EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

# Infanrix penta

(Diphtheria (D), Tetanus (T), Pertussis (Acellular, Component) (Pa), Hepatitis B (Rdna) (Hbv), Poliomyelitis (Inactivated) (Ipv) Vaccine (Adsorbed))

Procedure No. EMEA/H/C/000295/P46/059

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006



**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# I. EXECUTIVE SUMMARY

The MAH reported the safety data accrued in the Hib-MenCY-TT-011 study, which is the vaccination phase of a larger study evaluating the safety of the Hib-Men-CY-TT vaccine, which also includes the safety evaluation of the booster vaccination (Hib-MenCY-TT-012, not part of this overview). In addition, this report includes the extended safety follow-up phase of the Hib-MenCY-TT-011 study (preceding the booster vaccination) and pooled safety data from the Hib-MenCY-TT-009 study. Overall, the Hib-MenCY-TT vaccine has a similar safety profile as ActHib in the extended safety follow-up period with regard to the occurrence of serious adverse events, new onset of chronic disease, rash and emergency room visits.

No SmPC and PL changes are proposed.

# II. RECOMMENDATION[1]

The paediatric studies submitted by the MAH aimed at defining the safety profile of the Hib-MenCY-TT vaccine with respect to infrequent adverse events (i.e. SAEs, rash, ER visits and NOCD) in comparison with a US-licensed monovalent Hib control group. Overall, the safety profiles of the investigational Hib-MenCY-TT vaccine and the monovalent Hib vaccine were comparable regardless of the country in which the vaccinations were administered, the co-vaccination status or vaccination with other routinely administered vaccines, both in the single Hib-MenCY-TT-011 study data and the pooled study data (Hib-MenCY-TT-011 and -09).

Based on these results, discussed in detail by the MAH, the safety profile of the investigational vaccine is considered acceptable and no further action is required.

# III. INTRODUCTION

On 29th November 2012, the MAH submitted a completed paediatric study for Infanrix Penta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Infanrix Penta and that there is no consequential regulatory action.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the studies

Pharmaceutical formulations used in the study can be found in Table 3, dosage and administration of each vaccine are present in Table 4.



[1] *The recommendation from section V can be copied in this section*

**Table 3 Vaccine formulations, presentation and lot numbers**

| Vaccine | Formulation<br>One dose (0.5 mL) of vaccine contains | Presentation | Lot number |
|---|---|---|---|
| Hib-MenCY-TT vaccine (GSK Biologicals) | *Haemophilus influenzae* type b polysaccharide (2.5 µg) conjugated to tetanus toxoid 5 to 7 µg;<br>*Neisseria meningitidis* serogroup C capsular polysaccharide (5 µg) conjugated to tetanus toxoid 5 to 5.5 µg;<br>*Neisseria meningitidis* serogroup Y capsular polysaccharide (5 µg) conjugated to tetanus toxoid 5 to 7 µg;<br>Tetanus toxoid (total) ~18 µg; | Lyophilized: monodose vials, containing a white freeze dried pellet to be reconstituted before use with the saline diluent. Reconstituted vaccine is clear and colorless. | DMEHA-010A, -012A, -013A<br>Diluent AD02B091D |
| *ActHib* (Sanofi Pasteur) | PRP 10 µg;<br>tetanus toxoid 24 µg;<br>sucrose 8.5% | Lyophilized: monodose vials or pre-filled syringes, containing a white freeze dried pellet to be reconstituted before use with the saline diluent (0.4% NaCl). Reconstituted vaccine is clear and colorless. | Z0452 (vaccine) + Z6301 (diluent), UE917AA (vaccine) + UE699AA (diluent), Z1006 (vaccine) + Z6476 (diluent) |
| *Pediarix or Infanrix penta* (GSK Biologicals) | Diphtheria toxoid ≥30 IU (25 Lf),<br>Tetanus toxoid ≥40 IU (10 Lf),<br>Pertussis Toxoid 25 µg,<br>Filamentous Hemagglutinin 25 µg,<br>Pertactin 8 µg,<br>Hepatitis B Surface Antigen (recombinant) 10 µg,<br>Poliovirus type 1 (Mahoney) 40 D antigen units,<br>Poliovirus type 2 (MEF-1) 8 D antigen units,<br>Poliovirus type 3 (Saukett) 32 D antigen units,<br>Aluminum adjuvant not more than 0.85 mg by assay, | Liquid: monodose vials or pre-filled syringes containing a turbid white suspension | AC21B064A, -AC21B097A |
| *Prevnar or Prevenar (PCV7)* (Wyeth) | 2 µg each of saccharide of serotypes 4, 9V, 14, 18C, 19F and 23F, and 4 µg of serotype 6B (16 µg total saccharide), 20 µg of $CRM_{197}$ carrier protein, Aluminum as aluminum phosphate adjuvant 0.125 mg. | Liquid: monodose vials or pre-filled syringes containing a white suspension | Lots 18133, 18079, 20218 used in Mexico, commercial lots used in the US |

**Table 4 Dosage and Administration**

| Group | Visit | Vaccine | Route | Site | Side | Location |
|---|---|---|---|---|---|---|
| Hib-MenCY-TT group | 1,2,3 | Hib-MenCY-TT | IM | thigh | Right | Upper |
| | 1,2,3 | *Pediarix/Infanrix penta* | IM | thigh | Left | Upper |
| | 1,2,3 or local recommendation | *Prevnar* | IM | Anterolateral thigh or deltoid | Left | Lower |
| Hib group | 1,2,3 | *ActHib* | IM | thigh | Right | Upper |
| | 1,2,3 | *Pediarix/Infanrix penta* | IM | thigh | Left | Upper |

IM = Intramuscular

## IV.2 Clinical aspects

### 1. Introduction

The MAH submitted a final report(s) for: 105987 (Hib-MenCY-TT-011 [Primary study]) and a pooled results report for studies Hib-MenCY-TT-009 and -011.

### 2. Clinical studies under review

A phase III, single-blind, randomized, controlled, multinational study for the evaluation of safety of GSK Biologicals' *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT) compared to monovalent *Haemophilus influenzae* type b (Hib) control vaccine in healthy infants at 2, 4, 6, and 12 to 15 months of age. *Note: This study was conducted in two phases: primary vaccination (105987 [Hib-MenCY-TT-011]) and booster vaccination (105988 [Hib-MenCY-TT-012]). This report presents the results of the primary vaccination phase, including an extended safety follow-up and pooled safety data from Hib-MenCY-TT-009 study. This report does not discuss results of the booster vaccination study 105988 [Hib-MenCY-TT-012]).*

- **Description**

The purpose of this study is to complement study Hib-MenCY-TT-009/-010 in order to assess the safety profile of Hib-MenCY-TT vaccine with respect to infrequent adverse events (i.e. serious adverse events, emergency room [ER] visits, rash [e.g. hives, idiopathic thrombocytopenic purpura, petechiae], and new onset of chronic illnesses [e.g. autoimmune disorders, asthma, type I diabetes and allergies]). Therefore, the primary study objective will be exploratory and based on data from this study pooled with the data from study Hib-MenCY-TT-009/-010. Data from each study will be analyzed separately prior to pooling. Study Hib-MenCY-TT-009/010 is a multinational, Phase 3 safety, immunogenicity, and lot-to-lot consistency study of Hib-MenCY-TT vaccine versus monovalent Hib vaccine control.

- **Methods**

- Objective(s)

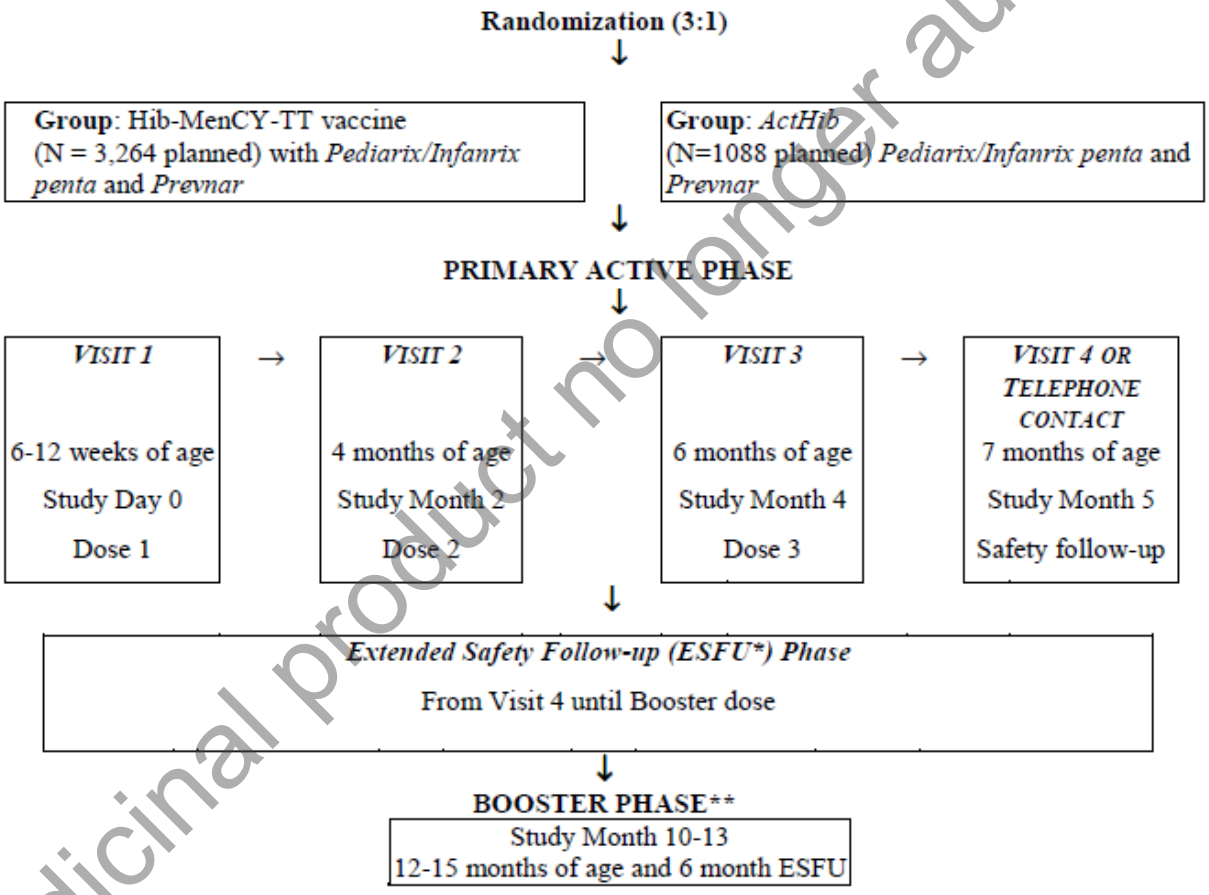
Primary Objective of the primary vaccination - Pooled dataset (i.e. Hib-MenCY-TT-011 and all subjects in Hib-MenCY-TT-009)

To evaluate the safety profile of Hib-MenCY-TT vaccine compared to *ActHIB* with respect to the occurrence of serious adverse events, new onset of chronic illnesses (e.g. autoimmune disorders, asthma, type I diabetes and allergies), rash (e.g. hives, idiopathic thrombocytopenic

purpura, petechiae) and ER visits within the primary vaccination course (from dose 1 up to Day 30 after dose 3 and from dose 1 up to the day preceding booster dose at 12-15 months of age).

<u>The secondary objective relates to the booster Vaccination - Pooled dataset (i.e. Hib-MenCY-TT-012 and all subjects in Hib-MenCY-TT-010)</u>
To evaluate the safety profile of Hib-MenCY-TT vaccine compared to *PedvaxHIB* with respect to the occurrence of serious adverse events, new onset of chronic illnesses (e.g. autoimmune disorders, asthma, type I diabetes and allergies), rash (e.g. hives, idiopathic thrombocytopenic purpura, petechiae) and ER visits within the booster vaccination course (from booster dose up to Day 30 after booster vaccination and from booster dose up to 6 months after booster vaccination). (Amended: 22-JAN-2007). *Note: the secondary objective pertains to the booster dose and is presented in a separate clinical report, and will not be further discussed in this report.*

- Study design




The Hib-MenCY-TT-011 study is a phase III, randomized, controlled, multinational study, with two parallel treatment groups:

- Treatment allocation: Central Randomization call-in System on internet (SBIR) with unbalanced allocation (3:1).
- Blinding: Single-blind.
- Investigational group: Hib-MenCY-TT vaccine.
- Control: Monovalent Hib vaccine (*ActHIB* for the Primary Phase; *PedvaxHIB* for the Booster Phase). (Amended: 22-JAN-2007)
- Co-administered vaccines:

Primary vaccination - Licensed *Pediarix/Infanrix penta* to subjects in all study groups. Subjects enrolled in the US should receive *Prevnar* according to a 2, 4, and 6 month schedule concomitantly with study vaccines if *Prevnar* is available. If *Prevnar* is in short supply, *Prevnar* should be given to study subjects according to revised recommendations as issued by the CDC. Administration of study vaccines should not be delayed if *Prevnar* is in short supply. Because *Prevnar* is routinely covered by US insurance plans, and because GSK has had difficulty obtaining enough *Prevnar* to conduct the current study, US investigators will supply *Prevnar* on their own accord to US subjects. For non-US subjects, only countries in which *Prevnar* (*Prevenar*) is licensed and permitted to be given according to the primary US schedule (2, 4, and 6 months) will participate in this study. Subjects enrolled in non-US countries should receive their primary series of *Prevnar* (*Prevenar*) at 2 ,4, and 6 months of age concomitantly with study vaccines. If *Prevnar* (*Prevenar*) is in short supply in non-US countries, *Prevnar* (*Prevenar*) should be given according to local recommendations and availability. Administration of study vaccines should not be delayed if *Prevnar* (*Prevenar*) is in short supply. GSK may provide *Prevnar* (*Prevenar*) to selected non-US countries if *Prevnar* (*Prevenar*) would be difficult to obtain or would otherwise represent a financial hardship to the parents of study subjects. Coadministration of Synagis® (Palivizumab, MedImmune), influenza vaccine and rotavirus vaccine are also permitted.

Booster vaccination (results not discussed in this report) - *All subjects enrolled in the booster phase should receive hepatitis A vaccine and influenza vaccine according to local recommendations. All subjects will receive Prevnar, M-M-R II and Varivax as study vaccines. M-M-R II and Varivax must be given according to current US labelling and ACIP recommendations (i.e. M-M-R II must be administered between 12 to 15 months of age. Varivax should be administered between 12 to 18 months of age). It is preferred that subjects receive Prevnar concomitantly at the booster phase between 12 to 15 months of age according to current US labelling and ACIP recommendations. It is the preference for subjects to receive Prevnar, M-M-R II and Varivax with the booster dose of Hib-MenCY-TT/PedvaxHIB.* (Amended: 22-JAN-2007).

- Study population /Sample size

Target enrolment for this study was 4,352 subjects (3,264 in the Hib-MenCY-TT vaccine group and 1,088 in the Hib control group). There were approximately 1,352 US subjects and 3,000 non-US subjects expected to participate in this study.

- Treatments

Vaccination schedule:
Primary Vaccination - Infants receiving Hib-MenCY-TT vaccine or *ActHIB*, each co-administered with *Pediarix/Infanrix penta*, will be vaccinated at 2, 4 and 6 months of age.
Booster Vaccination - Infants receiving Hib-MenCY-TT vaccine or *PedvaxHIB/ActHIB* will be vaccinated at 12 to 15 months of age.

- Outcomes/endpoints

Primary endpoints

Primary Vaccination - Pooled dataset: Hib-MenCY-TT-011 and all subjects in Hib-MenCY-TT-009
From dose 1 up to Day 30 after dose 3 (Vaccination phase)

- Occurrence of SAEs.
- Occurrence of new onset of chronic illness(es) (e.g., autoimmune disorders, asthma, type I diabetes and allergies).
- Occurrence of rash (e.g. hives, idiopathic thrombocytopenic purpura, petechiae).

- Occurrence of ER visits.

From Dose 1 through but excluding the booster dose (extended follow up phase)

- Occurrence of SAEs.
- Occurrence of new onset of chronic illness(es) (e.g., autoimmune disorders, asthma, type I diabetes and allergies).
- Occurrence of rash (e.g. hives, idiopathic thrombocytopenic purpura, petechiae).
- Occurrence of ER visits.

Secondary endpoints

Booster Vaccination - Pooled dataset: Hib-MenCY-TT-012 and all subjects in Hib-MenCY-TT-010

From booster dose up to Day 30 after booster vaccination

- Occurrence of SAEs.
- Occurrence of new onset of chronic illness(es) (e.g., autoimmune disorders, asthma, type I diabetes and allergies).
- Occurrence of rash (e.g. hives, idiopathic thrombocytopenic purpura, petechiae).
- Occurrence of ER visits.

From booster dose through the end of the 6-month safety follow-up

- Occurrence of SAEs.
- Occurrence of new onset of chronic illness(es) (e.g., autoimmune disorders, asthma, type I diabetes and allergies).
- Occurrence of rash (e.g. hives, idiopathic thrombocytopenic purpura, petechiae).
- Occurrence of ER visits.

- Statistical Methods

*Safety:*

The safety analysis was performed on the Primary Total Vaccinated cohort (pre-defined primary analysis), which included all enrolled subjects who had received at least one dose of study vaccine. In accordance with the protocol, a second analysis based on the Primary ATP safety cohort was not performed since less than 5% of enrolled subjects were not eligible for inclusion in the Primary ATP cohort for safety analysis.

Safety analyses presented in this report include data collected from Day 0 (first visit, first dose) through the day preceding the booster dose, which includes the ESFU (extended safety follow-up) which began the day after the 30 day follow-up for dose 3 and extended up until the booster dose administration.

*Primary phase, within group analyses:* From Dose 1 up to Day 30 after the third dose and from Day 0 through the ESFU, the number and percentage of subjects reporting the different categories of AEs were tabulated by group with exact 95% CI. The percentage of subjects with these different categories of AEs from Day 0 through the ESFU and its exact 95% CI were tabulated by group and by MedDRA preferred term.

*Primary phase, between group analyses:* The differences between the Hib-MenCY group and the Hib group were evaluated in terms of relative risks. The country specific relative risks were presented with their asymptotic 95% CI and their corresponding 2-sided P-value. The common relative risk across countries, its 95% CI and the corresponding 2-sided P-value were estimated based on exact conditional likelihood adjusted for the country effect. Potential safety signals were based on nominal P-value below 5%.

Statistical comparisons between the Hib-MenCY and the Hib groups were conducted for the time period from Day 0 through the ESFU. Statistical summary and comparison tables were also provided for the period from Day 0 through Day 30 (31 days) after dose 3 (Visit 4, Month 7) for the pooled analyses.

Safety analyses were also performed in subpopulations defined by the co-administration/ absence of co-administration of specified vaccines (*Pediarix* and *Prevnar*, *RotaTeq*, and

influenza vaccines). Statistical testing between treatment groups for these sub-categories was not performed. Acceptability of the pooling across countries and studies was checked by means of Breslow and Day tests.

**Potential safety signals were based on nominal P-value below 5%. Considering the multiplicity of comparisons and the exploratory nature of the evaluation, the risk of false safety signals is much larger than 5%. Therefore, any signal was further examined for clinical plausibility and relevance.**

- **Results**

- Recruitment/ Number analysed

Number of subjects in study Hib-MenCY-TT-011:
*Planned:*
4,352 subjects (3,264 in the Hib-MenCY group and 1,088 in the Hib control group: approximately 1,352 US subjects and 3,000 non-US subjects).

*Enrolled:*
4432* subjects, overall (3308 in the Hib-MenCY group and 1123 in the Hib control group). However, 40 subjects who participated at center 35785 were eliminated from all analyses as a result of Good Clinical Practice violations and protocol non-compliance at this center.
1366* subjects in the US (1009 in the Hib-MenCY group and 356 in the Hib control group), 3066 subjects in Mexico (2299 in the Hib-MenCY group and 767 in the Hib control group)
**1 enrolled subject was not assigned a group and not vaccinated.*

*Completed:*
4162 subjects, overall (3114 in the Hib-MenCY group and 1048 in the Hib control group)
1250 subjects in the US (924 in the Hib-MenCY group and 326 in the Hib control group)
2912 subjects in Mexico (2190 in the Hib-MenCY group and 722 in the Hib control group)

*Safety*: The Primary Total Vaccinated cohort consisted of all vaccinated subjects enrolled from the remaining centers (excluded subjects from center 35785)
4391 subjects, all sites (3278 in the Hib-MenCY group and 1113 in the Hib control group).
1325 subjects in the US (979 in the Hib-MenCY-TT vaccine group and 346 in the Hib control group)
3066 subjects in Mexico (2299 in the Hib-MenCY-TT vaccine group and 767 in the Hib control group)

Number of subjects in study Hib-MenCY-TT-011 ESFU:
*Enrolled:*
4391 subjects (3278 in the Hib-MenCY group and 1113 in the Hib control group)
*Completed (Primary Total Vaccinated cohort):*
4133 subjects (3087 in the Hib-MenCY group and 1046 in the Hib control group)

Number of subjects in study Hib-MenCY-TT-009/011 pooled dataset (Table 10):
*Enrolled:*
8872 subjects (6638 in the Hib-MenCY group and 2234 in the Hib control group) and one subject not assigned a group
*Completed:*
8011 subjects (6002 in the Hib-MenCY group and 2009 in the Hib control group)

*Safety*:

*Pooled Primary Total Vaccinated cohort:*
8571* subjects all sites (6414 in the Hib-MenCY group and 2157 in the Hib control group)
4101 subjects in the US (3062 in the Hib-MenCY-TT vaccine group and 1039 in the Hib control group)
3866 subjects in Mexico (2899 in the Hib-MenCY-TT vaccine group and 967 in the Hib control group)
604 subjects in Australia (453 in the Hib-MenCY-TT vaccine group and 151 in the Hib control group)
**301 subjects from a single study site (referred to as site 24660 in Hib-MenCY-TT-009 and as site 35785 in Hib-MenCY-TT-011) were eliminated from the pooled Primary Total Vaccinated cohort due to GCP non-compliance by the site despite remediation efforts by the Sponsor).*

**Table 10 Number of subjects vaccinated, completed and withdrawn with reason for withdrawal by country (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011)**

| Country | Group | Number of subjects | | | Reason for withdrawal | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Vaccinated | Completed | Withdrawn | A | B | C | D | E | F | G | H |
| United States | Hib-MenCY | 3062 | 2789 | 273 | 8 | 3 | 31 | 109 | 27 | 27 | 28 | 40 |
| | Hib | 1039 | 942 | 97 | 0 | 2 | 6 | 46 | 9 | 12 | 9 | 13 |
| | Total | 4101 | 3731 | 370 | 8 | 5 | 37 | 155 | 36 | 39 | 37 | 53 |
| Mexico | Hib-MenCY | 2899 | 2765 | 134 | 8 | 0 | 10 | 30 | 26 | 51 | 9 | 0 |
| | Hib | 967 | 917 | 50 | 5 | 0 | 5 | 10 | 13 | 12 | 5 | 0 |
| | Total | 3866 | 3682 | 184 | 13 | 0 | 15 | 40 | 39 | 63 | 14 | 0 |
| Australia | Hib-MenCY | 453 | 448 | 5 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 1 |
| | Hib | 151 | 150 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| | Total | 604 | 598 | 6 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 1 |
| Total | Hib-MenCY | 6414 | 6002 | 412 | 16 | 3 | 41 | 143 | 53 | 78 | 37 | 41 |
| | Hib | 2157 | 2009 | 148 | 5 | 2 | 11 | 57 | 22 | 24 | 14 | 13 |
| | Total | 8571 | 8011 | 560 | 21 | 5 | 52 | 200 | 75 | 102 | 51 | 54 |

Hib-MenCY = Hib-MenCY-TT + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
Total= Hib-MenCY-TT+*Pediarix* (+ *Prevnar*/*Prevenar* if available) and *ActHib* +*Pediarix* (+*Prevnar*/*Prevenar* if available)
Vaccinated = number of subjects who were vaccinated in the study
Completed = number of subjects who completed last study visit
Withdrawn = number of subjects who did not come for the last visit
Reasons for withdrawal (Reasons C-H: not related to any adverse event):
A = Serious Adverse Event
B = Non-Serious Adverse Event
C = Protocol Violation
D = Consent Withdrawal
E = Migration from study area
F = Lost to Follow-up (subject with incomplete vaccination course)
G = Lost to Follow-up (subject with complete vaccination course)
H = Others

- Baseline data

Primary analysis cohort- Hib-MenCY-TT-011 only
The summary of demographic characteristics for the Primary Total Vaccinated cohort is presented in Table 12.

**Table 12 Summary of demographic characteristics (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| | | Hib-MenCY N = 3278 | | Hib N = 1113 | |
|---|---|---|---|---|---|
| **Characteristics** | **Parameter or Category** | **Age in Days** | | **Age in Days** | |
| **Age at dose 1** | Mean | 58.6 | | 59.0 | |
| | Standard Deviation | 10.45 | | 10.39 | |
| | Median | 60.0 | | 60.0 | |
| | Minimum | 42 | | 42 | |
| | Maximum | 96 | | 91 | |
| **Age at dose 2** | Mean | 122.7 | | 122.8 | |
| | Standard Deviation | 11.24 | | 11.57 | |
| | Median | 122.0 | | 122.0 | |
| | Minimum | 91 | | 99 | |
| | Maximum | 238 | | 223 | |
| **Age at dose 3** | Mean | 186.1 | | 186.5 | |
| | Standard Deviation | 13.15 | | 14.08 | |
| | Median | 185.0 | | 184.0 | |
| | Minimum | 148 | | 156 | |
| | Maximum | 322 | | 312 | |
| | | **n** | **%** | **n** | **%** |
| **Gender** | Female | 1576 | 48.1 | 557 | 50.0 |
| | Male | 1702 | 51.9 | 556 | 50.0 |
| **Ethnicity** | American Hispanic or Latino | 2403 | 73.3 | 798 | 71.7 |
| | Not American Hispanic or Latino | 875 | 26.7 | 315 | 28.3 |
| **Race** | African heritage / African American | 89 | 2.7 | 29 | 2.6 |
| | American Indian or Aaskan native | 0 | 0.0 | 1 | 0.1 |
| | Asian - Central/South Asian heritage | 2 | 0.1 | 0 | 0.0 |
| | Asian - East Asian heritage | 1 | 0.0 | 1 | 0.1 |
| | Asian - Japanese heritage | 0 | 0.0 | 2 | 0.2 |
| | Asian - Southeast Asian heritage | 3 | 0.1 | 0 | 0.0 |
| | Native Hawaiian/other Pacific islander | 1 | 0.0 | 2 | 0.2 |
| | White - Arabic / North African heritage | 13 | 0.4 | 2 | 0.2 |
| | White - Caucasian/European heritage | 784 | 23.9 | 271 | 24.3 |
| | Other: Hispanic | 2309 | 70.4 | 770 | 69.2 |
| | Other | 76 | 2.3 | 35 | 3.1 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+*Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
N = total number of subjects
n/% = number / percentage of subjects in a given category

The demographic profile was similar between groups. The mean age for the Hib-MenCY and Hib groups at Visit 1 (dose 1) was 58.7 days (ranging from 42 to 96 days) with a mean age of 58.6 days in the Hib-MenCY group and 59.0 days in the Hib group. The distribution of males and females were comparable between groups: the percentage of males was 51.9% in the Hib-MenCY group and 50.0% in the Hib group. The predominant ethnicity in both groups for the Primary Total Vaccinated cohort was American Hispanic/Latino (73.3% in the Hib-MenCY group and 71.7% in the Hib group). The predominant race was Hispanic (70.4% in the Hib-MenCY group and 69.2% in the Hib group), followed by Caucasian (23.9% in the Hib-MenCY group and 24.3% in the Hib group).

Primary analysis - pooled studies Hib-MenCY-TT-011 and Hib-MenCY-TT-009

The summary of demographic characteristics is presented in Table 13 for the Primary Total Vaccinated cohort for the pooled studies.

The demographic profile of the two treatment groups of subjects in the pooled studies (Primary Total Vaccinated cohort) was comparable with respect to mean age, gender and racial distribution. The mean age at the time of the first vaccination visit was 61.0 and 61.1 days, Hib-MenCY and Hib groups, respectively and just over half of the subjects in each group were male (51.7% and 51.1%, respectively). The predominant ethnicity in both groups for the Primary Total Vaccinated cohort was American Hispanic/Latino (50.9% in the Hib-MenCY group and 50.1% in the Hib group). The predominant race was Hispanic (46.8% in the Hib-MenCY group and 46.3% in the Hib group), followed closely by Caucasian (43.5% in the Hib-MenCY group and 44.3% in the Hib group). African heritage/African American represented 4.5% per group.

On a per country basis for the pooled studies, the mean age at the time of the first dose in each of the three countries ranged from 57.9 days to 63.7 days for the Hib-MenCY group and from 58.1 days to 64 days in the Hib group. The percentage of males ranged from 51.4% to 52.5% in the Hib-MenCY group, and from 47.0% to 52.8% in the Hib group. Race distribution varied by country: Caucasian was the predominant race for both groups in the US and Australia (77.2% and 93.6% for the Hib-MenCY group, US and Australia, respectively and 77.9% and 96.7% for the Hib group, respectively). In Mexico for pooled studies, 99.8% of the Hib-MenCY group and 99.7% of the Hib group were Hispanic.

The demographic profile of the pooled Primary ATP Cohort for Safety was comparable to the pooled Primary Total Vaccinated cohort.

**Table 13 Summary of demographic characteristics (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-011 and Hib-MenCY-TT-009)**

| Characteristics | Category/Parameter | Hib-MenCY N = 6414 | | Hib N = 2157 | |
|---|---|---|---|---|---|
| | | Age (Days) | | Age (Days) | |
| Age at dose 1 | Mean | 61.0 | | 61.1 | |
| | SD | 9.60 | | 9.58 | |
| | Median | 62.0 | | 62.0 | |
| | Minimum | 37 | | 40 | |
| | Maximum | 111 | | 116 | |
| Age at dose 2 | Mean | 123.7 | | 123.7 | |
| | SD | 11.16 | | 10.96 | |
| | Median | 123.0 | | 123.0 | |
| | Minimum | 77 | | 93 | |
| | Maximum | 238 | | 223 | |
| Age at dose 3 | Mean | 186.9 | | 186.9 | |
| | SD | 13.75 | | 13.70 | |
| | Median | 186.0 | | 186.0 | |
| | Minimum | 131 | | 148 | |
| | Maximum | 322 | | 312 | |
| | | n | % | n | % |
| Gender | Female | 3099 | 48.3 | 1055 | 48.9 |
| | Male | 3315 | 51.7 | 1102 | 51.1 |
| Ethnicity | American Hispanic or Latino | 3264 | 50.9 | 1081 | 50.1 |
| | Not American Hispanic or Latino | 3150 | 49.1 | 1076 | 49.9 |
| Race | African heritage/ African Amer. | 288 | 4.5 | 97 | 4.5 |
| | American Indian or Alaskan native | 17 | 0.3 | 3 | 0.1 |
| | Asian - Central/South Asian heritage | 14 | 0.2 | 2 | 0.1 |
| | Asian - East Asian heritage | 9 | 0.1 | 4 | 0.2 |
| | Asian - Japanese heritage | 4 | 0.1 | 4 | 0.2 |
| | Asian - Southeast Asian heritage | 25 | 0.4 | 3 | 0.1 |
| | Native Hawaiian or other Pacific Islander | 8 | 0.1 | 5 | 0.2 |
| | White - Arabic / North African heritage | 40 | 0.6 | 14 | 0.6 |
| | White - Caucasian / European heritage | 2788 | 43.5 | 955 | 44.3 |
| | Other: Hispanic | 3000 | 46.8 | 999 | 46.3 |
| | Other | 221 | 3.4 | 71 | 3.3 |

Hib-MenCY = Hib-MenCY-TT + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
N = total number of subjects
n/% = number / percentage of subjects in a given category
SD = standard deviation

- Efficacy results

No immunogenicity/efficacy data were accrued for the Hib-MenCY-TT-011 study.

- Safety results

The primary analysis of safety was based on the Primary Total Vaccinated cohort. A second analysis based on the Primary ATP safety cohort was to be performed if more than 5% of enrolled subjects were not eligible for inclusion in the Primary ATP cohort for safety analysis.

Within group analysis Hib-MenCY-TT-011 data analyzed separately and for pooled data from both studies

From Dose 1 (Day 0) through the Day 30 after the third dose and from Day 0 through the ESFU, the number and percentage of subjects reporting SAEs, NOCD, rash and ER visits were tabulated by group with exact 95% CI.

The verbatim reports of each AE were reviewed by a physician and the signs and symptoms were coded according to the MedDRA Dictionary for Adverse Reaction Terminology. The assessment of an AE as a NOCD was reviewed by the GSK Medical Monitor and clarified with the investigator as necessary.

The percentage of subjects with AEs from Day 0 through Day 30 and from Day 0 through the ESFU and its exact 95% CI were tabulated by group and by MedDRA preferred term for the Hib-MenCY-TT-011 data analyzed separately and the pooled data; however, for the pooled data analysis, only the percentage of subjects with SAEs were tabulated by group and by MedDRA preferred term for data collected within 30 days after vaccination.

Between groups analysis

Hib-MenCY-TT-011 data analyzed separately and for pooled data from both studies.

Differences between the Hib-MenCY and Hib groups were evaluated from Day 0 through the ESFU for the primary phase and from Day 0 until 30 days after dose 3 and for SAEs, within 31 days after each dose.

Per the RAP, differences were quantified in terms of relative risk. Using these relative risk differences, the common relative risk across study-countries, its 95% CI and the corresponding 2-sided P-value were based on exact conditional likelihood approach adjusted for the study-country effect. A test for homogeneity between study-countries was based on the exact Breslow & Day test.

Differences of the relative risk of SAEs, rash, NOCD and AEs resulting in ER visits, reported from Day 0 through the ESFU, between the Hib-MenCY group and the Hib group with exact 95% CI and 2-sided P-value, were evaluated taking into account the study and country effects. These differences were also evaluated by MedDRA Primary System Organ Class and Preferred Term for each specific SAE/AE.

In order to assess the effect of co-/concomitant vaccination on the incidence of SAEs and specific AEs several logistic analyses were performed [Hosmer, 2000]. Logistic models were fitted from the pooled safety data from studies Hib-MenCY-TT-009 and Hib-MenCY-TT-011 (no logistic analysis was performed for individual studies). A logistic model was fitted for each of the endpoints (occurrence of any SAE, NOCD, rash and AE resulting in ER visit, from Day 0 through the ESFU).

Only the occurrence of any (SAE/Specific AE) event was considered. If however, statistically significantly different incidences of specific AE SOC/preferred terms was found between the two groups (from the statistical comparisons performed in the pooled data), a logistic regression was considered for these cases.

Each logistic model aimed at explaining the occurrence or not of a selected event by means of the different variables (i.e., study vaccine, priming status, study and country).

Logistic regression with Maximum Likelihood estimates and Wald significance tests were fitted. Due to the high skewness and correlation between several prognostic factors, the impact of co-vaccination of a specific vaccine was considered independently from the co-vaccination status of the other vaccines. It was then studied whether the difference between incidences in the Hib-MenCY group and the Hib group, were varying significantly according to the co-vaccination of certain vaccines or not. Hence, each logistic regression model consisted in the occurrence or not of a specific adverse event regressed on:

*the treatment (Hib-MenCY vs. Hib),
*the country
*the study
*the co-vaccination status (of interest)
*The interaction between the treatment and the co-vaccination status (of interest).

**Primary Total vaccinated cohort safety analysis- study Hib-MenCY-TT-011**

Incidence of adverse events- within group analyses

The safety profiles of Hib-MenCY-TT/*ActHib* vaccines were evaluated with respect to the occurrence specific AE categories (SAEs, NOCD, rash and AEs prompting ER visits) from dose 1 (Day 0) up to Day 30 after dose 3 and from Day 0 through the ESFU for the Primary Total Vaccinated cohort. Comparisons between groups were performed on data collected from Day 0 through the ESFU. Separate analyses were not planned or performed for data collected only during the ESFU period (from Visit 4 up through the end of the primary ESFU period).

Overall incidence AE by category

A comparison of percentages of subjects reporting each event category by treatment group is presented in Table 19.

**Table 19 Comparison of percentage of subjects reporting SAEs, NOCD, rash, and AEs resulting in ER visits, reported from Day 0 through the ESFU, overall corrected by country (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| | 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 | P-Value | P-value interact |
| At least one symptom | 654 | 20.0 | 18.6 | 21.4 | 232 | 20.8 | 18.5 | 23.4 | 0.96 | 0.87 | 1.07 | 0.5109 | 0.9388 |
| SAE | 157 | 4.8 | 4.1 | 5.6 | 48 | 4.3 | 3.2 | 5.7 | 1.11 | 0.88 | 1.41 | 0.3952 | 1.0000 |
| NOCD | 66 | 2.0 | 1.6 | 2.6 | 25 | 2.2 | 1.5 | 3.3 | 0.91 | 0.65 | 1.29 | 0.6362 | 0.7294 |
| Rash | 386 | 11.8 | 10.7 | 12.9 | 134 | 12.0 | 10.2 | 14.1 | 0.98 | 0.85 | 1.13 | 0.8388 | 0.6144 |
| ER visit | 198 | 6.0 | 5.2 | 6.9 | 69 | 6.2 | 4.9 | 7.8 | 0.99 | 0.81 | 1.21 | 0.9415 | 0.6992 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
RR = relative risk
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting 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)
P-Value = 2-sided Exact Stratified Test for the RR conditional to number of cases
P-Value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies and countries

During the period from Day 0 through the ESFU, 20.0% of the subjects in the Hib-MenCY group and 20.8% subjects in the Hib group reported at least one symptom within one of the specified categories. Rash was the most frequently reported adverse event (11.8% and 12.0%, Hib-MenCY and Hib groups, respectively).

As shown in Table 19 there were no statistically significant differences between groups in terms of the total number of adverse events reported, as well as the percentages of SAEs, NOCD, rash and AEs leading to an ER visit. No statistically significant differences were found with the Breslow and Day tests indicating that the differences between Hib-MenCY and Hib did not vary across countries.

SAEs

A comparison of the percentage of subjects reporting SAEs from Day 0 through the ESFU classified by MedDRA Primary System Organ Class and Preferred Term for study Hib-MenCY-TT-011 is provided in Table 20 (not shown in this report). The percentages of subjects reporting SAEs from Day 0 through Day 30 after the third dose, classified by MedDRA Primary System Organ Class and Preferred Term are provided in Supplement 35 (not shown in this report).

At least one SAE was reported by 157 subjects (4.8%) in the Hib-MenCY group and 48 subjects (4.3%) in the Hib group. None of the SAEs were related to or possibly related to vaccination as assessed by the investigators.

Differences based on p-values were observed for the following SAEs (using preferred MedDRA Primary System Organ Class and Preferred Term):

*Bronchiolitis (1.2% for Hib-MenCY vs. 0.5% from Hib, p=0.0081).

*Viral infection (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).

*Dehydration (0.2% for Hib-MenCY vs. 0.4% from Hib, p=0.0335).

All other SAEs were comparable between the two groups. Approximately 70 SAEs were included in Table 20.

Fatal SAEs

As shown in Table 34 (Subjects with SAEs reported from Day 0 through the day preceding booster dose, by country (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)), of the 205 subjects in both groups who experienced at least one SAE during the study period through the ESFU, 12 subjects died (seven in the Hib-MenCY group and five in the Hib group). Nine of the deaths were reported within the 30 day study interval after each vaccine dose (four in Hib-MenCY group and five in Hib group). Three additional deaths (two in the Hib-MenCY group and one in the Hib group) were reported outside of the 30 day interval after vaccination (one of which occurred during the ESFU period).

None of the fatalities were vaccine-related according to the investigator.

Fatalities reported in the Hib-MenCY-TT-011 study, per group, with day of onset, duration and outcome are shown in Table 21.

**Table 21 Fatalities reported in the Hib-MenCY-TT-011 study, per group, with day of onset, duration and outcome**

| Sub. No. | Age at onset weeks | Sex | Preferred term | Dose | Day of onset | Duration (days) | Outcome |
|---|---|---|---|---|---|---|---|
| Hib-MenCY group United States | | | | | | | |
| 7729 | 14 | M | Sudden infant death syndrome | 1 | 38 | 1 | Fatal |
| Hib-MenCY group, Mexico | | | | | | | |
| 28 | 12 | F | Hypovolaemic shock | 1 | 14 | 8 | Fatal |
| 636 | 21 | M | Bronchiolitis | 2 | 16 | 11 | Fatal |
| | 22 | | Dehydration | 2 | 24 | 3 | Fatal |
| | 22 | | Gastroenteritis | 2 | 24 | 3 | Fatal |
| 1359 | 44 | M | Pneumonia | 3 | 77 | 9 | Fatal |
| 1403 | 11 | F | Sudden infant death syndrome | 1 | 37 | 1 | Fatal |
| 4021 | 7 | F | Sudden infant death syndrome | 1 | 10 | 1 | Fatal |
| 4302 | 13 | F | Pneumonia | 1 | 26 | 2 | Fatal |
| Hib group, Mexico | | | | | | | |
| 1325 | 19 | M | Pneumonia | 2 | 13 | 30 | Fatal |
| | 24 | | Cardiac failure congestive | 2 | 42 | 1 | Fatal |
| 3381 | 10 | M | Pneumonia | 1 | 24 | 28 | Fatal |
| 3420 | 11 | F | Sudden infant death syndrome | 1 | 25 | 1 | Fatal |
| 3786 | 10 | M | Sudden infant death syndrome | 1 | 22 | 1 | Fatal |
| 4241 | 18 | M | Broncho pneumonia | 2 | 16 | 8 | Fatal |
| | 18 | | Pharyngitis | 2 | 16 | 8 | Fatal |

No fatal SAEs were reported in the Hib group, US sites.
M= male
F = female



New onset of chronic disease

A comparison of the percentages of subjects reporting NOCD, from Day 0 through the ESFU classified by MedDRA Primary System Organ Class and Preferred Term are listed in Table 22. The percentages of subjects reporting NOCD for the Hib-MenCY-TT-011 study, from Day 0 through the ESFU classified by MedDRA Primary System Organ Class and Preferred Term on a per country basis, are provided in Supplement 36 (US) and Supplement 37 (Mexico). The percentages of subjects reporting NOCD, from Day 0 through Day 30 after the third dose classified by MedDRA Primary System Organ Class and Preferred Term are provided in Supplement 38 (Supplements not shown in this report).

Overall, the number of subjects experiencing NOCD was comparable and uncommon between the two groups: 2.0% and 2.2%, Hib-MenCY group and Hib group, respectively (Table 22).

There were no statistically significant differences between groups with regard to any specific NOCD reported except for milk allergy which was reported with a higher incidence in the Hib group although the incidence in both groups was very low (1/3278 [0.0%] for Hib-MenCY vs. 3/1113 [0.3%] for Hib, p=0.0099). Approximately 30 NOCD's were summarised in Table 22.

**Table 22** **Comparison of percentage of subjects reporting NOCD, classified by MedDRA Primary System Organ Class and Preferred Term, reported from Day 0 through the ESFU, overall corrected by country (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| Class (Primary System Organ code) | Preferred Term (code) | Hib-MenCY N = 3278 | | | | Hib N = 1113 | | | | Relative Risk (Hib-MenCY over Hib) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | | | 95% CI* | | P-Value | P-value interact |
| | | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | | |
| At least one symptom | | 66 | 2.0 | 1.6 | 2.6 | 25 | 2.2 | 1.5 | 3.3 | 0.91 | 0.65 | 1.29 | 0.6362 | 0.7294 |
| Congenital, familial and genetic (disorders 10010331) | Atrial septal defect (10003664) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.06 | INF | 1.0000 | 1.0000 |
| | Macrocephaly (10050183) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.84 | 0.1324 | 1.0000 |
| Gastrointestinal disorders (10017947) | Coeliac disease (10009839) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Gastrooesophageal reflux disease (10017885) | 5 | 0.2 | 0.0 | 0.4 | 4 | 0.4 | 0.1 | 0.9 | 0.43 | 0.15 | 1.26 | 0.1324 | 1.0000 |
| General disorders and administration site conditions (10018065) | Developmental delay (10012559) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.84 | 0.1324 | 1.0000 |
| Immune system disorders (10021428) | Drug hypersensitivity (10013700) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Food allergy (10016946) | 5 | 0.2 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.78 | INF | 0.1021 | 1.0000 |
| | Hypersensitivity (10020751) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Milk allergy (10027633) | 1 | 0.0 | 0.0 | 0.2 | 3 | 0.3 | 0.1 | 0.8 | 0.12 | 0.01 | 0.65 | 0.0099 | 1.0000 |
| | Multiple allergies (10028164) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Seasonal allergy (10048908) | 3 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.41 | INF | 0.3356 | 1.0000 |
| Infections and infestations (10021881) | Otitis media (10033078) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.5 | 0.35 | 0.03 | 4.78 | 0.5482 | 1.0000 |
| | Otitis media chronic (10033081) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.84 | 0.1324 | 1.0000 |
| | Rhinitis (10039083) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |

| Class (Primary System Organ code) | Preferred Term (code) | Hib-MenCY N = 3278 | | | | Hib N = 1113 | | | | Relative Risk (Hib-MenCY over Hib) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | | | 95% CI* | | P-Value | P-value interact |
| | | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | | |
| Investigations (10022891) | Cardiac murmur (10007586) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Oxycorticosteroids increased (10033315) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.84 | 0.1324 | 1.0000 |
| Metabolism and nutrition disorders (10027433) | Failure to thrive (10016165) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Malnutrition (10061273) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.06 | INF | 1.0000 | 1.0000 |
| Musculoskeletal and connective tissue disorders (10028395) | Delayed fontanelle closure (10054034) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Torticollis (10044074) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| Nervous system disorders (10029205) | Dystonia (10013983) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| Renal and urinary disorders (10038359) | Vesicoureteric reflux (10047370) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| Respiratory, thoracic and mediastinal disorders (10038738) | Asthma (10003553) | 5 | 0.2 | 0.0 | 0.4 | 3 | 0.3 | 0.1 | 0.8 | 0.58 | 0.19 | 1.93 | 0.4188 | 1.0000 |
| | Bronchial hyperreactivity (10066091) | 4 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.5 | 1.37 | 0.27 | 13.24 | 1.0000 | 0.4407 |
| | Cough (10011224) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Dyspnoea (10013968) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Rhinitis allergic (10039085) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| Skin and subcutaneous tissue disorders (10040785) | Dandruff (10011859) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Dermatitis (10012431) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.23 | INF | 0.6085 | 1.0000 |
| | Dermatitis atopic (10012438) | 5 | 0.2 | 0.0 | 0.4 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.78 | INF | 0.1021 | 1.0000 |
| | Dermatitis contact (10012442) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.79 | 0.1268 | 1.0000 |
| | Eczema (10014184) | 30 | 0.9 | 0.6 | 1.3 | 10 | 0.9 | 0.4 | 1.6 | 1.04 | 0.62 | 1.82 | 0.9995 | 1.0000 |
| | Rash (10037844) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Seborrhoeic dermatitis (10039793) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting 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)
P-Value = 2-sided Exact Stratified Test for the RR conditional to number of cases
P-Value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies and countries



Rash

A comparison of the percentages of subjects reporting specific types of rash, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term is provided in Table 23. The percentages of subjects reporting specific types of rash on a per country basis are shown in Supplement 39 and Supplement 40. The percentages of subjects reporting specific types of rash, from Day 0 through Day 30 after the third dose, classified by MedDRA Primary

System Organ Class and Preferred Term is provided in Supplement 41 (Supplements not shown in this report).

**Table 23** **Comparison of percentage of subjects reporting rash, classified by MedDRA Primary System Organ Class and Preferred Term, reported from Day 0 through the ESFU, overall corrected by country (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| Primary System Organ Class (code) | Preferred Term (code) | Hib-MenCY N = 3278 | | | | Hib N = 1113 | | | | Relative Risk (Hib-MenCY overHib) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 95% CI | | | | 95% CI | | | 95% CI* | | P- | P value |
| | | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | Value | interact |
| At least one symptom | | 386 | 11.8 | 10.7 | 12.9 | 134 | 12.0 | 10.2 | 14.1 | 0.98 | 0.85 | 1.13 | 0.8388 | 0.6144 |
| Skin and subcutaneous tissue disorders (10040785) | Dandruff (10011859) | 3 | 0.1 | 0.0 | 0.3 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.41 | INF | 0.3356 | 1.0000 |
| | Dermatitis (10012431) | 14 | 0.4 | 0.2 | 0.7 | 4 | 0.4 | 0.1 | 0.9 | 1.20 | 0.53 | 3.03 | 0.8232 | 0.0860 |
| | Dermatitis allergic (10012434) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.5 | 0.35 | 0.03 | 4.78 | 0.5482 | 1.0000 |
| | Dermatitis atopic (10012438) | 61 | 1.9 | 1.4 | 2.4 | 14 | 1.3 | 0.7 | 2.1 | 1.48 | 0.97 | 2.32 | 0.0679 | 0.1114 |
| | Dermatitis contact (10012442) | 6 | 0.2 | 0.1 | 0.4 | 3 | 0.3 | 0.1 | 0.8 | 0.68 | 0.24 | 2.22 | 0.5989 | 0.6829 |
| | Dermatitis diaper (10012444) | 75 | 2.3 | 1.8 | 2.9 | 26 | 2.3 | 1.5 | 3.4 | 0.98 | 0.71 | 1.37 | 0.9502 | 0.3136 |
| | Eczema (10014184) | 65 | 2.0 | 1.5 | 2.5 | 28 | 2.5 | 1.7 | 3.6 | 0.80 | 0.58 | 1.12 | 0.2020 | 0.3985 |
| | Eczema asteatotic (10014190) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Eczema nummular (10014201) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.06 | INF | 1.0000 | 1.0000 |
| | Erythema (10015150) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.79 | 0.1268 | 1.0000 |
| | Exfoliative rash (10064579) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Intertrigo (10022622) | 1 | 0.0 | 0.0 | 0.2 | 1 | 0.1 | 0.0 | 0.5 | 0.34 | 0.02 | 4.71 | 0.5389 | 0.6570 |
| | Petechiae (10034754) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Prurigo (10037083) | 3 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.5 | 1.01 | 0.18 | 10.23 | 1.0000 | 1.0000 |
| | Pustular psoriasis (10037575) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Rash (10037844) | 135 | 4.1 | 3.5 | 4.9 | 44 | 4.0 | 2.9 | 5.3 | 1.04 | 0.82 | 1.34 | 0.7740 | 0.5474 |
| | Rash erythematous (10037855) | 6 | 0.2 | 0.1 | 0.4 | 4 | 0.4 | 0.1 | 0.9 | 0.52 | 0.20 | 1.47 | 0.2333 | 1.0000 |
| | Rash generalised (10037858) | 8 | 0.2 | 0.1 | 0.5 | 1 | 0.1 | 0.0 | 0.5 | 2.72 | 0.64 | 24.38 | 0.2560 | 1.0000 |
| | Rash macular (10037867) | 3 | 0.1 | 0.0 | 0.3 | 1 | 0.1 | 0.0 | 0.5 | 1.04 | 0.19 | 10.53 | 1.0000 | 1.0000 |
| | Rash maculo-papular (10037868) | 4 | 0.1 | 0.0 | 0.3 | 2 | 0.2 | 0.0 | 0.6 | 0.69 | 0.18 | 3.13 | 0.7422 | 1.0000 |
| | Rash papular (10037876) | 8 | 0.2 | 0.1 | 0.5 | 3 | 0.3 | 0.1 | 0.8 | 0.92 | 0.34 | 2.88 | 1.0000 | 1.0000 |
| | Rash scarlatiniform (10037890) | 2 | 0.1 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.23 | INF | 0.6175 | 1.0000 |
| | Seborrhoeic dermatitis (10039793) | 18 | 0.5 | 0.3 | 0.9 | 6 | 0.5 | 0.2 | 1.2 | 1.01 | 0.52 | 2.14 | 1.0000 | 1.0000 |
| | Swelling face (10042682) | 1 | 0.0 | 0.0 | 0.2 | 0 | 0.0 | 0.0 | 0.3 | INF | 0.07 | INF | 1.0000 | 1.0000 |
| | Urticaria (10046735) | 25 | 0.8 | 0.5 | 1.1 | 10 | 0.9 | 0.4 | 1.6 | 0.86 | 0.50 | 1.52 | 0.6443 | 0.8814 |
| | Urticaria papular (10046750) | 0 | 0.0 | 0.0 | 0.1 | 1 | 0.1 | 0.0 | 0.5 | 0.00 | 0.00 | 1.84 | 0.1324 | 1.0000 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit or 95% CI* = 95% confidence interval for relative risk (Exact Stratified Conditional to total number of cases)
P-Value = 2-sided Exact Stratified Test for the RR conditional to number of cases
P-Value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies and countries

Overall, the number of subjects experiencing rash was comparable between the two groups (11.8% of the subjects in the Hib-MenCY group and 12% in the Hib group, Table 23). The most common type of rash reported was "rash" followed by diaper rash and eczema in both groups. There was one case of petechiae reported in the Hib-MenCY group and none in the Hib group, urticaria (hives) was reported by 0.8% and 0.9% of the subjects in the Hib-MenCY group and Hib group, respectively, and idiopathic thrombocytopenic purpura was not reported.
There were no statistically significant differences between groups for any type of rash reported.

Emergency room (ER) visits

Table 24 (not shown here) presents a comparison of the percentage of subjects reporting adverse events resulting in an ER visit, reported from Day 0 of the first dose through the ESFU period for study Hib-MenCY-TT-011, classified by MedDRA Primary System Organ Class and Preferred Term. Table 24 contains approximately 100 different types of adverse events resulting in an ER visit.

The percentage of subjects reporting AEs resulting in an ER visit, presented on a per country basis are provided in Supplement 43. The percentage of subjects reporting AEs resulting in an ER visit from day 0 after dose 1 through Day 30 after dose 3, classified by MedDRA Primary System Organ Class and Preferred Term (Primary Total vaccinated cohort) is presented in Supplement 44 (Supplements not shown in this report).

Overall, the number of subjects with an AE resulting in an ER visit was comparable between the two groups: (6.0% of the subjects in the Hib-MenCY group and 6.2% in the Hib group). In both groups, pyrexia (0.9% in the Hib-MenCY group and 0.8% in the Hib group), bronchiolitis (0.8% in both groups) and gastroenteritis and otitis media (0.8% and 1.0%, Hib-MenCY and Hib groups, respectively for each AE) were the most frequently reported AEs resulting in an ER visit. All other AEs resulting in an ER visit were infrequently reported (<1.0% of subjects) in both groups.

There were no statistically significant differences between groups for any type of AE resulting in an ER visit reported except for the following:

*Abnormal faeces (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).

*Constipation (0.0% for Hib-MenCY vs. 0.3% from Hib, p=0.0099).

*Hair-thread tourniquet syndrome (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).

Incidence of adverse events in sub-groups defined by coadministration of other vaccines- within group analyses for Study Hib-MenCY-TT-011

Co-administration for the rotavirus vaccine, *Pediarix* and *Prevnar* vaccines was defined, per the RAP, as administration on the same day of a study vaccine dose. Concomitant administration for the influenza vaccines was defined, per the RAP, as administration between 28 days before to 7 days after a study vaccine dose. A summary of the concomitantly administered vaccines by dose for the Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011 is presented in Table 25.

**Table 25 Summary of concomitantly administered vaccines by dose (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| Previous Dose of Hib-MenCY-TT or Hib | Concomitant vaccine | Hib-MenCY N = 3278 | | Hib N = 1113 | | Total N = 4391 | |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % |
| 1 | Influenza | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | *RotaTeq* | 597 | 18.2 | 202 | 18.1 | 799 | 18.2 |
| | *Pediarix* | 3278 | 100 | 1113 | 100 | 4391 | 100 |
| | *Prevnar* | 3274 | 99.9 | 1112 | 99.9 | 4386 | 99.9 |
| 2 | Influenza | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | *RotaTeq* | 590 | 18.0 | 196 | 17.6 | 786 | 17.9 |
| | *Pediarix* | 3155 | 96.2 | 1071 | 96.2 | 4226 | 96.2 |
| | *Prevnar* | 3153 | 96.2 | 1071 | 96.2 | 4224 | 96.2 |
| 3 | Influenza | 27 | 0.8 | 14 | 1.3 | 41 | 0.9 |
| | *RotaTeq* | 569 | 17.4 | 189 | 17.0 | 758 | 17.3 |
| | *Pediarix* | 3120 | 95.2 | 1056 | 94.9 | 4176 | 95.1 |
| | *Prevnar* | 3115 | 95.0 | 1055 | 94.8 | 4170 | 95.0 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified dose in each group or in total
Any = number and percentage of subjects receiving at least one dose

At least 99.5% of the subjects in each group were fully co-vaccinated with *Pediarix* and *Prevnar* during the Hib-MenCY-TT-011 study. Most subjects (at least 98.7%, overall) did not receive a concomitant influenza vaccine and most did not receive a concomitant rotavirus vaccine (at least 80.7%, overall) during the study. Only 0.9% of all subjects in both groups received a concomitant

influenza vaccine, which was only given with dose 3 of the Hib-MenCY-TT and *ActHib* vaccines. Rotavirus vaccine was co-administered with 17.3% to 18.2% of each dose of Hib-MenCY-TT and *ActHib* vaccines.
On a per country basis, co-administration of other vaccines (*Pediarix*, *Prevnar,* rotavirus and influenza) with Hib-MenCY-TT and *ActHib* vaccines with each of the three doses was similar between countries except for rotavirus vaccine which was given with approximately 60% of each of the three doses of Hib-MenCY-TT and *ActHib* vaccines in the United States vs. 0% in Mexico. Thus, the analysis per rotavirus co-vaccination status was performed for the United States subjects only.

All subjects enrolled in Mexico were fully co-vaccinated with *Pediarix* and *Prevnar* vaccines and thus the analysis per full co-vaccination status was performed for the United States subjects only.
None of the Mexican subjects received an influenza vaccine co-administered with a study dose and therefore, the analysis per influenza co-vaccination status was only performed for subjects enrolled in the United States.

**Rap's comment**: The marked wording above is somewhat confusing in that all co-vaccination analyses were performed on United States subjects only.

*Presentation based on Pediarix and Prevnar vaccination status*
Subjects were grouped according to whether they were fully co-vaccinated with *Pediarix* and *Prevnar* (both vaccines co-administered with all Hib-MenCY-TT/*ActHib* vaccines doses) or not fully co-vaccinated (*Pediarix* or *Prevnar* not co-administered with all Hib-MenCY-TT/*ActHib* vaccines doses).
The percentage of subjects (United States sites only) with SAEs, NOCD, rash and AEs resulting in ER visits from Day 0 through the ESFU, grouped according to whether or not a subject was fully co-vaccinated with *Pediarix* and *Prevnar* vaccines are presented in Supplement 46.
The percentages of subjects reporting specific SAEs, NOCD, rash and AEs resulting in ER visits, respectively, from Day 0 through the ESFU by Primary Organ System Class and Preferred Term, based on *Pediarix* and *Prevnar* vaccination status, in United States (Primary Total Vaccinated cohort) are presented in Supplement 47, Supplement 48, Supplement 49 and Supplement 50 .
For the fully co-vaccinated sub-category, the percentages of subjects in each treatment group reporting SAEs, NOCD, rashes, and AEs leading to ER visits were comparable.
There were some observed differences between groups for the subset who were not fully co-vaccinated with *Pediarix* and *Prevnar*; however, the numbers of subjects in this group were small (18 and 4 subjects in the Hib-MenCY and Hib groups, respectively), and so clinically meaningful conclusions cannot be drawn.

**Supplement 46 Percentage of subjects with SAEs, NOCD, rash and AEs resulting in ER visits from Day 0 through the ESFU, by priming full co-vaccination status, for United States (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| | Not fully co-vaccinated | | | | | | | | Fully co-vaccinated | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hib-MenCY N = 18 | | | | Hib N = 4 | | | | Hib-MenCY N = 961 | | | | Hib N = 342 | | | |
| | | | 95% CI | | | | 95% CI | | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | 7 | 38.9 | 17.3 | 64.3 | 1 | 25.0 | 0.6 | 80.6 | 347 | 36.1 | 33.1 | 39.2 | 125 | 36.5 | 31.4 | 41.9 |
| SAE | 1 | 5.6 | 0.1 | 27.3 | 0 | 0.0 | 0.0 | 60.2 | 52 | 5.4 | 4.1 | 7.0 | 17 | 5.0 | 2.9 | 7.8 |
| New onset of chronic illness | 3 | 16.7 | 3.6 | 41.4 | 0 | 0.0 | 0.0 | 60.2 | 60 | 6.2 | 4.8 | 8.0 | 23 | 6.7 | 4.3 | 9.9 |
| Rash | 2 | 11.1 | 1.4 | 34.7 | 1 | 25.0 | 0.6 | 80.6 | 193 | 20.1 | 17.6 | 22.8 | 62 | 18.1 | 14.2 | 22.6 |
| Emergency room visit | 6 | 33.3 | 13.3 | 59.0 | 0 | 0.0 | 0.0 | 60.2 | 156 | 16.2 | 14.0 | 18.7 | 54 | 15.8 | 12.1 | 20.1 |

Fully co-vaccinated: subjects with *Pediarix* and *Prevnar* co-administered with all Hib-MenCY-TT/*ActHib* vaccines doses
Not fully co-vaccinated: subjects with *Pediarix* or *Prevnar* not co-administered with all Hib-MenCY/ *ActHib* vaccines doses.
Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

*Presentation based on rotavirus vaccination status*

Subjects were grouped according to whether they received the rotavirus vaccine, *RotaTeq* co-administered with all three Hib-MenCY-TT/*ActHib* vaccines doses (*completely covaccinated), RotaTeq* vaccine co-administered with at least one but not all Hib-MenCYTT/*ActHib* vaccines doses (partly co-vaccinated) or *RotaTeq* vaccine not co-administered with any Hib-MenCY-TT/*ActHib* vaccines dose (not co-vaccinated).

The percentages of subjects reporting specific SAEs, new onset of chronic illness, rash, and AEs resulting in ER visits through the entire ESFU period, based on rotavirus vaccination status, for US subjects by Primary Organ System Class and Preferred Term (Primary Total Vaccinated cohort) are presented in Supplement 51. Results in rotavirus fully-co-vaccinated, partially co-vaccinated and no-co-vaccinated cohorts were clinically within the same range for each category of AE.

The percentages of subjects reporting specific SAEs, NOCD, rash and AEs resulting in ER visits, respectively, from Day 0 through the ESFU, by priming rotavirus vaccination status, in United States (Primary Total Vaccinated cohort) are presented in Supplement 52, Supplement 53, Supplement 54, Supplement 55. The rates of reported SAEs, NOCD, rashes, and AEs resulting in ER visits were clinically within the same range in subjects from the United States regardless of rotavirus co-vaccination status.

**Supplement 51 Percentage of subjects with SAEs, NOCD, rash and AEs resulting in ER visits from Day 0 through the ESFU, by priming rotavirus vaccination status, in United States (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| AE category | Rotavirus vaccine not co-vaccinated | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Hib-MenCY N = 348 | | | | Hib N = 135 | | | |
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | 123 | 35.3 | 30.3 | 40.6 | 51 | 37.8 | 29.6 | 46.5 |
| SAE | 22 | 6.3 | 4.0 | 9.4 | 8 | 5.9 | 2.6 | 11.3 |
| New onset of chronic illness | 22 | 6.3 | 4.0 | 9.4 | 9 | 6.7 | 3.1 | 12.3 |
| Rash | 67 | 19.3 | 15.2 | 23.8 | 30 | 22.2 | 15.5 | 30.2 |
| Emergency room visit | 58 | 16.7 | 12.9 | 21.0 | 19 | 14.1 | 8.7 | 21.1 |
| | Rotavirus vaccine partly co-vaccinated | | | | | | | |
| | Hib-MenCY N = 103 | | | | Hib N = 34 | | | |
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | 33 | 32.0 | 23.2 | 42.0 | 13 | 38.2 | 22.2 | 56.4 |
| SAE | 2 | 1.9 | 0.2 | 6.8 | 3 | 8.8 | 1.9 | 23.7 |
| New onset of chronic illness | 8 | 7.8 | 3.4 | 14.7 | 1 | 2.9 | 0.1 | 15.3 |
| Rash | 23 | 22.3 | 14.7 | 31.6 | 6 | 17.6 | 6.8 | 34.5 |
| Emergency room visit | 10 | 9.7 | 4.8 | 17.1 | 5 | 14.7 | 5.0 | 31.1 |
| | Rotavirus vaccine fully co-vaccinated | | | | | | | |
| | Hib-MenCY N = 528 | | | | Hib N = 177 | | | |
| | | | 95% CI | | | | 95% CI | |
| | n | % | LL | LL | UL | % | LL | UL |
| At least one symptom | 198 | 37.5 | 33.4 | 28.0 | 42.5 | 35.0 | 28.0 | 42.5 |
| SAE | 29 | 5.5 | 3.7 | 1.3 | 7.2 | 3.4 | 1.3 | 7.2 |
| New onset of chronic illness | 33 | 6.3 | 4.3 | 4.0 | 12.2 | 7.3 | 4.0 | 12.2 |
| Rash | 105 | 19.9 | 16.6 | 10.3 | 21.4 | 15.3 | 10.3 | 21.4 |
| Emergency room visit | 94 | 17.8 | 14.6 | 11.7 | 23.3 | 16.9 | 11.7 | 23.3 |

Rotavirus vaccine completely co-vaccinated: subjects with *RotaTeq* vaccine co-administered with all three Hib-MenCY-TT/*ActHib* vaccines dose
Rotavirus vaccine partly co-vaccinated: subjects with *RotaTeq* vaccine co-administered with at least one but not all Hib-MenCY-TT/*ActHib* vaccines doses.
Rotavirus vaccine not co-vaccinated: subjects with *RotaTeq* vaccine not co-administered with any Hib-MenCY-TT/*ActHib* vaccines dose.
Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects in each group included in the considered cohort
n/% = number/percentage of subjects receiving the specified total number of doses
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit



*Presentation based on influenza vaccination status*

Subjects were grouped according to whether they received concomitant influenza vaccine (influenza vaccine concomitantly administered with at least one Hib-MenCY-TT/*ActHib* vaccine dose) or not (influenza vaccine not concomitantly administered with any Hib-MenCY-TT/*ActHib* vaccine dose).

The percentages of subjects with SAEs, NOCD, rash, and AEs resulting in ER visits through the entire ESFU period, based on influenza vaccination status, for US subjects (Primary Total Vaccinated cohort) are presented in Supplement 56. The percentages of subjects reporting specific SAEs, NOCD, rash and AEs resulting in ER visits from Day 0 through the ESFU, by influenza vaccination status, by Primary Organ System Class and Preferred Term, in United States (Primary Total Vaccinated cohort) are presented in Supplement 57 through Supplement 60.

For US subjects who were not given concomitant, influenza vaccine the percentages of subjects in each treatment group reporting SAEs, NOCD, rashes, and AEs leading to ER visits were comparable. There were some observed differences between groups for the subset who was given concomitant influenza vaccine; however, the numbers of subjects in this group was small

(27 and 14 subjects in the Hib-MenCY and Hib groups, respectively), and so clinically meaningful conclusions cannot be drawn.

**Supplement 56 Percentage of subjects with SAEs. NOCD, rash and AEs resulting in ER visits from Day 0 through the ESFU, by priming influenza vaccination status, for United States (Primary Total Vaccinated cohort, Study Hib-MenCY-TT-011)**

| | Influenza not co-vaccinated | | | | | | | | Influenza co-vaccinated | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hib-MenCY N = 952 | | | | Hib N = 332 | | | | Hib-MenCY N = 27 | | | | Hib N = 14 | | | |
| | | | 95% CI | | | | 95% CI | | | | 95% CI | | | | 95% CI | |
| | n | % | LL | UL | n | % | LL | UL | n | % | LL | UL | n | % | LL | UL |
| At least one symptom | 348 | 36.6 | 33.5 | 39.7 | 120 | 36.1 | 31.0 | 41.6 | 6 | 22.2 | 8.6 | 42.3 | 6 | 42.9 | 17.7 | 71.1 |
| SAE | 53 | 5.6 | 4.2 | 7.2 | 16 | 4.8 | 2.8 | 7.7 | 0 | 0.0 | 0.0 | 12.8 | 1 | 7.1 | 0.2 | 33.9 |
| New onset of chronic illness | 63 | 6.6 | 5.1 | 8.4 | 21 | 6.3 | 4.0 | 9.5 | 0 | 0.0 | 0.0 | 12.8 | 2 | 14.3 | 1.8 | 42.8 |
| Rash | 194 | 20.4 | 17.9 | 23.1 | 59 | 17.8 | 13.8 | 22.3 | 1 | 3.7 | 0.1 | 19.0 | 4 | 28.6 | 8.4 | 58.1 |
| Emergency room visit | 157 | 16.5 | 14.2 | 19.0 | 52 | 15.7 | 11.9 | 20.0 | 5 | 18.5 | 6.3 | 38.1 | 2 | 14.3 | 1.8 | 42.8 |

Hib-MenCY = Hib-MenCY + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* (+ *Prevnar*/*Prevenar* if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

*Adverse events leading to premature discontinuation of study vaccine and/or study*
study Hib-MenCY-TT-011
Among the 4391 subjects of the Primary Total Vaccinated cohort, 14 subjects were withdrawn from the active phase (9 in the Hib-MenCY group and 5 in the Hib group) due to an SAE and 1 subject (in the Hib group) due to an AE. Individual case narratives for these adverse events are provided in the SAE CIOMS Section 12.
The 15 withdrawals (9 in the Hib-MenCY group and 6 in the Hib group) were caused by the following AEs:
*five subjects died from sudden infant death syndrome, that occurred after the first dose (subject numbers 7729, 1403, 4021 in the Hib-MenCY group and numbers 3420 and 3786 in the Hib group)- not related to vaccination.
*four subjects died from pneumonia (number 4302 in the Hib-MenCY group and numbers 1325 [pneumonia and congestive heart failure], 3381, and 4241 in the Hib group). These four cases occurred after the first or second dose. None were related to vaccination.
*one subject (number 28 in the Hib-MenCY group) died from hypovolaemic shock 14 days after the first dose- not related to vaccination.
*one subject (636 in the Hib-MenCY group) died from bronchiolitis, dehydration and gastroenteritis 24 days after the second dose- not related to vaccination.
*one subject (number 3535 in the Hib-MenCY group) experienced nystagmus eight days after the first dose - not related to vaccination
*two subjects (numbers 4111 and 8922, in the Hib-MenCY group) experienced febrile seizure . 57 days after the first dose, and 65 days after the second dose, respectively not related to vaccination.
*one subject (number 6031, Hib group) experienced a non serious AE (pyrexia) on the day of the second dose which led to an ER visit. The parents withdrew their child from the study following this event. The AE was considered to be related to vaccination.
One additional subject (number 1359 in the Hib-MenCY group), experienced an AE that occurred 77 days after the third vaccine dose (i.e., during the ESFU period). This subject died following a diagnosis of pneumonia: this AE was considered by the investigator to be unrelated to vaccination.

*Safety conclusions for Hib-MenCY-TT-011*
There were no statistically significant differences between groups in terms of the total number of adverse events reported, as well as the percentages of SAEs, NOCD, rash and AEs leading to an ER visit.

At least one SAE was reported by 157 subjects (4.8%) in the Hib-MenCY group and 48 (4.3%) in the Hib group. None of the SAEs were related to or possibly related to vaccination as assessed by the investigators.
Differences for the individual SAE, NOCD, rash, and AE leading to ER visit terms were calculated based on relative risks, with statistical significance assigned to a p-value ≤0.05. Because of the large number of comparisons made, and because no multiplicity adjustments were made, the risk of detecting differences due to chance alone was high.
Nonetheless, incidences of SAEs using preferred MedDRA Primary System Organ Class and Preferred Term were comparable (p-value >0.05) between the two groups except for the following:
*SAE: Bronchiolitis (1.2% for Hib-MenCY vs. 0.5% from Hib, p=0.0081).
*SAE: Viral infection (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).
*SAE: Dehydration (0.2% for Hib-MenCY vs. 0.4% from Hib, p=0.0335).
There were 12 fatalities reported during the study (seven in the Hib-MenCY group and five in the Hib group), none of which were vaccine-related according to the investigator.
Overall, the percentage of subjects experiencing NOCD was uncommon and comparable between the two groups: 2.0% and 2.2%, Hib-MenCY group and Hib group, respectively.
There were no statistically significant differences between groups with regard to any specific NOCD reported except for milk allergy (0.0% for Hib-MenCY vs. 0.3% from Hib, p=0.0099).
Overall, the percentage of subjects experiencing any type of rash was comparable between the two groups (11.8% of the subjects in the Hib-MenCY group and 12.0% in the Hib group). There were no statistically significant differences between groups for any type of rash reported.
The number of subjects with an AE resulting in an ER visit was comparable between the two groups: (6.0% of the subjects in the Hib-MenCY group and 6.2% in the Hib group).
All other adverse events resulting in an ER visit were infrequently reported (<1.0% of subjects) in both groups.
There were no statistically significant differences between groups for any type of AE resulting in an ER visit reported except for the following:
*Abnormal feces (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).
*Constipation (0.0% for Hib-MenCY vs. 0.3% from Hib, p=0.0099).
* Hair-thread tourniquet syndrome (0.0% for Hib-MenCY vs. 0.2% from Hib, p=0.0088).
No statistically significant Breslow and Day test was found either overall per unsolicited symptom type or by preferred MedDRA Primary System Organ Class and Preferred Term indicating that the differences between Hib-MenCY and Hib groups did not vary across countries.
The few statistically significant differences did not amount to a clinically significant trend in the occurrence of any specific pathology and therefore, the overall safety profile regarding specific unsolicited symptoms of Hib-MenCY group is similar to that of the Hib group.

**Total vaccinated cohort analysis- pooled studies Hib-MenCY-TT-009 and -011**
Incidence of adverse events- within group analyses on pooled data
The primary study objective for the pooled data set was to evaluate the safety profile of Hib-MenCY-TT vaccine compared to *ActHib* vaccine with respect to the occurrence specific adverse event categories from Day 0 through Day 30 after the third dose and from Day 0 through the ESFU.
The descriptive and comparative analyses were conducted on the incidence of each category of AE for the period from Day 0 up to day 30 after the third dose and from Day 0 through the ESFU and are presented in section 7.3.1.1 (section not shown in this report).
For each specific AE category, the detailed descriptive and comparative analyses on the incidence of each AE classified by MedDRA for the period from Day 0 through the ESFU are presentedin section 7.3.1.2 to 7.3.1.5. The descriptive analyses from Day 0 to Day 30 after the third dose were performed on each dataset separately; see study report Hib-MenCY-TT-009 for data for that study and Section 7.2 for Hib-MenCY-TT-011. A comparison of percentage of subjects with SAEs reported within the 31-days (Days 0-30) post-vaccination period was provided in Supplement 67referred to in section 7.3.1.2.

The analyses per co-administration status presented in section 7.3.1.6.
The endpoints of interest for the pooled data are the same as those for the Hib-MenCYTT-011 data presented separately.

*Overall incidence by category*
The overall incidences of the specified categories of AEs per group reported from Day 0 through Day 30 after dose 3 are presented in Table 26 for the (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011).

**Table 26** **Comparison of percentage of subjects with SAEs, NOCD, rash and AEs resulting in ER visits from day 0 after dose 1 through Day 30 after dose 3 (Primary Total Vaccinated Cohort, Studies Hib-MenCY-TT-009 and -011)**

| | Hib-MenCY N = 6414 | | | | Hib N = 2157 | | | | Relative Risk (Hib-MenCY over Hib) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | | | 95% CI* | | | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | P-Value | P-value interact |
| At least one symptom | 975 | 15.2 | 14.3 | 16.1 | 334 | 15.5 | 14.0 | 17.1 | 0.98 | 0.90 | 1.08 | 0.7226 | 0.5603 |
| SAE | 173 | 2.7 | 2.3 | 3.1 | 57 | 2.6 | 2.0 | 3.4 | 1.02 | 0.82 | 1.27 | 0.8892 | 0.5281 |
| NOCD | 143 | 2.2 | 1.9 | 2.6 | 49 | 2.3 | 1.7 | 3.0 | 0.99 | 0.78 | 1.25 | 0.9453 | 0.9390 |
| Rash | 621 | 9.7 | 9.0 | 10.4 | 209 | 9.7 | 8.5 | 11.0 | 1.00 | 0.89 | 1.12 | 1.0000 | 0.7112 |
| ER visit | 259 | 4.0 | 3.6 | 4.5 | 91 | 4.2 | 3.4 | 5.2 | 0.96 | 0.81 | 1.15 | 0.6811 | 0.9033 |

HibMenCY = Hib-MenCY-TT + Pediarix ( + Prevnar/Prevenar if available)
Hib= ActHib + Pediarix ( + Prevnar/Prevenar if available)
AE=adverse event
SAE= serious adverse event
NOCD= new onset chronic disease
ER= emergency room
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting 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)
P-Value = 2-sided Exact Stratified Test for the RR conditional to number of cases
P-Value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies and countries

A comparison of percentages of subjects reporting each event category per treatment from Day 0 through the ESFU, in terms of relative risk for the Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011 is presented in Table 27.
A total of 22.0% subjects in the Hib-MenCY group and 22.6% subjects in the Hib group reported at least one symptom within one of the specified categories, during the protocol defined follow-up period for the pooled studies. Rash was the most frequently reported AE (13.3% and 13.4%, Hib-MenCY and Hib groups, respectively).

**Table 27** **Comparison of percentage of subjects reporting SAEs, NOCD, rash, and AEs resulting in ER visits, reported from Day 0 through the ESFU, overall corrected by study and country (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011)**

| | Hib-MenCY N = 6414 | | | | Hib N = 2157 | | | | Relative Risk (Hib-MenCY over Hib) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95% CI | | | | 95% CI | | | 95% CI* | | | |
| | n | % | LL | UL | n | % | LL | UL | RR | LL | UL | P-Value | P-value interact |
| At least one symptom | 1409 | 22.0 | 21.0 | 23.0 | 487 | 22.6 | 20.8 | 24.4 | 0.98 | 0.91 | 1.05 | 0.5188 | 0.7144 |
| SAE | 283 | 4.4 | 3.9 | 4.9 | 98 | 4.5 | 3.7 | 5.5 | 0.97 | 0.82 | 1.15 | 0.7588 | 0.7352 |
| NOCD | 229 | 3.6 | 3.1 | 4.1 | 77 | 3.6 | 2.8 | 4.4 | 1.00 | 0.83 | 1.21 | 1.0000 | 0.9258 |
| Rash | 856 | 13.3 | 12.5 | 14.2 | 288 | 13.4 | 11.9 | 14.9 | 1.00 | 0.91 | 1.10 | 0.9974 | 0.8166 |
| ER visit | 415 | 6.5 | 5.9 | 7.1 | 141 | 6.5 | 5.5 | 7.7 | 1.00 | 0.87 | 1.14 | 0.9822 | 0.4794 |

Hib-MenCY = Hib-MenCY-TT + Pediarix ( + Prevnar/Prevenar if available)
Hib = ActHib + Pediarix ( + Prevnar/Prevenar if available)
ESFU = Extended Safety Follow-up from visit 4 until booster vaccination at Study Month 10-13; for subjects who did not receive a full priming series, until all safety information was collected six months after the last vaccination and before the booster; and for subjects who did not receive a booster dose, until the last observation in the database.
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting 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)
P-Value = 2-sided Exact Stratified Test for the RR conditional to number of cases
P-Value interact = 2-sided Exact Breslow & Day Test for heterogeneity across studies and countries

There were no statistically significant differences in the overall rates of SAEs, NOCD, rashes, and AEs leading to ER visits between the two groups.
The overall incidences of the specified categories of AEs per group reported from Day 0 through the ESFU for the (Primary Total Vaccinated cohort, pooled studies Hib-MenCYTT-009 and -011), presented on a per country basis are provided in Supplement 61.
Overall, AE reporting appeared to be less frequent among subjects in Mexico compared to those in the US and Australia (for at least one symptom, NOCD, rash and ER visits).
SAEs appeared to be reported similarly among the three countries. The Breslow and Day tests were not statistically significant, indicating that the differences between Hib-MenCY and Hib did not vary across countries.

*SAEs - pooled studies*
A comparison of the percentages of subjects reporting SAEs in the pooled studies, classified by MedDRA Primary System Organ Class and Preferred Term for the period from Day 0 through the ESFU are presented in Table 28. The percentages of subjects reporting SAEs in the pooled studies, classified by MedDRA Primary System Organ Class and Preferred Term for the period from Day 0 through the ESFU are provided in Supplement 62, overall and per country in Supplement 63 (United States) and Supplement 64 (Mexico) and Supplement 65 (Australia).
A summary of subjects reporting SAEs within the 31 day follow-up after any Hib-MenCY-TT or *ActHib* vaccine dose per study is provided in Supplement 66. Supplement 67 provides a comparison of percentage of subjects with SAEs reported within the 31-days (Days 0-30) post-vaccination period, overall corrected by study and country (Primary Total Vaccinated Cohort, Studies Hib-MenCY-TT-009 and -011).
A listing of subjects with fatal SAEs by study and country are presented in Table 29. The SAE Council for International Organizations of Medical Sciences (CIOMS) reports and Summary of SAEs reported (Table 35) are provided in Section 12.1. One SAE (bronchiolitis in the HibMenCY-TT-009 study, subject 007) was erroneously attributed to the Hib-MenCY group instead of the Hib group. More detail is provided in the HibMenCY-TT-009 study report.

At least one SAE was reported for 4.4% of the subjects from the pooled studies in the Hib-MenCY group and for 4.5% in the Hib group. Based on the p-values, the difference in the

percentages of each type of SAE reported by preferred MedDRA Primary System Organ Class and Preferred Term were not statistically significant between groups except for the following:
*Incidences of SAEs that were statistically higher in the Hib-MenCY group:*
*SAE: bronchiolitis (0.9% vs. 0.5%, p=0.0155) and urinary tract infection (0.2% vs. 0.0%, p=0.0491).
*Incidences of SAEs that were statistically higher in the Hib group:*
*SAE: vomiting (0.0% vs. 0.1%, p=0.0409) and influenza (0.0% vs. 0.1%, p=0.0083) and bronchopneumonia ((0.3% vs. 0.6%, p= 0.0157).
As shown in Table 35, all except two SAEs were unrelated to vaccination according to the investigator. The two subjects with a vaccine-related SAE (numbers 342 and 4822 from the -009 study, Hib-MenCY group) experienced pyrexia on the day of the first dose, lasting three days with a maximum temperature of 103.3 °F rectal for subject 342 and 103.0 °F axillary for subject 4822. Both subjects recovered without sequelae.

The incidences of SAEs in each group appeared similar among the three countries. At least one SAE was reported within 31 days after a study vaccine dose for 1.8% (113/6414) subjects in the Hib-MenCY group and for 1.9% (41/2157) subjects in the Hib group. There were no statistically significant differences in the percentages of subjects reporting any specific SAE between groups based on p-values. Pyrexia reported after dose 1 in the Hib-MenCY-009 for two subjects (subject 342 and 4822), lasting three days, was determined by the investigator to be vaccine-related (Supplement 67).

Fatal SAEs - pooled studies
As shown in Table 29, for the pooled studies, 16 fatalities were reported (10 in the Hib-MenCY group and six in the Hib group). All were determined by the investigator to be unrelated to vaccination according to investigators.
Eleven of the 16 fatalities reported in the pooled studies occurred within the 30 day study interval after each vaccine dose (six in the Hib-MenCY group and five in the Hib group) as shown in Supplement 66.

New onset of chronic disease - pooled studies
A comparison of the percentages of subjects reporting NOCD, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term, for the pooled data are listed in Table 30**.** The percentages of subjects reporting NOCD, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term, for the pooled data, provided on a per country basis, are shown in Supplement 68 (US), Supplement 69 (Mexico) and Supplement 70 (Australia).
AE listings were reviewed by a GSK Medical Monitor for preferred terms potentially representing a NOCD, and these events were subsequently clarified with the investigator. The NOCD checkbox on the CRF was the ultimate definition for the inclusion of an event as an NOCD in this analysis.
Overall, the number of subjects experiencing NOCD was comparable and uncommon between the two groups: 3.6% of the subjects in each group reported at least one NOCD.
Based on p-values, percentages of the following NOCDs were shown to be statistically different between groups:
The incidence of food allergy was statistically higher in the Hib-MenCY group than in the Hib group (0.3% vs. 0.0%, p=0.0030).
The incidences of developmental delay (0.0% vs. 0.1%, p=0.0030) and bronchial hyperactivity (0.2% vs. 0.5%, p=0.0027) were statistically significantly lower in the Hib-MenCY group vs. the Hib group, respectively.

Rash - pooled studies
Comparisons of the percentages of subjects reporting rash, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term, for the pooled data are

listed in Table 31. The percentages of subjects reporting rash, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term, for the pooled data, provided on a per country basis, are shown in Supplement 71 (US), Supplement 72 (Mexico) and Supplement 73 (Australia).
Overall, the number of subjects experiencing rash was comparable between the two groups: 13.3% and 13.4% of the subjects in the Hib-MenCY and Hib groups, respectively, reported at least one rash.
Based on p-values, the only statistically significant difference between groups was in the incidence of dry skin which was higher in the Hib-MenCY group compared to the Hib group (0.1% vs. 0.0%, p=0.00351, respectively).
There were two cases of petechiae reported in the studies (Hib-MenCY group, subject 7596 in the Hib-MenCY-TT-011 study and subject 4861 in the Hib group of the Hib-MenCY-TT-009 study): the first case occurred 103 days after the third dose, lasted for 15 days, was graded as 2 and resolved within 15 days. This event was not considered as vaccine-related and the subject had no other symptom. The second case of petechiae occurred 20 days after the third dose and lasted for 14 days. This event was not considered to be vaccine-related according to the investigator.
Urticaria (hives) was reported by 0.7% of the subjects in each group, urticaria popular was reported by 0.0% and 0.1% of the subjects in the Hib-MenCY and Hib groups, respectively, and purpura was only reported by one subject (Hib-MenCY group, 1/6414=0.0%).

Emergency room (ER) visits- pooled studies
A comparison of the percentage of subjects reporting adverse events resulting in an ER visit reported from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term for the pooled studies is presented in Table 32.
The percentages of subjects with an AE resulting in an ER visit were the same for both groups (6.5% of the subjects in each group). The most frequently reported AEs resulting in an ER visit in both groups, Hib-MenCY and Hib, respectively, were bronchiolitis (0.7%, both groups), gastroenteritis (0.6% and 0.8%), otitis media (0.9% and 0.7%), pyrexia (0.8% and 0.7%) and upper respiratory tract infection (0.8% and 0.6%).
Based on p-values, the following statistically significant differences were found between groups with regard to AEs resulting in ER visits:
The incidences of viral gastroenteritis (0.2% vs. 0.0%, p=0.0059) and head injury (0.2% vs. 0.0%, p=0.0075) were higher in the Hib-MenCY group vs. the Hib group. Whereas the incidences of abnormal faeces (0.0% vs. 0.1%, p=0.0086), acute sinusitis (0.0% vs. 0.1%, p=0.0083), infectious croup (0.2% vs. 0.4%, p=0.0203), pharyngitis (0.0% vs. 0.1%, p=0.0410), arthropod bite (0.0% vs. 0.1%, p=0.0083) and hair-thread tourniquet syndrome (0.0% vs. 0.1%, p=0.0086) were higher in the Hib group.
The percentages of subjects reporting AEs leading to an ER visit, from Day 0 through the ESFU, classified by MedDRA Primary System Organ Class and Preferred Term, for the pooled data, provided on a per country basis, are shown in Supplement 74 (US), Supplement 75 (Mexico) and Supplement 76 (Australia).

Incidence of adverse events based on co-administration of other vaccines- within group analyses on pooled data
All subjects from the pooled database were fully co-vaccinated with *Prevnar* and *Pediarix* in Mexico and in Australia; thus, the analyses per full co-vaccination status were performed for the United States subjects only. Because 93.0% of the Mexican subjects and 99.7% of the Australia subjects did not receive an influenza vaccine concomitant with a study dose, the analysis per influenza co-vaccination status was only performed for the United States subjects. Likewise, for the analysis per rotavirus co-vaccination status was only performed for the United States subjects since 100% of the Mexican subjects and 96.9% of the Australia subjects did not receive a rotavirus co-vaccination.

Co-administration for the rotavirus vaccine, *Pediarix* and *Prevnar* vaccines was defined, per RAP, as administration on the same day of a study vaccine dose. Concomitant administration for the influenza vaccines was defined, per RAP, as administration between 28 days before to 7 days after a study vaccine dose.
A summary of concomitantly administered vaccines by dose, for the Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011 is provided in Table 33.

**Table 33 Summary of concomitantly administered vaccines by dose (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011)**

| | | Hib-MenCY N = 6414 | | Hib N = 2157 | | Total N = 8571 | |
|---|---|---|---|---|---|---|---|
| Previous Dose | Parameters or Categories | n | % | n | % | n | % |
| 1 | Influenza | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | *RotaTeq* | 937 | 14.6 | 312 | 14.5 | 1249 | 14.6 |
| | *Pediarix* | 6413 | 100 | 2155 | 99.9 | 8568 | 100 |
| | *Prevnar* | 6406 | 99.9 | 2154 | 99.9 | 8560 | 99.9 |
| 2 | Influenza | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| | *RotaTeq* | 923 | 14.4 | 299 | 13.9 | 1222 | 14.3 |
| | *Pediarix* | 6175 | 96.3 | 2066 | 95.8 | 8241 | 96.1 |
| | *Prevnar* | 6173 | 96.2 | 2067 | 95.8 | 8240 | 96.1 |
| 3 | Influenza | 320 | 5.0 | 107 | 5.0 | 427 | 5.0 |
| | *RotaTeq* | 888 | 13.8 | 291 | 13.5 | 1179 | 13.8 |
| | *Pediarix* | 6079 | 94.8 | 2038 | 94.5 | 8117 | 94.7 |
| | *Prevnar* | 6055 | 94.4 | 2032 | 94.2 | 8087 | 94.4 |

Hib-MenCY = Hib-MenCY-TT + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
Hib = *ActHib* + *Pediarix* ( + *Prevnar*/*Prevenar* if available)
N = number of subjects in each group or in total included in the considered cohort
n/% = number/percentage of subjects receiving the specified dose in each group or in total
Any = number and percentage of subjects receiving at least one dose

Most subjects (99.3%) were co-administered both *Pediarix* and *Prevnar* with either Hib-MenCY-TT or Hib vaccine. Only 12.7% of all subjects in the pooled studies received a concomitant influenza vaccination and 12.2% received full vaccination course of coadministered rotavirus vaccine (another 3.7% received partial co-administration of rotavirus vaccine).

*Presentation based on Pediarix and Prevnar vaccination status*
The percentage of subjects with SAEs, NOCD, rash, and AEs resulting in ER visits from Day 0 through the day preceding the booster dose, based on full co-vaccination status with co-administered *Pediarix* and *Prevnar* (i.e. fully co-vaccinated or not), for US subjects (pooled Primary Total Vaccinated cohort, studies Hib-MenCY-TT-009 and -011) are presented in Supplement 78.
The percentage of subjects reporting specific SAEs, NOCD, rash and AEs resulting in ER visits, based on whether subjects received co-administered *Pediarix* and *Prevnar* are presented in Supplement 79, Supplement 80, Supplement 81 and Supplement 82, respectively, from Day 0 through the day preceding the booster dose, by priming full covaccination status, for US subjects (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011).
For the fully co-vaccinated sub-category, the percentages of subjects in each treatment group for the pooled studies, reporting SAEs, NOCD, rashes, and AEs leading to ER visits were comparable. There were some observed differences between groups for the subset who were not fully co-vaccinated; however, the numbers of subjects in this group were small (47 and 16 subjects in the Hib-MenCY and Hib groups, respectively), and so clinically meaningful conclusions cannot be drawn.

*Presentation based on Rotavirus vaccination status*
The percentage of subjects with SAEs, NOCD, rash, and AEs resulting in ER visits from Day 0 through the day preceding the booster dose, based on rotavirus vaccination status, for US subjects (pooled Primary Total Vaccinated cohort pooled studies Hib-MenCYTT-009 and -011) are presented in Supplement 83. The percentage of subjects reporting specific SAEs, NOCD,

rash and AEs resulting in ER visits, based on whether subjects received co-administered rotavirus vaccine are presented in Supplement 84 through Supplement 87, respectively. Results in fully-co-vaccinated, partially co-vaccinated and no-co-vaccinated cohorts for subjects in the US were within the same range for each category of AE for the two treatment groups.

*Presentation based on Influenza virus vaccination status*
The percentage of subjects with SAEs, NOCD, rash, and AEs resulting in emergency room visits from Day 0 through the ESFU period based on influenza vaccination status, for US subjects (Primary Total Vaccinated cohort, pooled studies Hib-MenCY-TT-009 and -011) are presented Supplement 88**.**
The percentage of subjects reporting specific SAEs, NOCD, rash and AEs resulting in ER visits, based on whether subjects received co-administered influenza vaccine are presented in Supplement 89 through Supplement 92, respectively.
For US subjects who were not given concomitant, influenza vaccine the percentages of subjects in each treatment group reporting SAEs, NOCD, rashes, and AEs leading to ER visits were comparable. There were some observed differences between groups for the subset who was given concomitant influenza vaccine; however, the numbers of subjects in this group was small (27 and 14 subjects in the Hib-MenCY and Hib groups, respectively), and so clinically meaningful conclusions cannot be drawn.

*Logistic regression analysis*
Logistic regression analyses were performed in order to evaluate any differences between incidences in the Hib-MenCY group and the Hib group with regard to concomitant administration of *Prevnar*, *Pediarix*, rotavirus and influenza virus vaccinations. Analyses by specific AE type, model selection are provided in Supplement 93 through Supplement 131. Note that a logistic regression model was performed of each AE type and for each preferred term for which statistically significantly different incidences between the two groups were found.
Based on these comparisons, differences between incidences in the Hib-MenCY group and the Hib group did not vary significantly according to the co-vaccination of *Prevnar*, *Pediarix*, rotavirus and influenza virus vaccines.

<u>Safety conclusions for pooled studies Hib-MenCY-TT-011 and -009 data, within group analyses</u>
Overall, the Hib-MenCY-TT vaccine appeared to be comparable to the US-licensed *ActHib* with respect to AEs reported during the period from Day 0 through the ESFU (end of ESFU period).
A total of 22.0% subjects in the Hib-MenCY group and 22.6% subjects in the Hib group reported at least one symptom within one of the specified categories, during the protocol defined follow-up period for the pooled studies.
Specific categories of AEs were reported as follows:
**SAEs**: At least one SAE was reported for 4.4% and 4.5% of the subjects from the pooled studies in the Hib-MenCY group and Hib group, respectively.
**NOCD:** Overall, the number of subjects experiencing NOCD was comparable and uncommon between the two groups: 3.6% of the subjects in each group reported at least one NOCD.
**Rash**: rash was the most frequently reported AE (13.3% and 13.4%, Hib-MenCY and Hib groups, respectively).
**AEs leading to ER visits:** The percentages of subjects with an AE resulting in an ER visit were the same for both groups (6.5% of the subjects in each group). The most frequently reported adverse events resulting in an ER visit in both groups, Hib-MenCY and Hib, respectively, were bronchiolitis (0.7%, both groups), gastroenteritis (0.6% and 0.8%), otitis media (0.9% and 0.7%), pyrexia (0.8% and 0.7%) and upper respiratory tract infection (0.8% and 0.6%).

*Specific SAEs reported by preferred MedDRA Primary System Organ Class and Preferred Term*
Differences for the individual SAE, NOCD, rash, and AE leading to ER visit terms were calculated based on relative risks, with statistical significance assigned to p-value ≤0.05. Because of the large number of comparisons made, and because no multiplicity adjustments

were made, the risk of detecting differences due to chance alone was high. Nonetheless, based on p-values, the difference in the percentages of each type of SAE reported by preferred MedDRA Primary System Organ Class and Preferred Term were not statistically significant between groups except for the following:

- The incidence in the Hib-MenCY group was statistically significantly lower than in the Hib group for vomiting (0.0% vs. 0.1%, p=0.0409) and influenza (0.0% vs. 0.1%, p=0.0083).

The incidence in the Hib-MenCY group was statistically significantly higher than in the Hib group for bronchiolitis (0.9% vs. 0.5%, p=0.0155) and urinary tract infection (0.2% vs. 0.0%, p=0.0491). Note that one case of bronchiolitis was inadvertently attributed to the Hib-MenCY group instead of the Hib group; however, this would not have changed the finding of statistical significance.
All except two SAEs were unrelated to vaccination according to the investigator. The two subjects with a vaccine-related SAE experienced pyrexia on the day of the first dose, lasting three days. Both subjects recovered from the event.
Sixteen fatalities were reported: 10 in the Hib-MenCY group and six in the Hib group, none of which were determined by the investigator to be vaccine-related.

*Specific NOCDs reported by preferred MedDRA Primary System Organ Class and Preferred Term*
Based on p-values, the percentages of the following NOCDs were shown to be statistically different between groups:

- The incidence of food allergy was statistically higher in the Hib-MenCY group than in the Hib group (0.3% vs. 0.0%, p=0.0030)
- The incidences of developmental delay (0.0% vs. 0.1%, p=0.0030) and bronchial hyperactivity (0.2% vs. 0.5%, p=0.0027) were statistically significantly lower in the Hib-MenCY group vs. the Hib group.

*Specific cases of rash reported by preferred MedDRA Primary System Organ Class and Preferred Term*
Based on p-values, the only statistically significant difference between groups was in the incidence of dry skin which was higher in the Hib-MenCY group compared to the Hib group (0.1% vs. 0.0%, p=0.00351, respectively).
There were two cases of petechiae reported in the studies (one occurred 103 days after the third dose, and the other occurred 20 days after the third dose). Neither case was related to vaccination according to the investigator.
Urticaria (hives) was reported by 0.7% of the subjects in each group, urticaria popular was reported by 0.0% and 0.1% of the subjects in the Hib-MenCY and Hib groups, respectively, and purpura was reported by one subject in the Hib-MenCY group (0.0% of the subjects in each group).

*Specific AEs leading to an ER visit reported by preferred MedDRA Primary System Organ Class and Preferred Term*
Based on p-values, the following statistically significant differences were found between groups with regard to an AE resulting in an ER visit: The incidences of viral gastroenteritis (0.2% vs. 0.0%, p=0.0059) and head injury (0.2% vs. 0.0%, p=0.0075) were higher in the Hib-MenCY group vs. the Hib group.
The incidences of abnormal feces (0.0% vs. 0.1%, p=0.0086), acute sinusitis (0.0% vs. 0.1%, p=0.0083), infectious croup (0.2% vs. 0.4%, p=0.0203), pharyngitis (0.0% vs. 0.1%, p=0.0410), arthropod bite (0.0% vs. 0.1%, p=0.0083) and hair-thread tourniquet syndrome (0.0% vs. 0.1%, p=0.0086) were higher in the Hib group.

*Homogeneity of results across countries and co-vaccination status*
No statistically significant Breslow and Day test was found either overall per unsolicited symptom type or by preferred MedDRA Primary System Organ Class and Preferred Term indicating, that the differences between Hib-MenCY and Hib did not vary across countries.

According to the results of the logistic regressions differences between incidences of AEs in the Hib-MenCY group and the Hib group, did not vary significantly with coadministration of the other planned vaccines (*Pediarix*, *Prevnar*, *RotaTeq* and influenza virus vaccines).
Given the small observed differences (even in the statistically significant differences), the overall safety profile regarding specific unsolicited symptoms of Hib-MenCY group is very similar to the one of the Hib group.

### 3. Discussion on clinical aspects

This clinical report represents pooled data from the studies Hib-MenCY-TT-011 and -009, which included 8873 enrolled subjects from the US, Mexico and Australia, and of which 8571 were vaccinated (6414 received Hib-MenCY-TT vaccine and 2157 received Hib vaccine), 8011 that completed the study and 7986 that completed the ESFU (extended safety follow-up).
The demographic profile of the two treatment groups of subjects in the pooled studies' Total Vaccinated Cohort was comparable with respect to mean age, gender and racial distribution. Of the 8571 subjects vaccinated with either Hib-MenCY-TT or Hib vaccine, 99.3% received co-administration of *Prevnar* and *Pediarix,* 12.7% received coadministration of an influenza vaccine and 15.9% were co-administered at least one dose of rotavirus vaccine.
The purpose of this study is to complement study Hib-MenCY-TT-009/-010 in order to define the safety profile of the Hib-MenCY-TT vaccine with respect to infrequent adverse events (i.e. SAEs, rash, ER visits, and new onset of chronic illnesses). Conclusions for the pooled dataset are as follows:
Overall, the Hib-MenCY-TT vaccine was comparable to the US-licensed *ActHib* with respect to AEs reported during the period from Day 0 through the ESFU period. AEs that had a statistically higher incidence in the Hib-MenCY group were reported with a frequency of less than 1% and were unrelated to the Hib-MenCY-TT vaccination.
There were no vaccine-related SAEs reported in the Hib-MenCY-TT-011 study. In the Hib-MenCY-TT-009 study, two SAEs were related to vaccination according to the investigator. Both were cases of pyrexia on the day of the first dose, lasting three days, reported in the Hib-MenCY group. Both subjects recovered from the event.
None of the fatalities reported in the pooled studies were determined by the investigator to be vaccine-related.
No statistically significant Breslow and Day test was found either overall per unsolicited symptom type or by MedDRA Primary System Organ Class and Preferred Term indicating that the (absence of) difference between Hib-MenCY and Hib did not seem to vary across country.
Based on results of the logistic regressions, the differences between incidences in the Hib-MenCY group and the Hib group did not vary significantly according to the co-vaccination of *Pediarix*, *Prevnar*, influenza and *RotaTeq* vaccines.
Hib-MenCY-TT was found to have a clinically-acceptable safety profile in the pooled studies and in the Hib-MenCY-TT-011 study.
Thus, the overall comparability of safety profiles between the investigational Hib-MenCY group and the US-licensed monovalent Hib control group was demonstrated regardless of the country where vaccinations were administered or of the co-vaccination of other routinely-administered vaccines. There were very few statistically significant differences in the relative risks for specific AE terms. These differences must be interpreted with caution, given the large number of comparisons made, and the fact that no multiplicity adjustments were made.
For example, bronchiolitis as an SAE was the only SAE that was reported statistically significantly more frequently in the Hib-MenCY group, yet the incidence of other clinically related AEs such as bronchitis, bronchopneumonia, croup, bronchial hyper reactivity and bronchospasm were not statistically different between the groups.
Additionally, the incidence of the bronchiolitis reported was low (39/3278 subjects) and none of the cases were causally related to vaccination, according to the investigator.
Given the large sample size, the likelihood of even a small difference becoming statistically significant is greater than with a small sample size. Note that there was one case attributed to the Hib-MenCY group instead of Hib group, although this would not have changed the

significance based on the p-value. Moreover, the incidence of NOCD of bronchial hyperreactivity (a chronic illness associated with wheezing that is on the clinical continuum with bronchiolitis) was statistically significantly lower in the Hib-MenCY group as compared to the Hib group.
With regard to NOCDs, food allergy as an NOCD for the pooled dataset was statistically significantly higher in the Hib-MenCY group than in the Hib group, yet for the Hib-MenCY-TT-011 study, milk allergy was statistically significantly lower in the Hib-MenCY group than in the Hib group.
In summary, based on the pooled datasets of Hib-MenCY-TT-009 and Hib-MenCY-TT-011 studies, a priming schedule at 2, 4, and 6 months of age with Hib-MenCY-TT coadministered with routinely-recommended paediatric vaccines is clinically acceptable.

# V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The paediatric studies submitted by the MAH aimed at defining the safety profile of the Hib-MenCY-TT vaccine with respect to infrequent adverse events (i.e. SAEs, rash, ER visits and NOCD) in comparison with a US-licensed monovalent Hib control group. Overall, the safety profiles of the investigational Hib-MenCY-TT vaccine and the monovalent Hib vaccine were comparable regardless of the country in which the vaccinations were administered, the co-vaccination status or vaccination with other routinely administered vaccines, both in the single Hib-MenCY-TT-011 study data and the pooled study data (Hib-MenCY-TT-011 and -09).

- **Recommendation**

Based on these results, discussed in detail by the MAH, the safety profile of the investigational vaccine is considered acceptable and no further action is required.

# VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable