports on 11 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 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 vaccination 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), 7,521 infants received at least one dose of the Hib-MenCY-TT vaccine as part of the 3-dose primary vaccination course starting from 6 weeks of age. In the five studies of the fourth dose phase (Hib-MenCY-TT-004, Hib-MenCY-TT-006, Hib-MenCY-TT-008, Hib-MenCY-TT-010 and Hib-MenCYTT-012), 7,023 subjects received a dose of the Hib-MenCY-TT vaccine. Of these, 6,686 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 regarding safety there were no meaningful differences between HibMenCY-TT and Hib vaccines. The statistical analyses were performed for each study separately and then for the pooled data from different studies which 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 separate (particular) studies but were not for all different studies. The study protocols were 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 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 the 11 studies under review were comparable or not.

Detailed assessment of the vaccine safety was done 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 Hip-MenCY-TT-009 phase, the 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). Altogether 4180 subjects were eligible for inclusion in 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 vaccine or at least one dose of the ActHib vaccine, respectively.

The applicant reported that, in the pooled Hib-MenCY lot groups, compliance for reactogenicity reporting 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 Hip-MenCY-TT-010 phase, the analysis of safety was performed on the Fourth Dose Total Vaccinated Cohort. It 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 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: Difference between ActHib and Hib-MenCY groups in the incidence of fever above 39.5°C during the 4-day (Days 0-3) follow-up period after each dose and the overall differences calculated for the Primary Total Vaccinated Cohort

							Difference in percentage (Hib minus Hib-MenCY)		
	Hib			Hib-MenCY			95% CI		
	N	n	%	N	n	%	%	LL	UL
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	3069	46	1.5	0.09	-0.70	1.12

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

Hib = ActHIB + Pediarix (+ Prevnar if available)

N = Number of subjects with at least one documented dose

n/% = number/percentage of subjects reporting a specified symptom

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

The lower limit of the standardized asymptotic 95% CI for the group difference [Hib-MenCY group (3 lots pooled) minus the ActHib group] 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 above the pre-specified limit of -2.4% and satisfies the acceptable safety criterion related to temperature.

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 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

DOSE 1	Hib-MenCY					Hib				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
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	2.3	1044	25	2.4	1.6	3.5
Any antipyretic	3136	1528	48.7	47.0	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	Hib-MenCY					Hib				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
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	Hib-MenCY					Hib				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
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	8.0	10.1	983	79	8.0	6.4	9.9
OVERALL/DOSE	Hib-MenCY					Hib				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
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	Hib-MenCY					Hib				
				95% CI					95% CI	
	N	n	%	LL	UL	N	n	%	LL	UL
Any	3136	2261	72.1	70.5	73.7	1044	785	75.2	72.5	77.8
Any antibiotic	3136	250	8.0	7.0	9.0	1044	82	7.9	6.3	9.7
Any antipyretic	3136	2045	65.2	63.5	66.9	1044	719	68.9	66.0	71.7
Prophylactic antipyretic	3136	666	21.2	19.8	22.7	1044	216	20.7	18.3	23.3

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

Hib = ActHIB + Pediarix (+ Prevnar if available)

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

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

Table 4.2.3: Concomitant use of any medication during four days after vaccinations by country

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

Observed 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 the 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.

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 events symptoms (solicited and unsolicited) during the 4 days (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/subject	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%)

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

ActHib = ActHIB + Pediarix (+ Prevnar if available)

For overall/subject: N= number of subjects with at least one administered dose

n%= number/percentage of subjects presenting at least one type of symptom whatever the study vaccine was administered

Table 4.2.4 demonstrates that over 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 were similar 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 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 experienced at least one of these unsolicited adverse events was similar in both vaccination groups.

Adverse events for extended follow-up

Cases of observed SAEs, new onset of chronic disease (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 the fourth dose was administered, 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 of these events that may have taken place since the last study contact. A summary of registered events is given in Table 4.2.5.

Table 4.2.5: Summary of observed SAE, NOCD, rashes, and AE resulting in ER visits 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)

	Hib-MenCY		ActHib	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=3136		N=1044	
At least one symptom	755	0.241	255	0.244
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	0.054

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

ActHib = ActHIB + Pediarix (+ Prevnar if available)

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)

N = number of subjects with at least one administered dose

REVIEWER'S COMMENTS:

In the Hib-MenCY-TT-009 phase, the overall rates of incidences 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 (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 (2 in US and 2 in Mexico) cases; one case was baby shaken syndrome and one was 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 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 due to a serious adverse event (all Hib-MenCY recipients) and four due to non-serious adverse event (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 the 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 *M-M-R II* 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) would 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-MenCY and Hib groups in percentage of subjects reporting fever greater than 39.5°C during the 4-day post-vaccination period

Symptoms	Type	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)

Hib-MenCY = Hib-MenCY-TT + M-M-R II + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

Hib = PedvaxHIB + M-M-R II + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

N = Number of subjects with the documented dose

n/% = number/percentage of subjects reporting a specified symptom

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

REVIEWER’S COMMENTS:

As can be seen in Table 4.2.6, the pre-specified non-inferiority hypothesis corresponding to the safety endpoint “temperature” was met. However, the dataset on which safety statistical analyses were performed was created by pooling datasets from three countries. Countries under consideration, especially US and Mexico, are different with respect to the 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. 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 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

Cases of observed SAEs, new onsets of chronic disease (NOCD, e.g. onsets of type I diabetes, allergies, asthma and autoimmune disorders), rash (like: 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 observed SAE, NOCD, rashes, and AE resulting in ER visits during 6 months of the follow-up after the fourth dose vaccination (Fourth Dose Total Vaccinated Cohort)

	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

Hib-MenCY = Hib-MenCY-TT + M-M-R II + Varivax + Prevnar primed with Hib-MenCY-TT + Pediarix + Prevnar

PedvaxHib = PedvaxHIB + M-M-R II + Varivax + Prevnar primed with ActHIB + Pediarix + Prevnar

At least one symptom = at least one symptom experienced (regardless of the MedDRA Primary System Organ Class)

N = number of subjects with the administered dose

Table 4.2.7 demonstrates that there was no significant difference between the Hib-MenCY and PedvaxHib groups in the overall incidence 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 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 severe trauma suffered in a motor vehicle accident.

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

Study Hip-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.

Objective

The primary objective was to evaluate the safety profile of Hib-MenCY-TT vaccine as compared to ActHib with respect to the occurrence of SAEs, NOCD, rash, and AEs resulting in ER visits 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 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 in study Hib-MenCY-TT-011, 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 observed SAEs, NOCD, rashes, and AEs resulting in ER visits from Day 0 after Dose 1 through Day 30 after Dose 3 (Total Vaccination Cohort)

	Hib-MenCY N = 3278				Hib N = 1113			
	n	%	95% CI		n	%	95% CI	
			LL	UL			LL	UL
At least one AE	422	12.9	11.7	14.1	149	13.4	11.4	15.5
SAE	109	3.3	2.7	4.0	33	3.0	2.0	4.1
NOCD	50	1.5	1.1	2.0	18	1.6	1.0	2.5
Rash	243	7.4	6.5	8.4	81	7.3	5.8	9.0
AEs resulting in ER visit	114	3.5	2.9	4.2	44	4.0	2.9	5.3

Table 4.3.2: Summary of observed SAEs, NOCD, rashes, and AEs resulting in ER visits from Day 0 after Dose 1 through the day preceding Dose 4 (Total Vaccination Cohort)

	Hib-MenCY N = 3278				Hib N = 1113				Relative Risk (Hib-MenCY over Hib)		
	95% CI				95% CI				95% CI*		
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
At least one AE	654	20.0	18.6	21.4	232	20.8	18.5	23.4	0.96	0.87	1.07
SAE	157	4.8	4.1	5.6	48	4.3	3.2	5.7	1.11	0.88	1.41
NOCD	66	2.0	1.6	2.6	25	2.2	1.5	3.3	0.91	0.65	1.29
Rash	386	11.8	10.7	12.9	134	12.0	10.2	14.1	0.98	0.85	1.13
AEs resulting in ER visit	198	6.0	5.2	6.9	69	6.2	4.9	7.8	0.99	0.81	1.21

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

Hib = ActHIB + Pediarix (+ Prevnar if available)

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

N = number of subjects with at least one administered dose

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

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

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

REVIEWER'S COMMENTS:

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 the 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 datasets.

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

Please note that there were twelve deaths [seven deaths in the Hib-MenCY group (in that, three deaths were Sudden Infant Death Syndrome (SIDS)) and five deaths in the Hib group (in that, 2 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 the safety of the fourth dose of Hib-MenCY-TT vaccine as compared to PedvaxHib, both co-administered with MM-R II, 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 the 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 of follow-up after Dose 4 are presented in Table 4.3.3 and Table 4.3.4, respectively.

Table 4.3.3: Summary of observed SAEs, NOCD, rashes, and AEs resulting in ER visits reported within the 31-day (Days 0-30) post-vaccination period after Dose 4 by treatment group

	Hib-MenCY N = 3010				Hib N = 1010			
			95% CI				95% CI	
	n	%	LL	UL	n	%	LL	UL
At least one specific AE	164	5.4	4.7	6.3	59	5.8	4.5	7.5
SAE	12	0.4	0.2	0.7	1	0.1	0.0	0.6
NOCD	12	0.4	0.2	0.7	6	0.6	0.2	1.3
Rash	123	4.1	3.4	4.9	41	4.1	2.9	5.5
ER visit	29	1.0	0.6	1.4	16	1.6	0.9	2.6

Hib-MenCY = Hib-MenCY-TT + M-M-R II + Varivax (+ Prevnar) primed with Hib-MenCY-TT + Pediarix (+ Prevnar)

Hib = PedvaxHIB + M-M-R II + Varivax (+ Prevnar) primed with ActHIB + Pediarix (+ Prevnar)

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

N = number of subjects with the administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

Table 4.3.4: Summary of observed SAEs, NOCD, rashes, and AEs resulting in ER visits reported during the 6 months follow-up after the fourth dose (Fourth Dose Total Vaccinated Cohort)

AE category	Hib-MenCY N = 3010				Hib N = 1010				Relative Risk (Hib-MenCY over Hib)		
			95% CI				95% CI		RR	95% CI*	
	n	%	LL	UL	n	%	LL	UL		LL	UL
At least one specific AE in a specific category	395	13.1	11.9	14.4	137	13.6	11.5	15.8	0.98	0.85	1.13
SAE	72	2.4	1.9	3.0	18	1.8	1.1	2.8	1.34	0.93	1.99
NOCD	50	1.7	1.2	2.2	18	1.8	1.1	2.8	0.95	0.65	1.44
Rash	227	7.5	6.6	8.5	82	8.1	6.5	10.0	0.94	0.79	1.13
ER visit	129	4.3	3.6	5.1	48	4.8	3.5	6.3	0.92	0.73	1.18

Hib-MenCY = Hib-MenCY-TT + M-M-R II + Varivax (+ Prevnar) primed with Hib-MenCY-TT + Pediarix (+ Prevnar)

Hib = PedvaxHIB + M-M-R II + Varivax (+ Prevnar) primed with ActHIB + Pediarix (+ Prevnar)

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

N = number of subjects with at least one administered dose

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

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

REVIEWER'S COMMENTS:

Based on 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 (Days 0-30) and 6 months after Dose 4 were almost similar in the Hib-MenCY and the Hib groups. However, a 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 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 the primary health care utilization in the US and Mexico.

Table 4.3.5: Percentages of subjects with SAEs, NOCD, rash, and AEs resulting in ER visits during 6 months of follow-up after the booster, per country

United States		Hib-MenCY N = 864				Hib N = 304			
		95% CI				95% CI			
		n	%	LL	UL	n	%	LL	UL
At least one specific AE		268	31.0	27.9	34.2	94	30.9	25.8	36.4
SAE		23	2.7	1.7	4.0	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	11.0	19.3
Mexico		Hib-MenCY N = 2146				Hib N = 706			
		95% CI				95% CI			
		n	%	LL	UL	n	%	LL	UL
At least one specific AE		127	5.9	5.0	7.0	43	6.1	4.4	8.1
SAE		49	2.3	1.7	3.0	14	2.0	1.1	3.3
NOCD		0	0.0	0.0	0.2	0	0.0	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	1.0	3	0.4	0.1	1.2

REVIEWER’S GENERAL COMMENTS RELATED TO SAFETY ANALYSES:

The applicant submitted large safety datasets in this submission. The applicant presented only a statistical summary of adverse events occurrences that did not provide a complete safety profile of four doses of MenHibrix vaccine. Statistical analyses taking into account the longitudinal structure of the safety data, missing data, and influence of some covariates like “country” and “medication used” may reduce the magnitude of possible biases and improve the precision of the results. Therefore, the statistical reviewer recommends that the applicant apply these types of analyses to the safety dataset.

5. Summary and Conclusion

5.1 Statistical Issues

GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid conjugate vaccine. Clinical development of this vaccine, which was originally designated Hib-MenCY-TT, 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 application was to provide data to support the applicant’s claim that, 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.

In the case of Study Hib-MenCY-TT-009/010, the first co-primary objective (the lot-to-lot consistency of 3 manufacturing lots of Hib-MenCY-TT vaccine) was met for all comparisons except two (for which the success criteria were narrowly missed). The estimated values of geometric mean titers (GMTs) for the three lots were comparable for the C serogroup. However, for the Y serogroup, there were some differences in estimated GMT values. Statistical analyses showed differences in GMTs especially for lot A compared to lot B. There could be a few reasons why the hypotheses related to the lot-to-lot consistency were not all met: for instance, a small number of subjects included in these analyses, a manufacturing inconsistency, and 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.

It is of interest to note that the applicant assumed that, for both (the primary and the fourth dose) phases of the study, objectives should be assessed in a hierarchical manner according to the order presented in the protocol. This means that an objective could only be considered to be met if the statistical criteria for all previous objectives were met. In this study, the first co-primary objective was not fully met. The two out of nine hypotheses were not met due to near misses of the two equivalence margins.

Despite not meeting the first co-primary lot-to-lot hypotheses, other pre-defined co-primary hypotheses were checked and met statistical significance criteria. However, testing of these hypotheses was based on immunogenicity datasets with 30% missing data. This large amount of missing data could introduce biases into the study results. As a consequence, it is possible that the original randomization scheme was not preserved in the statistical analyses. Additionally, some of the immunogenicity hypotheses were defined after locking the study data. This was an inappropriate procedure and it could also introduce biases into the results.

Moreover, it should be emphasized that data on which hypotheses were tested exhibited some flaws. For example:

1. A total of 35% (389/1084) of subjects were not eligible for inclusion into the Primary ATP Cohort for Immunogenicity Analyses.
2. The Fourth Dose ATP Immunogenicity Cohort (521 subjects) was not a subset of the Primary ATP Immunogenicity Cohort (695 subjects) because 29% of the subjects of the Fourth Dose ATP Immunogenicity Cohort were not included in the Primary ATP Immunogenicity Cohort.
3. In the case of testing the co-primary objective #2 [testing PRP (Polyribosylribitol phosphate) antibody response on the ATP Primary Immunogenicity Cohort], over 37% (502/ 816) of the immunogenicity data was missing.

4. Approximately 70% of subjects from the Primary Total Vaccinated Cohort were included in testing the 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.

For safety assessment of the 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”) and showed that regarding safety there were no meaningful differences between HibMenCY-TT and Hib vaccines. The statistical analyses were performed for each study separately and then for the pooled data from different studies, which were dissimilar with respect to both the study protocols and study populations (studies were conducted in Australia, Mexico, and the USA). The demographic profiles with respect to mean age, gender, and racial distributions for both groups were comparable within separate studies but were not similar for the different studies. Additionally, the study protocols were 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 enrollment. A similar exclusion criterion was not applied in study Hib-MenCY-TT-009.

In summary, the applicant’s safety assessment did not supply a comprehensive safety profile of infants/toddlers vaccination with four doses of Hib-MenCY-TT (MenHibrix), from a statistical perspective. Statistical analyses taking into account the longitudinal structure of the safety data, missing data, and influence of some covariates like “country” and “medication used” may reduce the magnitude of possible biases and improve the precision of the results. Therefore, this type of statistical analyses should be applied to the infants’ safety data.

5.2. Recommendations

Based on the review of the submitted materials received up to date, the statistical reviewer recommends sending a CR letter that would include the following statistical concerns related to study Hib-MenCY-TT-009/010:

- 1) During the pre-BLA meeting, you were asked to include in the immunogenicity clinical datasets additional information on the hSBA assays, namely, an assay run identification number for each subject serum. In your SAS “serocod” immunogenicity clinical dataset, this information is missing. Therefore, please resubmit the serology datasets including assay identification numbers. Additionally, please perform statistical analyses to evaluate the influence of the factor “Assay” on the estimates of the primary and secondary endpoints related to MenC and MenY. Please submit a SAS statistical program that you plan to use for the above mentioned analysis.
- 2) In Module 5 of the BLA, you included some SAS programs (folder 5.3.5.1.25.3.2, Analysis Program). However, the program folder did not contain a sub-folder with

“batch” and “macro” sub-folders. Therefore, to support your statistical results, please submit clear and well documented utilized SAS analysis programs with all relevant macros.

- 3) In the primary phase of the study, 4441 subjects were enrolled and vaccinated in 91 study centers. The number of subjects per center ranged from 1 to 800. There were twenty three centers which enrolled less than 10 subjects. Please explain the reasons for the small enrollments in these centers.
- 4) For the Cohort 1 population, please perform descriptive statistical analyses showing the influence of the factors “race,” “center,” and “gender” on the immune responses (GMTs/GMCs) after the 3rd and the 4th doses of Hib-MenCY-TT vaccine.
- 5) The Fourth Dose ATP Immunogenicity Cohort (521 subjects) does not constitute a subset of the Primary ATP Immunogenicity Cohort (695 subjects). There are some subjects in the Fourth Dose ATP Immunogenicity Cohort who are not included in the Primary ATP Immunogenicity Cohort. Please:
 - a) Summarize the reasons why some infants from the Primary ATP Immunogenicity Cohort were not included in the Fourth dose ATP Immunogenicity Cohort
 - b) Evaluate the influence of an “indication factor” on GMT or GMC after the fourth dose. The definition of this factor would be as follows: factor is equal to 0 if a subject is in the Fourth Dose ATP Immunogenicity Cohort but he/she was not in the Primary ATP Immunogenicity Cohort; otherwise the factor is equal to 1.
- 6) Please build a model that adequately describes the profile of log antibody titer (MenC, MenY and PRP) over time (Primary and Fourth Dose Phases). You may utilize longitudinal, mixed effect models (e.g., Verbeke, G. and Molenbeeghs, G, “Linear Mixed Models for Longitudinal data”, Verbeke, G. and Kenward, M. “Missing Data in Clinical Studies”). Please submit a corresponding SAS program and a serology dataset in a special format (subject ID, Subject’s Visit, Date of Visit, titer, identification number of assay run, etc.).
- 7) With regard to hSBA MenC and MenY titers, please perform statistical analyses to show whether the time elapsed between sera collection and assay run had any influence on the collected titer after the 3rd dose, before 4th dose, and after the 4th dose of Hib-MenCY-TT vaccination. Please submit a corresponding SAS program with adequate dataset.
- 8) 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 M-M-R II and Varivax at 12 to 15 months of age, namely, geometric mean of the ratios of the individual post-fourth dose to pre-fourth dose hSBA titers. Please test the hypotheses related to objective #4 with adjustment for the

factors “assay runs” and “time elapsed between sera collection and assay run.” Please submit the corresponding SAS program.

- 9) 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) after any dose 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. You tested this hypothesis based on the pooled dataset from three countries: US, Mexico, and Australia. These countries appear to differ with respect to primary health care and demographic factors. Additionally, over 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 antipyretic medication is correlated with occurrences of fever events. Thus, it appears that distributions of fever events by study group alone may not supply unbiased results. Therefore, please retest this hypothesis utilizing longitudinal, mixed effects logistic models (e.g., Geert Molenberghs and Geert Verbeke, 2004, Meaningful Statistical Model Formulations for Repeated Measures, Statistica Sinica 14; Dimitrienko, A., Molenbeghs, G., Chuang-Stein, C. and Offen, W., “Analysis of Clinical Trials Using SAS®: A Practical Guide”) adjusting for factors “country,” and “use of concomitant medication.” Please send to the Agency the SAS program used for this problem.
- 10) For any occurrence of grade 3 unsolicited symptoms (Primary Total Vaccinated Cohort), please perform statistical analyses utilizing longitudinal, mixed-effects logistic models (e.g., Geert Molenberghs and Geert Verbeke, 2004, Meaningful Statistical Model Formulations for Repeated Measures, Statistica Sinica 14; Dimitrienko, A., Molenbeghs, G., Chuang-Stein, C. and Offen, W., “Analysis of Clinical Trials Using SAS®: A Practical Guide”) adjusting for the factors “use of concomitant medication” and “country.” Please send to the Agency the SAS program used for this problem.