Primary Study vaccine

GlaxoSmithKline (GSK) Biologicals’ *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined (Hib-MenCY-TT [GSK792014]).

Other Study vaccine(s)

- GSK Biologicals’ combined diphtheria-tetanus-acellular pertussis-hepatitis B surface antigen-inactivated poliovirus (DTPa-HBV-IPV) vaccine (Pediarix®)
- GlaxoSmithKline (GSK) Biologicals’ oral live attenuated human rotavirus (HRV) vaccine (Rotarix®)
- GlaxoSmithKline (GSK) Biologicals’ hepatitis A vaccine, inactivated (strain HM 175, MRC-5 cells) (Havrix®)
- Merck & Co, Inc. [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] (PedvaxHIB®)
- Pfizer’s Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) (Prevnar 13®)

eTrack study number and Abbreviated Title(s)

112931 (HIB-MENCY-TT-016)

Investigational New Drug (IND) number

11,706

EudraCT number

2013-003459-39

Date of protocol

Final: 17 December 2012

Date of protocol amendment

Amendment 1 Final: 03 September 2013

Amendment 2 Final: 16 June 2014

Title

Immunogenicity, safety and reactogenicity of GSK Biologicals’ Hib-MenCY-TT vaccine 792014 compared to Merck & Co, Inc. Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) vaccine in healthy infants and toddlers.

Detailed Title

A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.
Confidential

112931 (HIB-MENCY-TT-016)
Protocol Amendment 2 Final

eTrack study number and Abbreviated Title(s)
112931 (HIB-MENCY-TT-016)

Investigational New Drug (IND) number
11,706

EudraCT number
2013-003459-39

Detailed Title
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Co-ordinating author(s)

PPD, Science Writer

Contributing authors

(Amended: 16 June 2014)

- PPD, Clinical Research and Development Lead, Vaccine Discovery and Development
- PPD, Medical Affairs Lead
- PPD, Study Delivery Manager
- PPD, Local Delivery Lead
- PPD, Study Delivery Lead
- PPD, GVCL Study Manger, Vaccine Discovery and Development, Business and Decision, contractor for GSK Biologicals
- PPD, GVCL Project Manager, Vaccine Discovery and Development
- PPD, Director, Statistical Manager
- PPD, Study Data Manager, Business and Decision, contractor for GSK Biologicals
- PPD, Safety Physician, Vaccine Discovery and Development
- PPD, Senior Manager, Global Regulatory Affairs-Vaccines

GSK Biologicals’ Protocol DS v 14.0

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Protocol Amendment 2 Sponsor Signatory Approval

cTrack study number and Abbreviated Title(s) 112931 (HIB-MENCY-TT-016)

IND number 11,706
EudraCT number 2013-003459-39
Date of protocol amendment Amendment 2 Final: 16 June 2014

Detailed Title A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.

Sponsor signatory Marie Van Der Wielen, Director, Vaccine Discovery and Development, Neisseria Vaccines

Signature

Date
### Protocol Amendment 2 Rationale

<table>
<thead>
<tr>
<th>Amendment number:</th>
<th>Amendment 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale/background for changes:</strong></td>
<td></td>
</tr>
<tr>
<td>In order to provide the opportunity for subjects in the control group to receive a meningococcal vaccine, which is not routinely administered in the US to this age group, the protocol has been amended to state that: “...a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by the study sponsor, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.”</td>
<td></td>
</tr>
<tr>
<td>Additionally,</td>
<td></td>
</tr>
<tr>
<td>- Distribution of a diary card for recording of medications/vaccinations post dose 2 of <em>Havrix</em> has been added.</td>
<td></td>
</tr>
<tr>
<td>- Treatment allocation is by component rather than dose.</td>
<td></td>
</tr>
<tr>
<td>- Text mentioning that subjects who do not continue in the booster phase will be contacted for safety information via a phone script at the ESFU timepoint has been added.</td>
<td></td>
</tr>
<tr>
<td>- The safety contact fax information has been updated.</td>
<td></td>
</tr>
<tr>
<td>- There have been a few changes in the contributing authors.</td>
<td></td>
</tr>
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</table>
Protocol Amendment 2 Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments or protocol administrative changes, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GlaxoSmithKline (GSK) Biologicals.

- To assume responsibility for the proper conduct of the study at this site.

- That I am aware of, and will comply with, ‘Good Clinical Practice’ (GCP) and all applicable regulatory requirements.

- To ensure that all persons assisting me with the study are adequately informed about the GSK Biologicals’ investigational vaccine(s) and other study-related duties and functions as described in the protocol.

- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory’s current certification or Quality Assurance procedure manual.

- To ensure that no clinical samples (including serum samples) are retained onsite or elsewhere without the approval of GSK Biologicals and the express written informed consent of the subject and/or the subject’s legally acceptable representative.

- To perform no other biological assays on the clinical samples except those described in the protocol or its amendment(s).

- To co-operate with a representative of GSK Biologicals in the monitoring process of the study and in resolution of queries about the data.

- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator’s ownership interest in the sponsor or the investigational vaccine(s), and more generally about his/her financial ties with the sponsor. GSK Biologicals will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK Biologicals with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).

- Agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study.

- Agree that GSK Biologicals may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

- Agree to provide GSK Biologicals with an updated Curriculum Vitae and other documents required by regulatory agencies for this study.
eTrack study number and Abbreviated Title(s) 112931 (HIB-MENCY-TT-016)
IND number 11,706
EudraCT number 2013-003459-39
Date of protocol amendment Amendment 2 Final: 16 June 2014
Detailed Title A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.
Investigator name
Signature
Date
Sponsor Information

1. Sponsor

GlaxoSmithKline Biologicals
2301 Renaissance Boulevard RN0220, P.O. Box 61540 King of Prussia, PA 19406-2772

2. Sponsor Medical Expert for the Study

Refer to the local study contact information document.

3. Sponsor Study Monitor

Refer to the local study contact information document.

4. Sponsor Study Contact for Reporting of a Serious Adverse Event

GSK Biologicals Central Back-up Study Contact for Reporting SAEs: refer to protocol Section 8.4.2.
SYNOPSIS

Detailed Title
A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.

Indication
Active immunization in infants and toddlers for the prevention of invasive diseases caused by Haemophilus influenzae type b (Hib) and Neisseria meningitidis serogroups C (MenC) and Y (MenY) at months 2, 4, 6 and 12 to 15.

Rationale for the study and study design
The purpose of this study is to demonstrate the acceptability of the co-administration of Rotarix, Prevnar 13 and Havrix with GSK Biologicals’ Hib-MenCY-TT vaccine. This will be accomplished via demonstration of the non-inferiority of the immunogenicity of Rotarix and Prevnar 13 when co-administered with Hib-MenCY-TT + Pediarix as compared to the immunogenicity of Rotarix and Prevnar 13 co-administered with US-licensed PedvaxHIB + Pediarix and the non-inferiority of the immunogenicity of Havrix and Prevnar 13 when co-administered with Hib-MenCY-TT as compared to the immunogenicity of Havrix and Prevnar 13 co-administered with PedvaxHIB. In addition, the safety and reactogenicity of the vaccine regimens, and the immunogenicity to PRP, MenC and MenY induced by vaccination with Hib-MenCY-TT and PedvaxHIB will be summarized descriptively.

Objective(s)

Co-Primary
Before concluding on the primary objectives for Rotarix, Prevnar 13, and Havrix, the following objective needs to be reached:

• To demonstrate the non-inferiority of a four dose vaccination course of Hib-MenCY-TT co-administered with Prevnar 13 and Havrix compared to a three dose vaccination course of PedvaxHIB co-administered with Prevnar 13 and Havrix in terms of anti-PRP concentration.

Criterion for non-inferiority (1 month post dose 4):
Lower limit of the standardized asymptotic 95% CI for the difference (HibCY group minus the PedHIB group) in the
percentage of subjects with anti-PRP concentrations $\geq 1.0$ μg/mL is $\geq -10\%$ (clinical limit for non-inferiority).

To conclude independently on the following primary objectives of Epoch 001 or Epoch 002, a Bonferroni correction will be used to evaluate these objectives (2.5% two-sided for Epoch 001 and 2.5% two-sided for Epoch 002). As per the hierarchical procedure, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch.

**Epoch 001:**

1. To demonstrate the non-inferiority of a 2-dose primary vaccination course of *Rotarix* co-administered with Hib-MenCY-TT, *Pedia* and *Prevnar 13* compared to that of *Rotarix* co-administered with *PedvaxHIB*, *Pedia* and *Prevnar 13* in terms of *Rotarix* IgA GMCs.

   **Criteria for non-inferiority (2 months post-dose 2):**
   
   Lower limit of the two-sided standardized asymptotic 97.5% CI on the ratio of anti-rotavirus IgA GMC (HibCY group over PedHIB group) $\geq 0.5$ (clinical limit for non-inferiority).

2. To demonstrate the non-inferiority of a 3-dose primary vaccination course of *Prevnar 13* co-administered with Hib-MenCY-TT, *Rotarix* and *Pedia* compared to that of *Prevnar 13* co-administered with *PedvaxHIB*, *Rotarix* and *Pedia* in terms of *S. pneumoniae* GMCs.

   **Criteria for non-inferiority (1 month after the third dose):**
   
   Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is $\geq 0.5$ (clinical limit for non-inferiority).

**Epoch 002:**

1. To demonstrate the non-inferiority of a 2-dose vaccination course of *Havrix* when the first dose is co-administered with Hib-MenCY-TT and *Prevnar 13* at 12 to 15 months of age compared to that of *Havrix* when the first dose is co-administered with *PedvaxHIB* and *Prevnar 13* at 12 to 15 months of age.

   **Criteria for non-inferiority (1 month after the second Havrix vaccination)**
Lower limit of the two-sided standardized asymptotic 97.5% CI on the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-HAV concentrations ≥15 mIU/mL is ≥10% (clinical limit for non-inferiority).

2. To demonstrate the non-inferiority of a 4-dose vaccination course of Prevnar 13 co-administered with Hib-MenCY-TT and Havrix compared to that of Prevnar 13 co-administered with PedvaxHIB and Havrix in terms of S. pneumoniae GMCs.

Criteria for non-inferiority (1 month after the fourth dose):

Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is ≥0.5 (clinical limit for non-inferiority).

Secondary

Immunogenicity:

- To evaluate the anti-PRP immune response 2 months post-dose 2 (PedHib group only), 1 month post-dose 3 and 1 month post-dose 4 (HibCY group only) after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate hSBA-MenC and hSBA-MenY immune response 1 month post-dose 3 and 1 month post-dose 4 after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate anti-rotavirus IgA immune response 2 months after the 2nd dose of Rotarix vaccination.

- To evaluate anti-S. pneumoniae immune response above thresholds 1 month post-dose 3 and 1 month post-dose 4 after Prevnar 13 vaccination.

- To evaluate anti-HAV immune response 1 month post-dose 1 and 1 month post-dose 2 after Havrix vaccination.

Safety

- To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Rotarix, Pediarix and Prevnar 13 and of PedvaxHIB co-administered with Rotarix, Pediarix and Prevnar 13.
To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Havrix and Prevnar 13 and of PedvaxHIB co-administered with Havrix and Prevnar 13.

Experimental design: Phase IIIB, open-label, randomized, controlled, multi-centric, single-country study with two parallel groups.

Duration of the study: 17-20 months

The study will consist of two epochs:
- Epoch 001: starting at Visit 1 (Day 0) and ending at the day preceding Visit 5 (Month 10-13, fourth dose vaccination)
- Epoch 002: starting at Visit 5 (Month 10-13) and ending at Visit 8 (Month 17-20, 31 days after the 2\textsuperscript{nd} Havrix vaccination).

Synopsis Table 1  Study groups and epochs foreseen in the study

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Number of subjects</th>
<th>Age (Min/Max)</th>
<th>Epochs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 001</td>
</tr>
<tr>
<td>HibCY</td>
<td>300</td>
<td>6 - 12 weeks</td>
<td>x</td>
</tr>
<tr>
<td>PedHIB</td>
<td>300</td>
<td>6 – 12 weeks</td>
<td>x</td>
</tr>
</tbody>
</table>

Synopsis Table 2  Epoch 001 study groups and treatment names foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>HibCY x X</td>
</tr>
<tr>
<td></td>
<td>NaCl*</td>
<td>PedHIB x x</td>
</tr>
<tr>
<td>Pediarix</td>
<td>DTPa-HBV-IPV</td>
<td>X</td>
</tr>
<tr>
<td>Prevenar 13</td>
<td>Prevenar 13</td>
<td>X</td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Rotarix</td>
<td>HRV</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CaCO\textsubscript{3}</td>
<td>X</td>
</tr>
</tbody>
</table>

*The lyophilized pellet of Hib-MenCY-TT and Rotarix vaccine are to be reconstituted with the supplied saline.

Synopsis Table 3  Epoch 002 study groups and treatment names foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>HibCY x X</td>
</tr>
<tr>
<td></td>
<td>NaCl*</td>
<td>PedHIB x x</td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Havrix</td>
<td>HAV</td>
<td>x</td>
</tr>
</tbody>
</table>
*The lyophilized pellet of Hib-MenCY-TT is to be reconstituted with the supplied saline.
• Control: PedvaxHIB

• Visits: Eight scheduled visits per subject* at Month 0 (Visit 1), Month 2 (Visit 2), Month 4 (Visit 3 Sub-cohorts HibCY 1, 2 and PedHIB 1, 2 only), Month 5 (Visit 4, Sub-cohorts HibCY 1, 3 and PedHIB 1, 3 only), Month 10-13 (Visit 5), Month 11-14 (Visit 6 Sub-cohorts HibCY 1, 2, 3 and PedHIB 1, 2, 3 only), Month 16-19 (Visit 7) and Month 17-20 (Visit 8, Sub-cohorts HibCY 2, 3 and PedHIB 2, 3 only).

*Note: All subjects will come back to each visit for safety assessment. Those visits where Sub-cohorts are mentioned above indicates those subjects that will have blood drawn at that visit.

• Vaccination schedule:
  - IM injection of Hib-MenCY-TT at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - IM injection of PedvaxHIB at Day 0, Months 2 and 10-13 (2, 4 and 12-15 months of age).
  - IM injection of Pediarix at Day 0, Months 2 and 4 (2, 4 and 6 months of age).
  - IM injection of Prevnar 13 at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - Oral administration of Rotarix at Day 0 and Month 2 (2 and 4 months of age).
  - IM injection of Havrix at Months 10-13 (12-15 months of age) and 16-19 (18-21 months of age).

Note: The booster dose of Infanrix will be provided by GSK outside of the study and is allowed at any time during the window between Day 30 post-dose 4 and 30 days prior to the administration of the 2nd dose of Havrix. Additionally, a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.

• Treatment allocation: 600 subjects 6-12 weeks of age will be randomized 1:1 to receive either the Hib-MenCY-TT or PedvaxHIB vaccine. Assignment to the blood sample sub-cohort will depend on the date of enrolment of the subject. The first 200 will be assigned to blood sample sub-cohort 3, the next 200 will be assigned to blood sample sub-cohort...
2 and the last 200 will be assigned to blood sample cohort 1. Within each blood sample sub-cohort subjects will be randomized 1:1 to either HibCY or PedHIB groups resulting in the following treatment group BS cohorts:

- Hib-MenCY-TT treatment group BS cohorts = HibCY1, HibCY2, or HibCY3.
- PedvaxHIB treatment group BS cohorts = PedHIB1, PedHIB2 or PedHIB3.

- Blinding: Open

**Synopsis Table 4  Blinding of study epochs**

<table>
<thead>
<tr>
<th>Study Epochs</th>
<th>Study Groups</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch 001</td>
<td>HibCY; PedHIB</td>
<td>open</td>
</tr>
<tr>
<td>Epoch 002</td>
<td>HibCY; PedHIB</td>
<td>open</td>
</tr>
</tbody>
</table>

Note: An observer-blind design for this study is not possible due to the fact that subjects in the HibCY group receive 3 doses of vaccine in Epoch 001 and subjects in the PedHIB group only receive two.

- Blood sampling:

  **Epoch 001:**

  - The following subcohorts will have a blood draw before the 3rd vaccination dose at Month 4 (Visit 3)

    BS cohorts:
    - HibCY1
    - HibCY2
    - PedHIB1
    - PedHIB2

  - The following subcohorts will have a blood draw 1 month post-third dose at Month 5 (Visit 4)

    BS cohorts:
    - HibCY1
    - HibCY3
    - PedHIB1
    - PedHIB2

  **Epoch 002:**

  - The following subcohorts will have a blood draw 1 month post-fourth dose (Visit 6)

    BS cohorts:
    - HibCY1
    - HibCY2
• HibCY3
• PedHIB1
• PedHIB2
• PedHIB3

– The following subcohorts will have a blood draw 1 month after the 2nd Havrix vaccination (Visit 8)

BS cohorts:
• HibCY2
• HibCY3
• PedHIB2
• PedHIB3

Therefore, each subject has 3 blood draws throughout the study.

• Type of study: self-contained
• Data collection: Electronic Case Report Form (eCRF)

Number of subjects

Total enrolment for the study will be 600 healthy subjects 6-12 weeks of age.

Endpoint(s)

Primary

• Immunogenicity with respect to the components of the co-administered vaccines:
  – Anti-PRP antibody concentrations ≥1.0 µg/mL (1 month post-dose 4 HibCY group, 1 month post-dose 3 PedHIB group).
  – Anti-rotavirus serum IgA GMCs (2 months post-dose 2 of Rotarix)
  – Anti-HAV antibody concentrations ≥15 mIU/mL (1 month post-dose 2 of Havrix)
  – Anti-S. pneumoniae GMCs (1 month post-dose 3)
  – Anti-S. pneumoniae GMCs (1 month post-dose 4)

Secondary

Immunogenicity

• Immunogenicity with respect to the components of the investigational vaccine:
  – Anti-PRP antibody concentrations ≥0.15 µg/mL and GMCs (2 months post-dose 2 [PedHib group only], 1 month post-dose 3 and 1 month post-dose 4 [HibCY group only]).
Anti-PRP antibody concentrations ≥1.0 µg/mL 2 months post-dose 2 (PedHib group only) and 1 month post-dose 3 (HibCY group only).

hSBA-MenC and hSBA-MenY antibody titers ≥1:4, ≥1:8, ≥1:16, ≥1:32 and GMTs (1 month post-dose 3 and 1 month post-dose 4).

Immunogenicity with respect to the components of the co-administered vaccines:

- Anti-rotavirus IgA antibody concentrations ≥20 U/mL (2 months post-dose 2 of Rotarix).
- Anti-HAV antibodies ≥15 mIU/mL and GMCs (1 month post-dose 1 of Havrix).
- Anti-HAV GMCs (1 month post-dose 2 of Havrix).
- S. pneumoniae antibody concentrations ≥0.15 µg/mL, ≥0.26 µg/mL and ≥0.35 µg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in Prevnar 13 (1 month post-dose 3 and 1 month post-dose 4).

Safety and Reactogenicity

- Occurrence of each solicited adverse event 4 days (Day 0 to Day 3) after all vaccines post-primary and post-fourth dose.
  - Local symptoms
  - General symptoms

- Occurrence of unsolicited symptoms 31 days (Day 0 to Day 30) after all vaccines post-primary and post-fourth dose.

- Occurrence throughout the study of SAEs from Day 0 to study end.
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<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>ATP</td>
<td>According-to-protocol</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DT</td>
<td>Diphtheria</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria, Tetanus, Pertussis vaccine</td>
</tr>
<tr>
<td>DTPa</td>
<td>Diphtheria, Tetanus, Acellular Pertussis vaccine</td>
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<td>DTPa-HBV-IPV</td>
<td>Diphtheria and Tetanus Toxoids and Acellular Pertuss Adsorbed Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<td>eTDP</td>
<td>Electronic temperature deviation form</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EL.U</td>
<td>ELISA Unit</td>
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<tr>
<td>FAX</td>
<td>Facsimile</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration, United States</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GE</td>
<td>Gastroenteritis</td>
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<tr>
<td>GMC</td>
<td>Geometric Mean Concentration</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric Mean Titer</td>
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<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HAV</td>
<td>Hepatitis A Vaccine</td>
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<td>HepB</td>
<td>Hepatitis B</td>
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<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
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Hib-MenCY-TT  
*Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine combined

HRV  
Human Rotavirus Vaccine

hSBA  
Serum bactericidal assay (using human complement)

hSBA-MenC  
Serum bactericidal assay to *N. meningitidis* serogroup C (using human complement)

hSBA-MenY  
Serum bactericidal assay to *N. meningitidis* serogroup Y (using human complement)

ICH  
International Committee on Harmonization

ICF  
Informed Consent Form

IEC  
Independent Ethics Committee

IM  
Intramuscular

IMP  
Investigational Medicinal Product

IND  
Investigational New Drug

IRB  
Institutional Review Board

IU  
International Unit

LAR  
Legally Acceptable Representative

LL  
Lower Limit

MedDRA  
Medical Dictionary for Regulatory Activities

μg  
Microgram

MenC  
*N. meningitidis* serogroup C

MenY  
*N. meningitidis* serogroup Y

mg  
Milligram

mIU  
Milli-international Units

mL  
Milliliter

NOCI  
New Onset of Chronic Illness(es)
<table>
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<tr>
<td>PRP</td>
<td>Polyribosylribitol phosphate</td>
</tr>
<tr>
<td>PT</td>
<td>Pertussis Toxoid</td>
</tr>
<tr>
<td>RDE</td>
<td>Remote Data Entry</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAS®</td>
<td>Statistical Analysis System</td>
</tr>
<tr>
<td>SBIR</td>
<td>Simply the Better Internet Randomization</td>
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<tr>
<td>SCID</td>
<td>Severe Combined Immunodeficiency Syndrome</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SPM</td>
<td>Study Procedures Manual</td>
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<tr>
<td>TT</td>
<td>Tetanus toxoid</td>
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<tr>
<td>UL</td>
<td>Upper Limit</td>
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<td>US</td>
<td>United States</td>
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<tr>
<td>Vacc</td>
<td>Vaccination</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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GLOSSARY OF TERMS

**Adverse event:**
Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

**Blinding:**
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required, in case of a serious adverse event. In an open-label study, no blind is used. Both the investigator and the subject know the identity of the treatment assigned.

**Child in Care**
A child who has been placed under the control or protection of an agency, organization, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a child in care can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The definition of a child in care does not include a child who is adopted or has an appointed legal guardian.

**Eligible:**
Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.

**Epoch:**
An epoch is a well defined part of a protocol that covers a set of consecutive time-points. Generally, an epoch is self-contained and allows to perform a data analysis to address some of the trial objectives (e.g. primary, fourth dose, yearly follow-ups,…).

**eTrack:**
GSK’s clinical trials tracking tool
Evaluable: Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in the according-to-protocol (ATP) analysis.

Immunological correlate of protection: The defined humoral antibody response above which there is a high likelihood of protection in the absence of any host factors that might increase susceptibility to the infectious agent.

Investigation vaccine/product (Synonym of Investigational Medicinal Product) A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Medical Monitor: An individual medically qualified to assume the responsibilities of the sponsor (GSK Biologicals) especially in regards to the ethics, clinical safety of a study and the assessment of adverse events.

Protocol amendment: ICH defines a protocol amendment as: “A written description of a change(s) to or formal clarification of a protocol.” GSK Biologicals further details this to include a change to an approved protocol that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study.

Protocol administrative change: A protocol administrative change addresses changes to only logistical or administrative aspects of the study. N.B. Any change that falls under the definition of a protocol amendment (e.g. a change that affects the safety of subjects, scope of the investigation, study design, or scientific integrity of the study) MUST be prepared as an amendment to the protocol.

Randomization: Process of random attribution of treatment to subjects in order to reduce bias of selection

Self-contained study Study with objectives not linked to the data of another study.

Site Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of clinical studies at one or more investigational sites.
Solicited adverse event: Adverse events (AEs) to be recorded as endpoints in the clinical study. The presence/occurrence/intensity of these events is actively solicited from the subject or an observer during a specified post-vaccination follow-up period.

Study Monitor: An individual assigned by the sponsor who is responsible for assuring proper conduct of a clinical study.

Subject: Term used throughout the protocol to denote an individual that has been contacted in order to participate or participates in the clinical study, either as a recipient of the investigational product(s) or as a control.

Subject number: A unique number identifying a subject, assigned to each subject consenting to participate in the study.

Treatment: Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject, identified by a unique number, according to the study randomization or treatment allocation.

Treatment number: A unique number identifying a treatment to a subject, according to the study randomization or treatment allocation.

Unsolicited adverse event: Any adverse event (AE) reported in addition to those solicited during the clinical study. Also any “solicited” symptom with onset outside the specified period of follow-up for solicited symptoms will be reported as an unsolicited adverse event.
The following trademarks are used in the present protocol.

**Note:** In the body of the Protocol (including the synopsis), the names of the vaccines/products and/or medications will be written without the subscript symbol™ or ®.

<table>
<thead>
<tr>
<th>Trademarks of the GlaxoSmithKline group of companies</th>
<th>generic description</th>
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<tr>
<td>Pediarix®</td>
<td>Diphtheria and Tetanus Toxoids and Acellular Pertuss Adsorbed Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined</td>
</tr>
<tr>
<td>Rotarix®</td>
<td>Human Rotavirus Vaccine Live Oral</td>
</tr>
<tr>
<td>Havrix®</td>
<td>Hepatitis A Vaccine, Inactivated</td>
</tr>
<tr>
<td>MenHibrix®</td>
<td>Meningococcal Groups C and Y and <em>Haemophilus</em> b Tetanus Toxoid Conjugate Vaccines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trademarks not owned by the GlaxoSmithKline group of companies</th>
<th>generic description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevnar 13® (Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.)</td>
<td>Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM₁₉₇ Protein)</td>
</tr>
<tr>
<td>Mencevo® (Novartis Vaccines and Diagnostics, Inc.)</td>
<td>Meningococcal Groups A, C, W-135, and Y Polysaccharide CRM₁₉₇ Conjugate Vaccine</td>
</tr>
<tr>
<td>Menactra® (Sanofi Pasteur Inc.)</td>
<td>Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine</td>
</tr>
<tr>
<td>PedvaxHIB® (Merck Sharp &amp; Dohme Corp., a subsidiary of Merck &amp; Co, Inc.)</td>
<td><em>Haemophilus</em> b Conjugate Vaccine (Meningococcal Protein Conjugate)</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

1.1. Background (Amended: 16 June 2014)

Historically, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumonia* (*S. pneumoniae*), and *Neisseria meningitidis* have caused most cases of bacterial meningitis in the United States (US). Following the licensing and introduction of Hib-conjugate vaccines and *S. pneumoniae* conjugate vaccines in the routine infant immunization schedule in the US, there has been a dramatic reduction in the incidence of diseases caused by Hib and *S. pneumoniae*. Thus, *Neisseria meningitidis* has become a leading cause of bacterial meningitis in the US, with serogroups B, C and Y being responsible for the majority of cases [Cohn, 2010].

Meningococcal disease continues to be endemic in both developed countries, such as the US and European nations, and developing countries [Connolly, 1999] and is associated with high case-fatality rates (5%-15%) even where adequate medical services are available [WHO, 2002]. Meningococcal disease also causes substantial morbidity: 11%-19% of survivors have sequelae (e.g., neurologic disability, limb loss, hearing loss) [Kirsch, 1996; Edwards, 1981]. *Neisseria meningitidis* has become a leading cause of bacterial meningitis in the US after dramatic reductions in the incidence of *Streptococcus pneumoniae* and Hib infections have been achieved as a result of using conjugate vaccines [CDC, 2005].

Non-conjugated vaccines, consisting of meningococcal capsular polysaccharide of serogroups A, C, W-135 and Y, were developed and have been effective in the control of epidemic disease due to *N. meningitidis* of the related serogroups and the prevention of the secondary cases of disease in household contacts [Greenwood, 1978]. They have also been used for vaccination of special risk groups including individuals with asplenia or complement system deficiencies and are indicated for travellers to epidemic or hyperendemic areas [De Wals, 2001; Mimouni, 1998; Peltola, 1998; Morley, 2001; Salleras, 2001].

The shortcomings of the polysaccharide vaccines are well known and expected given the T-cell independent nature of the immune response that they elicit. As for other vaccines successfully developed against polysaccharide-encapsulated bacteria like *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, chemical conjugation of the polysaccharide to a protein carrier converts the T-cell independent response into a T-cell dependent anti-polysaccharide antibody response. This T-cell dependent response elicited by conjugate vaccines leads to anticapsular humoral response in children less than 2 years of age and a strong anamnestic (memory) response to a booster dose of the vaccine [Tan, 2010]. In addition, Hib and pneumococcal conjugate vaccines have been reported to reduce asymptomatic carriage of their respective bacteria, thereby protecting unvaccinated individuals through a herd immunity effect, which could be anticipated for the meningococcal conjugate vaccines as well [Mohle-Boetani, 1993; O'Brien, 2007].

Similar herd immunity effects were also observed following implementation of meningococcal serogroup C conjugate vaccine (MCC) immunization programs in the UK and the Netherlands [Trotter, 2009; Maiden, 2002].
The dramatic presentation and associated morbidity and mortality of *N. meningitidis* infections have made the development of safe and effective vaccines an important public health priority in the US. Menactra® (Sanofi Pasteur Inc. Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) is a quadrivalent meningococcal conjugate vaccine, which is comprised of the polysaccharide capsules of serogroups A, C, Y and W-135 each individually conjugated to diphtheria toxoid. This vaccine was approved by the US Food and Drug Administration (FDA) in January 2005 for use in individuals 11 to 55 years of age to be administered as a single dose. In October 2007, FDA expanded licensure of Menactra to include children 2 to 10 years of age. In April 2011, the license for Menactra was expanded further to include a two dose schedule for toddlers to be administered at 9 and 12 months of age. In February 2010, a second quadrivalent meningococcal conjugate vaccine, Menveo® (Novartis Vaccines and Diagnostics, Inc. Meningococcal Groups A, C, W-135, and Y Polysaccharide CRM197 Conjugate Vaccine), was licensed in the US for individuals 11-55 years of age, also to be administered as a single dose. In January 2011, FDA expanded licensure of Menveo to include children 2-10 years of age and further expanded to 2 months of age in August 2013.

GSK Biologicals has developed a Hib-MenCY-TT conjugate vaccine (*MenHibrix*) using TT as the carrier protein for the Hib and the meningococcal components to be administered as a four dose vaccination series at 2, 4, 6 and 12-15 months of age. On June 14th, 2012 *MenHibrix* was approved by the FDA for use in infants. This vaccine will allow vaccination against serogroups C and Y meningococcal disease without increasing the number of injections required to fully vaccinate a child according to the routine childhood schedule.

Data from previous phase III studies in infants given one dose of Hib-MenCY-TT at 2, 4 and 6 months (N= 4180) and a fourth dose (N= 3692) at 12-15 months have shown the GSK Biologicals' Hib-MenCY-TT vaccine to be safe and immunogenic when given as a fourth vaccination course to infants/toddlers. In addition, Hib-MenCY-TT vaccine did not appear to interfere with the immune response of other concomitantly administered routine vaccines such as *Pediarix*, *Prevnar* and *M-M-R II* and *Varivax* [Marshall, 2011; Bryant, 2012].

Please refer to the current Investigator Brochure for a review of the pre-clinical and clinical studies, and the potential risks and benefits of Hib-MenCY-TT.


### 1.2. Rationale for the study and study design

#### 1.2.1. Rationale for the study

The purpose of this study is to demonstrate the acceptability of the co-administration of Rotarix, Prevnar 13 and Havrix with GSK Biologicals’ Hib-MenCY-TT vaccine. This will be accomplished via demonstration of the non-inferiority of the immunogenicity of Rotarix and Prevnar 13 when co-administered with Hib-MenCY-TT + Pediarix as compared to the immunogenicity of Rotarix and Prevnar 13 co-administered with US-
licensed PedvaxHIB + Pediarix and the non-inferiority of the immunogenicity of Havrix and Prevnar 13 when co-administered with Hib-MenCY-TT as compared to the immunogenicity of Havrix and Prevnar 13 co-administered with PedvaxHIB. In addition, the safety and reactogenicity of the vaccine regimens, and the immunogenicity to PRP, MenC and MenY induced by vaccination with Hib-MenCY-TT and PedvaxHIB will be summarized descriptively.

1.2.2. Rationale for the study design

The study is designed as a randomized, controlled study with two parallel groups (the HibCY or PedHIB group). Within each group, subjects will be further sub-randomized into six blood draw sub-cohorts to reduce the number of blood draws per subject while still maintaining power for the objectives (See study design Section 3). The comparator and co-administered vaccines administered in this study are part of the standard care for infants and toddlers in the US. The immunogenicity of Havrix is only being assessed post-dose 2 since the vaccination course for this vaccine is only completed after the second dose.

2. OBJECTIVE(S)

2.1. Co-Primary objective(s)

Co-Primary

Before concluding on the primary objectives for Rotarix, Prevnar 13, and Havrix, the following objective needs to be reached:

- To demonstrate the non-inferiority of a four dose vaccination course of Hib-MenCY-TT co-administered with Prevnar 13 and Havrix compared to a three dose vaccination course of PedvaxHIB co-administered with Prevnar 13 and Havrix in terms of anti-PRP concentration.

**Criterion for non-inferiority (1 month post dose 4):**

Lower limit of the standardized asymptotic 95% CI for the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-PRP concentrations \( \geq 1.0 \mu g/mL \) is \( \geq 10\% \) (clinical limit for non-inferiority).

To conclude independently on the following primary objectives of Epoch 001 or Epoch 002, a Bonferroni correction will be used to evaluate these objectives (2.5% two-sided for Epoch 001 and 2.5% two-sided for Epoch 002). As per the hierarchical procedure, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch (see Section 10.3).

**Epoch 001:**

1. To demonstrate the non-inferiority of a 2-dose primary vaccination course of Rotarix co-administered with Hib-MenCY-TT, Pediarix and Prevnar 13 compared to that of Rotarix co-administered with PedvaxHIB, Pediarix and Prevnar 13 in terms of Rotarix IgA GMCs.
**Criteria for non-inferiority (2 months post-dose 2):**

Lower limit of the two-sided standardized asymptotic 97.5% CI on the ratio of anti-rotavirus IgA GMC (HibCY group over PedHIB group) ≥0.5 (clinical limit for non-inferiority).

2. To demonstrate the non-inferiority of a 3-dose primary vaccination course of Prevnar 13 co-administered with Hib-MenCY-TT, Rotarix and Pediarix compared to that of Prevnar 13 co-administered with PedvaxHIB, Rotarix and Pediarix in terms of S. pneumoniae GMCs.

**Criteria for non-inferiority (1 month after the third dose):**

Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is ≥0.5 (clinical limit for non-inferiority).

**Epoch 002:**

1. To demonstrate the non-inferiority of a 2-dose vaccination course of Havrix when the first dose is co-administered with Hib-MenCY-TT and Prevnar 13 at 12 to 15 months of age compared to that of Havrix when the first dose is co-administered with PedvaxHIB and Prevnar 13 at 12 to 15 months of age.

**Criteria for non-inferiority (1 month after the second Havrix vaccination)**

Lower limit of the two-sided standardized asymptotic 97.5% CI on the difference (HibCY group minus the PedHIB group) for the percentage of subjects with anti-HAV concentrations ≥15 mIU/mL is ≥-10% (clinical limit for non-inferiority).

2. To demonstrate the non-inferiority of a 4-dose vaccination course of Prevnar 13 co-administered with Hib-MenCY-TT and Havrix compared to that of Prevnar 13 co-administered with PedvaxHIB and Havrix in terms of S. pneumoniae GMCs.

**Criteria for non-inferiority (1 month after the fourth dose):**

Lower limit of the two-sided 97.5% CI on the GMC ratio (HibCY group over PedHIB group) for antibodies to S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F is ≥0.5 (clinical limit for non-inferiority).

Refer to Section 10.1 for the definition of the primary endpoints.

### 2.2. Secondary objective(s)

**Secondary Immunogenicity:**

- To evaluate the anti-PRP immune response 2 months post-dose 2 (PedHib group only), 1 month post-dose 3 and 1 month post-dose 4 (HibCY group only) after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate hSBA-MenC and hSBA-MenY immune response 1 month post-dose 3 and 1 month post-dose 4 after Hib-MenCY-TT or PedvaxHIB vaccination.

- To evaluate anti-rotavirus IgA immune response 2 months after the 2nd dose of Rotarix vaccination.
To evaluate anti-S. pneumoniae immune response above thresholds 1 month post-dose 3 and 1 month post-dose 4 after Prevnar 13 vaccination.

To evaluate anti-HAV immune response 1 month post-dose 1 and 1 month post-dose 2 after Havrix vaccination.

**Safety**

To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Rotarix, Pediarix and Prevnar 13 and of PedvaxHIB co-administered with Rotarix, Pediarix and Prevnar 13.

To evaluate the safety and reactogenicity of Hib-MenCY-TT co-administered with Havrix and Prevnar 13 and of PedvaxHIB co-administered with Havrix and Prevnar 13.

Refer to Section 10.2 for the definition of the secondary endpoints.
3. STUDY DESIGN OVERVIEW (AMENDED 16 JUNE 2014)

Randomization 1:1 (N=600)

HibCY Group (N=300)
- Hib-MenCY-TT
  + Rotarix
  + Prevnar 13
  + Pediarix
- Hib-MenCY-TT
  + Rotarix
  + Prevnar 13
  + Pediarix
- Hib-MenCY-TT
  + Rotarix
  + Prevnar 13
  + Pediarix

PedHIB Group (N=300)
- PedvaxHIB
  + Rotarix
  + Prevnar 13
  + Pediarix
- PedvaxHIB
  + Rotarix
  + Prevnar 13
  + Pediarix
- Prevnar 13
  + Pediarix

Visit 1
Day 0
6-12 wks

Visit 2
Month 2
4 Mo

Visit 3
Month 4
6 Mo
Sub-cohort = HibCY 1, 2 & PedHIB 1, 2

Visit 4
Month 5
7 Mo
Sub-cohort = HibCY 1, 3 & PedHIB 1, 3

Visit 5
Month 10-13
12-15 Mo

Visit 6
Month 10-13
12-15 Mo

Visit 7
Month 16-19
18-21 Mo

Visit 8
Month 17-20
19-22 Mo

* BS = Blood sample
Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the outline of study procedures (Section 5.5), are essential and required for study conduct.

- **Experimental design**: Phase IIIB, open-label, randomized, controlled, multi-centric, single-country study with two parallel groups.
- **Duration of the study**: 17-20 months

The study will consist of two epochs:

- **Epoch 001**: starting at Visit 1 (Day 0) and ending at the day preceding Visit 5 (Month 10-13, fourth dose vaccination)
- **Epoch 002**: starting at Visit 5 (Month 10-13) and ending at Visit 8 (Month 17-20, 31 days after the 2nd Havrix vaccination).

### Table 1  
**Study groups and epochs foreseen in the study**

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Number of subjects</th>
<th>Age (Min/Max)</th>
<th>Epochs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epoch 001</td>
</tr>
<tr>
<td>HibCY</td>
<td>300</td>
<td>6 - 12 weeks</td>
<td>x</td>
</tr>
<tr>
<td>PedHIB</td>
<td>300</td>
<td>6 – 12 weeks</td>
<td>x</td>
</tr>
</tbody>
</table>

### Table 2  
**Epoch 001 study groups and treatment names foreseen in the study**

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HibCY</td>
</tr>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NaCl*</td>
<td></td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>Prevenar 13</td>
<td>X</td>
</tr>
<tr>
<td>Rotarix</td>
<td>HRV</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CaCO₃*</td>
<td>X</td>
</tr>
</tbody>
</table>

*The lyophilized pellet of Hib-MenCY-TT and Rotarix vaccine are to be reconstituted with the supplied saline.*

### Table 3  
**Epoch 002 study groups and treatment names foreseen in the study**

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HibCY</td>
</tr>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>NaCl*</td>
<td></td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>Prevenar 13</td>
<td>X</td>
</tr>
</tbody>
</table>

*The lyophilized pellet of Hib-MenCY-TT is to be reconstituted with the supplied saline.*
• Control: PedvaxHIB

• Visits: Eight scheduled visits per subject* at Month 0 (Visit 1), Month 2 (Visit 2), Month 4 (Visit 3 Sub-cohorts HibCY 1, 2 and PedHIB 1, 2 only), Month 5 (Visit 4, Sub-cohorts HibCY 1, 3 and PedHIB 1, 3 only), Month 10-13 (Visit 5), Month 11-14 (Visit 6 Sub-cohorts HibCY 1, 2, 3 and PedHIB 1, 2, 3 only), Month 16-19 (Visit 7) and Month 17-20 (Visit 8, Sub-cohorts HibCY 2, 3 and PedHIB 2, 3 only).

*Note: All subjects will come back to each visit for safety assessment. Those visits where Sub-cohorts are mentioned above indicates those subjects that will have blood drawn at that visit.

• Vaccination schedule:
  - IM injection of Hib-MenCY-TT at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - IM injection of PedvaxHIB at Day 0, Months 2 and 10-13 (2, 4 and 12-15 months of age).
  - IM injection of Pediarix at Day 0, Months 2 and 4 (2, 4 and 6 months of age).
  - IM injection of Prevnar 13 at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - Oral administration of Rotarix at Day 0 and Month 2 (2 and 4 months of age).
  - IM injection of Havrix at Months 10-13 (12-15 months of age) and 16-19 (18-21 months of age).

Note: The booster dose of Infanrix will be provided by GSK outside of the study and is allowed at any time during the window between Day 30 post-dose 4 and 30 days prior to the administration of the 2nd dose of Havrix. Additionally, a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.

• Treatment allocation: 600 subjects 6-12 weeks of age will be randomized 1:1 to receive either the Hib-MenCY-TT or PedvaxHIB vaccine. Assignment to the blood sample sub-cohort will depend on the date of enrolment of the subject. The first 200 will be assigned to blood sample sub-cohort 3, the next 200 will be assigned to blood sample sub-cohort 2 and the last 200 will be assigned to blood sample cohort 1. Within each blood sample sub-cohort subjects will be randomized 1:1 to either HibCY or PedHIB groups resulting in the following treatment group BS cohorts:
  - Hib-MenCY-TT treatment group BS cohorts = HibCY1, HibCY2, or HibCY3.
  - PedvaxHIB treatment group BS cohorts = PedHIB1, PedHIB2 or PedHIB3.

• Blinding: Open
Table 4  Blinding of study epochs

<table>
<thead>
<tr>
<th>Study Epochs</th>
<th>Study Groups</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch 001</td>
<td>HibCY ; PedHIB</td>
<td>open</td>
</tr>
<tr>
<td>Epoch 002</td>
<td>HibCY ; PedHIB</td>
<td>open</td>
</tr>
</tbody>
</table>

Note: An observer-blind design for this study is not possible due to the fact that subjects in the HibCY group receive 3 doses of vaccine in Epoch 001 and the subjects in the PedHIB group only receive two.

- Blood sampling:

**Epoch 001:**

The following subcohorts will have a blood draw before the 3\textsuperscript{rd} vaccination dose at Month 4 (Visit 3)

BS cohorts:
- HibCY1
- HibCY2
- PedHIB1
- PedHIB2

The following subcohorts will have a blood draw 1 month post-third dose at Month 5 (Visit 4)

BS cohorts:
- HibCY1
- HibCY3
- PedHIB1
- PedHIB2

**Epoch 002:**

The following subcohorts will have a blood draw 1 month post-fourth dose (Visit 6)

BS cohorts:
- HibCY1
- HibCY2
- HibCY3
- PedHIB1
- PedHIB2
- PedHIB3
The following subcohorts will have a blood draw 1 month after the 2nd Havrix vaccination (Visit 8)

BS cohorts:
- HibCY2
- HibCY3
- PedHIB2
- PedHIB3

Therefore, each subject has 3 blood draws throughout the study.

- Type of study: self-contained
- Data collection: Electronic Case Report Form (eCRF)

4. STUDY COHORT

4.1. Number of subjects/centres

Target enrolment will be 600 subjects, 200 in each of the three sub-cohorts (1, 2 and 3). Within each blood sample sub-cohort subjects will be randomized 1:1 to either HibCY or PedHIB groups. Enrolment will be terminated when the target number of subjects in each sub-cohort is reached. Refer to Section 10.3 for a detailed description of the criteria used in the estimation of sample size.

The study will be conducted at multiple centers within the United States. More than 10 centers are currently estimated to participate in this study.

In order to more fully utilize centers whose recruitment rates are greater than anticipated, an over-randomization of approximately 20% will be prepared.

Potential subjects for inclusion in the study (i.e., age appropriate subjects with appropriate vaccination history) will be identified by the investigator prior to study start in order to ensure maximum efficiency in enrolment.

The duration of the first Epoch of the study will be approximately 10-13 months per subject (starting at Visit 1 and ending at the day preceding Visit 5). The duration of the second Epoch of the study (starting at Visit 5 and ending at Visit 8) will be approximately 7 months per subject. Total duration of the study for each subject will be approximately 17-20 months.

Actual numbers of subjects enrolled versus target numbers of subjects enrolled will be assessed on a continuous basis utilizing an internet-based randomization system (SBIR). Monitoring of actual enrolment against target enrolment will be performed.

The recruitment period for the study is anticipated to be approximately 6 months.
### Table 5  Sub-cohorts

<table>
<thead>
<tr>
<th>BS cohorts*</th>
<th>Description</th>
<th>No of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HibCY1</td>
<td>A sub-set of approximately 33% of subjects enrolled in the HibCY group</td>
<td>100</td>
</tr>
<tr>
<td>HibCY2</td>
<td>A sub-set of approximately 33% of subjects enrolled in the HibCY group</td>
<td>100</td>
</tr>
<tr>
<td>HibCY3</td>
<td>A sub-set of approximately 33% of subjects enrolled in the HibCY group</td>
<td>100</td>
</tr>
<tr>
<td>PedHIB1</td>
<td>A sub-set of approximately 33% of subjects enrolled in the PedHIB group</td>
<td>100</td>
</tr>
<tr>
<td>PedHIB2</td>
<td>A sub-set of approximately 33% of subjects enrolled in PedHIB group</td>
<td>100</td>
</tr>
<tr>
<td>PedHIB3</td>
<td>A sub-set of approximately 33% of subjects enrolled in PedHIB group</td>
<td>100</td>
</tr>
</tbody>
</table>

* One subject is assigned to a single BS cohort.

### 4.2. Inclusion criteria for enrolment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Subjects’ parent(s)/Legally Acceptable Representative(s) [LAR(s)] who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g. completion of the diary cards, return for follow-up visits).
- A male or female between, and including, 6 and 12 weeks of age at the time of the first vaccination.
- Written informed consent obtained from the parent(s)/LAR(s) of the subject.
- Healthy subjects as established by medical history and clinical examination before entering into the study.
- Born full-term (i.e. born after a gestation period of at least 37 weeks inclusive).
- Infants who have not received a previous dose of hepatitis B vaccine or those who have received only 1 dose of hepatitis B vaccine administered at least 30 days prior to enrolment.

### 4.3. Exclusion criteria for enrolment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Child in care
  
  Please refer to the GLOSSARY OF TERMS for the definition of child in care.
• Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the dose of study vaccine or planned use during the study period.

• Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs since birth prior to the first vaccine dose. For corticosteroids, this will mean prednisone ≥ 0.5 mg/kg/day, or equivalent. Inhaled and topical steroids are allowed.

• Previous vaccination against *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, rotavirus, pneumococcus, hepatitis A and/or poliovirus; more than one previous dose of hepatitis B vaccine.

• Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before and ending 30 days after the dose of vaccines. Subjects may receive inactivated influenza vaccine or pandemic influenza vaccines any time during the study according to the national recommendation. Measles, mumps, rubella and varicella vaccination are allowed 30 days before or 30 days after the final vaccination of Hib-MenCY-TT or *PedvaxHIB*.

• History of *Neisseria meningitidis*, *Haemophilus influenzae* type b, diphtheria, tetanus, pertussis, pneumococcus, hepatitis B, hepatitis A, rotavirus, and/or poliovirus disease.

• Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing required).

• History of allergic disease or reactions likely to be exacerbated by any component of the vaccines, including dry natural latex rubber. Hypersensitivity to any component of the vaccines, including gelatin or neomycin.

• Major congenital defects or serious chronic illnesses.

• History of any neurologic disorders or seizures. A single, simple febrile seizure is allowed.

• Subjects with history of intussusceptions or uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusceptions.

• Acute disease and/or fever at the time of enrolment.
  - Fever is defined as temperature ≥38.0°C/100.4°F by any method. The preferred route for recording temperature in Epoch 001 will be rectal and axillary in Epoch 002.
  - Subjects with minor illness (such as mild diarrhoea, mild upper respiratory infection) without fever may, be enrolled at the discretion of the investigator.

• Administration of immunoglobulins and/or blood products since birth or planned administration during the study period.
5. CONDUCT OF THE STUDY

5.1. Regulatory and ethical considerations, including the informed consent process

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with the ICH Guideline for Good Clinical Practice (GCP), all applicable subject privacy requirements and the guiding principles of the Declaration of Helsinki.

The study has been designed and will be conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the paediatric population (ICH E11) and all other applicable ethical guidelines.

GSK will obtain favourable opinion/approval to conduct the study from the appropriate regulatory agency, in accordance with applicable regulatory requirements, prior to a site initiating the study in that country.

Conduct of the study includes, but is not limited to, the following:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject’s parent(s)/LAR(s) informed consent.
- Investigator reporting requirements as stated in the protocol.

GSK will provide full details of the above procedures to the investigator, either verbally, in writing, or both.

Freely given and written informed consent must be obtained from each subject and/or each subject’s parent(s)/LAR(s), as appropriate, prior to participation in the study.

GSK Biologicals will prepare a model Informed Consent Form (ICF) which will embody the ICH GCP and GSK Biologicals required elements. While it is strongly recommended that this model ICF is to be followed as closely as possible, the informed consent requirements given in this document are not intended to pre-empt any local regulations which require additional information to be disclosed for informed consent to be legally effective. Clinical judgement, local regulations and requirements should guide the final structure and content of the local version of the ICF.

The investigator has the final responsibility for the final presentation of the ICF, respecting the mandatory requirements of local regulations. The ICF generated by the investigator with the assistance of the sponsor’s representative must be acceptable to GSK Biologicals and be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC.
5.2. **Subject identification and randomisation of treatment**

Treatment allocation: 600 subjects will be enrolled. The first 200 will be enrolled in the blood sample sub-cohort 3, the next 200 in the blood sample sub-cohort 2 and the last 200 in the blood sample cohort 1. Within each blood sample sub-cohort subjects will be randomized 1:1 to either HibCY or PedHIB groups resulting in the following treatment group BS cohorts (see the study procedures table in Section 5.5 for the blood sampling schedule):

- **Hib-MenCY-TT** treatment group BS cohorts = HibCY1, HibCY2, or HibCY3.
- **PedvaxHIB** treatment group BS cohorts = PedHIB1, PedHIB2 or PedHIB3.

5.2.1. **Subject identification**

Subject numbers will be assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

5.2.2. **Randomisation of treatment**

5.2.2.1. **Randomisation of supplies**

The randomisation of supplies within blocks will be performed at GSK Biologicals, using MATerial EXcellence (MATEX), a program developed for use in Statistical Analysis System (SAS®) (Cary, NC, USA) by GSK Biologicals. Entire blocks will be shipped to the study centres /warehouse(s).

To allow GSK Biologicals to take advantage of greater rates of recruitment than anticipated at individual centres in this multi-centre study and to thus reduce the overall study recruitment period, an over-randomisation of supplies will be prepared.

5.2.2.2. **Treatment allocation to the subject (Amended: 16 June 2014)**

The treatment numbers will be allocated by *component*.

5.2.2.2.1. **Study group and treatment number allocation**

Allocation of the subject to a study group at the investigator site will be performed using a randomisation system on internet (SBIR). The randomization will be stratified within each sub-cohort i.e. for each sub-cohort, a minimization algorithm with center as minimization factor will be used. Target distribution of the population across the six BS is shown in Table 6.

After obtaining the signed and dated ICF and having checked the eligibility of the subject, the site staff in charge of the vaccine administration will access SBIR. Upon providing the subject identification number, the randomisation system will determine the study group and will provide the treatment number to be used for each dose.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.
When SBIR is not available, please refer to the SBIR user guide or the Study Procedures Manual (SPM) for specific instructions.

Table 6  Number of subjects required for enrolment

<table>
<thead>
<tr>
<th>BS COHORT</th>
<th>Number of subjects to be enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>HibCY1</td>
<td>~100</td>
</tr>
<tr>
<td>HibCY2</td>
<td>~100</td>
</tr>
<tr>
<td>HibCY3</td>
<td>~100</td>
</tr>
<tr>
<td>PedHIB1</td>
<td>~100</td>
</tr>
<tr>
<td>PedHIB2</td>
<td>~100</td>
</tr>
<tr>
<td>PedHIB3</td>
<td>~100</td>
</tr>
</tbody>
</table>

5.2.2.2.2. Treatment number allocation for subsequent doses

For each dose subsequent to the first dose, the study staff in charge of the vaccine administration will access SBIR, provide the subject identification number, and the system will provide a treatment number consistent with the allocated study group.

The number of each administered treatment must be recorded in the eCRF on the Vaccine Administration screen.

5.2.3. Allocation of subjects to assay subsets

Refer to Section 4.1 for a description of BS cohorts and to Table 12 for the assay timepoints for the pre-specified BS cohorts.

5.3. Method of blinding

This study will be conducted in an open manner, since the presentation and number of vaccines to be administered per visit differ for each group.

The laboratory in charge of the laboratory testing will be blinded to the treatment, and codes will be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

5.4. General study aspects

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying SPM. The SPM provides the investigator and the site personnel with administrative and detailed technical information that does not impact the safety of the subjects.
### 5.5. Outline of study procedures

#### Table 7  List of study procedures, Epoch 001 *(Amended: 16 June 2014)*

<table>
<thead>
<tr>
<th>Age</th>
<th>6-12 weeks</th>
<th>4 months</th>
<th>6 months</th>
<th>7 months</th>
<th>12-15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch</td>
<td>Epoch 001</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Visit</td>
<td>Visits 1</td>
<td>Visits 2</td>
<td>Visits 3</td>
<td>Visits 4</td>
<td>ESFU1</td>
</tr>
<tr>
<td>Visit 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESFU1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sampling timepoint</strong></td>
<td><strong>Timing</strong></td>
<td><strong>DAYS 0</strong></td>
<td><strong>MONTHS 2</strong></td>
<td><strong>MONTHS 4</strong></td>
<td><strong>MONTHS 5</strong></td>
</tr>
<tr>
<td>Informed consent</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demography</td>
<td>●</td>
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<tr>
<td>Check inclusion criteria</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check exclusion criteria</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check contraindications</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
</tr>
<tr>
<td>Check warnings and precautions</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
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<td></td>
</tr>
<tr>
<td>Vaccination History</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History-directed physical examination</td>
<td>○</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-vaccination measurement of body temperature (rectal)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measure/record length and weight</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood sampling for antibody determination (5 mL)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td>○</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recording of treatment number</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record time between reconstitution of Hib-MenCY-TT and vaccination</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination with Hib-MenCY-TT</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination with PedvaxHiB</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination with Rotarix</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination with Pediarix</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination with Prevnar 13</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject will be observed for 30 minutes after each vaccination</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>6-12 weeks</td>
<td>4 months</td>
<td>6 months</td>
<td>7 months</td>
<td>12-15 months</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Epoch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td>VISIT 1</td>
<td>VISIT 2</td>
<td>VISIT 3</td>
<td>VISIT 4</td>
<td>ESFU¹</td>
</tr>
<tr>
<td></td>
<td>SAFETY (ALL SUBJECTS)</td>
<td>BLOOD DRAW IMMUNOGENICITY (SUB-COHORTS HibCY1, HibCY2, PedHIB1 and PedHIB2) and SAFETY (ALL SUBJECTS)</td>
<td>BLOOD DRAW IMMUNOGENICITY (SUB-COHORTS HibCY1, HibCY3, PedHIB1 and PedHIB3) and SAFETY (ALL SUBJECTS)</td>
<td>ESFU¹ UP TO THE DAY PRECEDING THE START OF EPOCH 002</td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>DAYS 0</td>
<td>MONTHS 2</td>
<td>MONTHS 4</td>
<td>MONTHS 5</td>
<td>MONTHS 10-13</td>
</tr>
<tr>
<td>Sampling timepoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dispense diary cards, measurement gauge, thermometer, and tip sheet</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily post-vaccination recording of solicited symptoms (Day 0 to Day 3) on a diary card</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily post-vaccination recording of unsolicited AEs (Day 0 to Day 30)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Return of diary cards (solicited and unsolicited symptoms)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary card transcription</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record any concomitant medications/vaccination¹</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Record any intercurrent medical conditions⁵,⁶</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Reporting of SAEs, SAEs related to study participation or to a concurrent GSK medication/vaccine or any fatal SAE⁴,⁷</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

● is used to indicate a study procedure that requires documentation in the individual eCRF.
○ is used to indicate a study procedure that does not require documentation in the individual eCRF.

¹ An extended safety follow-up will be done up to the start of Epoch 002 (Visit 5). **If a subject does not return for Visit 5 (Epoch 002), study personnel will review the subject's electronic medical records and/or contact the subject’s parent/guardian by phone to obtain the subject’s safety information.**

² Recording of any meningococcal, pneumococcus, Hib, diphtheria, tetanus, pertussis, poliovirus, rotavirus and/or HepB vaccination since birth.

³ 2/3 of the subjects will have a blood draw at Visit 3 and at Visit 4.

⁴ Refer to Section 6.6. Note: Record any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.

⁵ Occurrence of meningococcal diseases should be documented in the SAE screen in the eCRF since the last visit.

⁶ Refer to Section 6.7.

⁷ SAEs are collected from Day 0 until study end.
Table 8  List of study procedures, Epoch 002 (Amended: 16 June 2014)

<table>
<thead>
<tr>
<th>Age</th>
<th>12 – 15 months</th>
<th>13 – 16 months</th>
<th>18 – 21 months</th>
<th>19 – 22 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch 002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISIT 5</td>
<td>VISIT 6</td>
<td>VISIT 7</td>
<td>VISIT 8</td>
<td></td>
</tr>
<tr>
<td>BLOOD DRAW</td>
<td>2nd DOSE OF HAVRIX</td>
<td>IMMUNOGENICITY (ALL SUBJECTS)</td>
<td>IMMUNOGENICITY (SUB-COHORTS HIBCY2, HIBCY3, PEDHIB2, PEDHIB3) AND SAFETY (ALL SUBJECTS)</td>
<td></td>
</tr>
<tr>
<td>IMMUNOGENICITY (ALL SUBJECTS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAFETY (ALL SUBJECTS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>MONTHS 10-13</td>
<td>MONTHS 11-14</td>
<td>MONTHS 16-19</td>
<td>MONTHS 17-20</td>
</tr>
<tr>
<td>Sampling timepoint</td>
<td>Post-Vacc4</td>
<td>Post-Vacc4</td>
<td>Post-Vacc4</td>
<td>Post-Vacc5</td>
</tr>
<tr>
<td>Check contraindications</td>
<td>○</td>
<td>○</td>
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<td>○</td>
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<tr>
<td>Check warnings and precautions</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pre-vaccination measurement of body temperature (Axillary)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Blood sampling for antibody determination (5 mL)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Recording of treatment number</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Record time between reconstitution of Hib-MenCY-TT and vaccination</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination with Hib-MenCY-TT</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination with PedvaxHIB</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination with Havrix</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Vaccination with Prevnar 13</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Subject will be observed for 30 minutes after each vaccination</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Dispense diary cards</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Daily post-vaccination recording of solicited symptoms (Day 0 to Day 3) on a diary card</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Recording of medications/vaccinations Post-dose 2 of Havrix on the diary card</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Return of diary cards (solicited and unsolicited symptoms)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Return of diary cards (medications/vaccinations Post-dose 2 of Havrix)</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Daily post-vaccination recording of unsolicited AEs (Day 0 to Day 30)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Diary card transcription</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Record any concomitant medications/vaccination²</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Record any intercurrent medical conditions³⁴</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>
### Age Categories

<table>
<thead>
<tr>
<th>Age</th>
<th>12 – 15 months</th>
<th>13 – 16 months</th>
<th>18 – 21 months</th>
<th>19 – 22 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch 002</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>VISIT 5</th>
<th>VISIT 6</th>
<th>VISIT 7</th>
<th>VISIT 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BLOOD DRAW IMMUNOGENICITY (ALL SUBJECTS)</td>
<td>2ND DOSE OF HAVRIX</td>
<td>BLOOD DRAW IMMUNOGENICITY (SUB-COHORTS HibCY2, HibCY3, PEDHIB2, PEDHIB3) AND SAFETY (ALL SUBJECTS)</td>
</tr>
</tbody>
</table>

#### Timing

<table>
<thead>
<tr>
<th>Timing</th>
<th>MONTHS 10-13</th>
<th>MONTHS 11-14</th>
<th>MONTHS 16-19</th>
<th>MONTHS 17-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampling timepoint</td>
<td>Post-Vacc4</td>
<td>Post-Vacc5</td>
<td>Post-Vacc5</td>
<td>Post-Vacc5</td>
</tr>
</tbody>
</table>

**Reporting of SAEs, SAEs related to study participation or to a concurrent GSK medication/vaccine or any fatal SAE**

1. All subjects will have blood drawn at Visit 6. 2/3 of the subjects will have blood drawn at Visit 8.
2. Refer to Section 6.6. Note: Record any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.
3. Occurrence of meningococcal diseases should be documented in the SAE screen in the eCRF.
4. Refer to Section 6.7.
5. SAEs are collected from Day 0 until study end.

---

*● is used to indicate a study procedure that requires documentation in the individual eCRF.*

*○ is used to indicate a study procedure that does not require documentation in the individual eCRF.*

---

**Study conclusion of Epoch 002**

1. All subjects will have blood drawn at Visit 6. 2/3 of the subjects will have blood drawn at Visit 8.
It is the investigator’s responsibility to ensure that the intervals between visits/contacts are strictly followed. These intervals determine each subject’s evaluability in the according-to-protocol analyses.

**Table 9  Intervals between study visits**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Optimal length of interval¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth → Visit 1</td>
<td>6-12 weeks</td>
</tr>
<tr>
<td>Visit 1 → Visit 2</td>
<td>49-83 days</td>
</tr>
<tr>
<td>Visit 2 → Visit 3</td>
<td>56-90 days²</td>
</tr>
<tr>
<td>Visit 3 → Visit 4</td>
<td>30-48 days²</td>
</tr>
<tr>
<td>Birth → Visit 5</td>
<td>12-15 months⁵</td>
</tr>
<tr>
<td>Visit 5 → Visit 6</td>
<td>30-48 days³</td>
</tr>
<tr>
<td>Visit 5 → Visit 7</td>
<td>180-210 days</td>
</tr>
<tr>
<td>Visit 7 → Visit 8</td>
<td>30-48 days¹</td>
</tr>
</tbody>
</table>

¹Subjects will not be eligible for inclusion in the According to Protocol cohort for analysis if they make the study visit outside this interval and are not within the age range specified for each visit (See Table 7 and Table 8).
²Advisory Committee on Immunization Practices (ACIP) recommendation states that the minimum age of the last HepB dose is 24 weeks and this last dose should be administered at least 8 weeks after the previous dose.
³It is preferred that subjects come in for this visit after 30 days. If subjects return for this visit prior to 30 days they should take home the diary card and continue to record unsolicited safety information until 30 days post-vaccination and return it upon their next visit.
⁴For Visit 3 to Visit 4, Visit 5 to Visit 6 and Visit 7 to Visit 8, an interval of 21-48 days will be considered for the ATP cohort for immunogenicity. Refer to Section 10.4 for the definition of the cohorts for analysis.
⁵From the day the subject turns 12 months to the day before turning 16 months.

5.6. **Detailed description of study procedures**

5.6.1. **Informed consent**

The signed informed consent of the subject’s parent(s)/LAR(s) must be obtained before study participation. Refer to Section 5.1 for the requirements on how to obtain informed consent. This will be recorded in the eCRF.

5.6.2. **Check inclusion and exclusion criteria**

Check all inclusion and exclusion criteria as described in Sections 4.2 and 4.3 before enrolment.

5.6.3. **Collect demographic data**

Record demographic data such as age, gender and race in the subject’s eCRF.

5.6.4. **Medical history**

Obtain the subject’s medical history by interview and/or review of the subject’s medical records and record any pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination in the eCRF.
5.6.5. **History directed physical examination**

Perform a history directed physical examination at Visit 1. If the investigator determines that the subject’s health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled.

Treatment of any abnormality observed during this examination has to be performed according to local medical practice outside this study or by referral to an appropriate health care provider.

5.6.6. **Check contraindications, warnings and precautions to vaccination**

Contraindications, warnings and precautions to vaccination must be checked at the beginning of each vaccination visit. Refer to Sections 6.4 and 6.5 for more details.

5.6.7. **Assess pre-vaccination body temperature**

The axillary, rectal, oral or tympanic body temperature of all subjects needs to be measured prior to any study vaccine administration. The preferred route for recording temperature in Epoch 001 will be rectal and axillary in Epoch 002. If the subject has fever [fever is defined as temperature ≥38.0°C/100.4°F by any method] on the day of vaccination, the vaccination visit will be rescheduled within the allowed interval for this visit (see Table 9).

5.6.8. **Study group and treatment number allocation**

Study group and treatment number allocation will be performed as described in Section 5.2. The number of each administered treatment must be recorded in the eCRF.

5.6.9. **Sampling**

Refer to the Module on Biospecimen Management in the SPM for detailed instructions for the collection, handling and processing of the samples.

5.6.9.1. **Blood sampling for safety or immune response assessments**

As specified in the List of Study Procedures in Section 5.5 (Table 7 and Table 8), blood samples are taken during certain study visits. Refer to the Module on Biospecimen Management in the SPM for general handling of blood samples.

- A volume of approximately 5 mL of whole blood (approximately 1.8 mL serum) should be drawn from all subjects for each analysis of humoral immune response. After centrifugation, serum samples should be kept at -20°C/-4°F or below until shipment. Refer to the SPM for more details on sample storage conditions.

5.6.10. **Study Vaccine(s) administration**

- After completing the required procedures prior to vaccination, study vaccines will be administered following the detailed description of the vaccine administration
procedure given in Section 6. If the investigator or delegate determines that the subject’s health on the day of vaccination temporarily precludes vaccination, the visit will be rescheduled within the interval for this visit.

- The subjects will be observed closely for at least 30 minutes following the administration of the vaccines, with appropriate medical treatment readily available in case of anaphylaxis.

### 5.6.11. Check and record concomitant medication/vaccination and intercurrent medical conditions

Concomitant medication/vaccination must be checked and recorded in the eCRF as described in Section 6.6. Note: Record any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.

Intercurrent medical conditions must be checked and recorded in the eCRF as described in Section 6.7.

### 5.6.12. Recording of AEs and SAEs (Amended 16 June 2014)

- Refer to Section 8.3 for procedures for the investigator to record AEs and SAEs. Refer to Section 8.4 for guidelines on how to submit SAE reports to GSK Biologicals.
- The subjects’ parent(s)/LAR(s) will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.
- At visits 1, 2, 3 and 5, diary cards will be provided to the subject’s parent(s)/LAR(s). The subject’s parent(s)/LAR(s) will record body (rectal or axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. The subject’s parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit.
- **Diary cards will be provided to the subject’s parent(s)/LAR(s) at Visit 7. The subject’s parent(s)/LAR(s) will record any medications/vaccinations given/received (i.e. on the day of vaccination and during the next 30 days occurring after vaccination, as well as any anti-pyretics administered within 6 hours prior to and 12 hours following vaccination. The subject’s parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at Visit 8.**
- Collect and verify completed diary cards during discussion with the subject’s parent(s)/LAR(s) on Visits 2, 3, 4, 6 and 8.
- Any unreturned diary cards will be sought from the subject’s parent(s)/LAR(s) through telephone call(s) or any other convenient procedure. The investigator will transcribe the collected information into the eCRF in English. Do not solicit specific information through the phone call.
5.6.13. Procedures during the extended safety follow-up period of Epoch 001 (Amended: 16 June 2014)

Note that some of the procedures to be performed during the extended safety follow-up period of Epoch 001 (such as recording of SAEs, recording of concomitant medications/vaccinations not allowed during the epoch) are also performed during the active phase of Epochs 001 and 002 and are described in Section 5.6.

If a subject does not return for Visit 5 (Epoch 002), study personnel will review the subject’s electronic medical records and/or contact the subject’s parent/guardian by phone to obtain the subject’s safety information.

5.6.14. Study conclusion (Amended 16 June 2014)

5.6.14.1. Epoch 001 study conclusion

Data analysis for safety and immunogenicity will proceed for Epoch 001 when all data has been collected up to study end.

5.6.14.2. Epoch 002 study conclusion

The study will be concluded upon the final blood draw at visit 8 of Epoch 002. Data analysis for the safety and immunogenicity for Epoch 002 will proceed when all data collected up to Visit 8 of Epoch 002 have been cleaned and frozen.

The investigator will:

• review data collected to ensure accuracy and completeness
• complete the Study Conclusion screen in the eCRF.

5.7. Biological sample handling and analysis

Please refer to the SPM for details on biospecimen management (handling, storage and shipment).

Samples will not be labelled with information that directly identifies the subject but will be coded with the identification number for the subject (subject number).

Under the following circumstances, additional testing on the samples may be performed by GSK Biologicals outside the scope of this protocol:

• Collected samples may be used in other assays, for test improvement or development of analytical methods related to the study vaccines and its constituents or the disease under study.
• Collected samples may be used for purposes related to the quality assurance of data generated linked to the study vaccines or the disease under study, such as for maintenance of assays described in this protocol and comparison between analytical methods and/or laboratories.
Information on further investigations and their rationale can be obtained from GSK Biologicals.

Any sample testing will be done in line with the consent of the individual subject’s parent(s)/LAR(s).

Refer also to the Investigator Agreement, where it is noted that the investigator cannot perform any other biological assays except those described in the protocol or its amendment(s).

If additional testing is performed, the marker priority ranking given in Section 5.7.4 may be changed.

Collected samples will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless local rules, regulations or guidelines require different timeframes or different procedures, which will then be in line with the subject consent. These extra requirements need to be communicated formally to and discussed and agreed with GSK Biologicals.

5.7.1. Use of specified study materials

When materials are provided by GSK Biologicals, it is MANDATORY that all clinical samples (including serum samples) be collected and stored exclusively using those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from the ATP analysis (See Section 10.4 for the definition of study cohorts/data sets to be analysed). The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement. However, when GSK Biologicals does not provide material for collecting and storing clinical samples, appropriate materials from the investigator’s site must be used. Refer to the Module on Clinical Trial Supplies in the SPM.

5.7.2. Biological samples

Table 10  Biological samples

<table>
<thead>
<tr>
<th>Sample type</th>
<th>Quantity</th>
<th>Unit</th>
<th>Timepoint</th>
<th>Blood sample sub-cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>approximately 5 ml</td>
<td>Visit 3</td>
<td>HibCY1, HibCY2, PedHIB1, PedHIB2</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>approximately 5 ml</td>
<td>Visit 4</td>
<td>HibCY1, HibCY3, PedHIB1, PedHIB3</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>approximately 5 ml</td>
<td>Visit 6</td>
<td>HibCY1, HibCY2, HibCY3, PedHIB1, PedHIB2, PedHIB3</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>approximately 5 ml</td>
<td>Visit 8</td>
<td>HibCY2, HibCY3, PedHIB2, PedHIB3</td>
<td></td>
</tr>
</tbody>
</table>

* Refer to Section 5.2 for blood sample sub-cohort description.

5.7.3. Laboratory assays

Please refer to APPENDIX A for a detailed description of the assays performed in the study. Please refer to APPENDIX B for the address of the clinical laboratories used for sample analysis.
Table 11  Humoral Immunity (Antibody determination)

<table>
<thead>
<tr>
<th>System</th>
<th>Component</th>
<th>Assay Method</th>
<th>Test kit/ Manufacturer</th>
<th>Assay Unit</th>
<th>Assay Cut-off</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>Rotavirus Ab. IgA</td>
<td>Enzyme Linked Immuno Sorbent Assay</td>
<td>NA</td>
<td>unit per milliliter</td>
<td>20</td>
<td>GSK Biologicals*</td>
</tr>
<tr>
<td>Serum</td>
<td>Hepatitis A Virus Ab</td>
<td>Enzyme Linked Immuno Sorbent Assay</td>
<td>NA</td>
<td>milli-international unit per milliliter</td>
<td>15</td>
<td>GSK Biologicals*</td>
</tr>
<tr>
<td>Serum</td>
<td>Haemophilus influenza type b.Polyribosyl Ribitol Phosphate Ab</td>
<td>Enzyme Linked Immuno Sorbent Assay</td>
<td>NA</td>
<td>µg/ml</td>
<td>.15</td>
<td>GSK Biologicals*</td>
</tr>
<tr>
<td>Serum</td>
<td>Neisseria meningitidis Serogroup Y L3v S1975 Ab</td>
<td>Serum Bactericidal Assay using human complement</td>
<td>NA</td>
<td>1/dilution</td>
<td>4</td>
<td>GSK Biologicals*</td>
</tr>
<tr>
<td>Serum</td>
<td>Neisseria meningitidis Serogroup C L3v C11 Ab</td>
<td>Serum Bactericidal Assay using human complement</td>
<td>NA</td>
<td>1/dilution</td>
<td>4</td>
<td>GSK Biologicals*</td>
</tr>
<tr>
<td>Serum</td>
<td>Pneumococcal antigens</td>
<td>Enzyme Linked Immuno Sorbent Assay</td>
<td>NA</td>
<td>µg/mL</td>
<td>0.15</td>
<td>Dr. Goldblatt Institute of Child Health</td>
</tr>
</tbody>
</table>

§Refer to APPENDIX B for the laboratory addresses

*GSK Biologicals laboratory refers to the Global Vaccines Clinical Laboratories (GVCL) in Wavre, Belgium; Laval, Canada.

The GSK Biologicals’ clinical laboratories have established a Quality System supported by procedures. The activities of GSK Biologicals’ clinical laboratories are audited regularly for quality assessment by an internal (sponsor-dependent) but laboratory-independent Quality Department.
5.7.4. Biological samples evaluation

5.7.4.1. Immunological read-outs

Table 12  Immunological read-outs

<table>
<thead>
<tr>
<th>Blood sampling timepoint</th>
<th>Sub-cohort Name</th>
<th>No. subjects</th>
<th>Component</th>
<th>Components priority rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 3 months 4</td>
<td>HibCY1</td>
<td>~100</td>
<td>anti-Rota IgA, anti-PRP*</td>
<td>anti-Rota IgA, anti-PRP</td>
</tr>
<tr>
<td></td>
<td>HibCY2</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB1</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB2</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 4 months 5</td>
<td>HibCY1</td>
<td>~100</td>
<td>anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, anti-PRP**, hSBA-MenC, hSBA-MenY,</td>
<td>anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, anti-PRP, hSBA-MenC, hSBA-MenY,</td>
</tr>
<tr>
<td></td>
<td>HibCY3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB1</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 6 months 11-14</td>
<td>HibCY1</td>
<td>~100</td>
<td>anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, anti-PRP, hSBA-MenC, hSBA-MenY, Anti-HAV,</td>
<td>anti-PRP, anti-S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, hSBA-MenC, hSBA-MenY, Anti-HAV,</td>
</tr>
<tr>
<td></td>
<td>HibCY2</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HibCY3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB1</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB2</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 8 months 17-20</td>
<td>HibCY2</td>
<td>~100</td>
<td>anti-HAV</td>
<td>anti-HAV</td>
</tr>
<tr>
<td></td>
<td>HibCY3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB2</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PedHIB3</td>
<td>~100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Anti-PRP will only be tested for Sub-cohort PedHIB1 and PedHIB2 at this timepoint.
**Anti-PRP will only be tested for Sub-cohort HibCY1 and HibCY3 at this timepoint.
†Note: Subjects in the PedHIB group will have blood drawn Post-dose 3 after PedvaxHIB vaccination at this timepoint.

In case of insufficient blood sample volume to perform assays for all antibodies, the samples will be analysed according to priority ranking provided in Table 12.

5.7.5. Immunological correlates of protection

Antibodies against Rotavirus:

The presence of rotavirus-specific IgA at the mucosal surface (reflected in stool samples) and in serum after natural infection is predictive of protection against rotavirus, however, this has not always been proven to be true after vaccination [Clark, 2008]. Nevertheless,
measurement of serum and stool IgA levels by ELISA [Bernstein, 1999] are still the best measure of protection against rotavirus after a vaccination series has been completed.

**Antibodies against Hepatitis A:**

Prior to licensure of vaccines for Hepatitis A (HAV), it was generally accepted that concentrations of anti-HAV 10-20 mIU/mL 1 to 2 months after prophylactic administration of immune globulin offered protection against HAV. In vitro studies of cultured HAV also indicated that antibody <20 mIU/mL showed high neutralizing capabilities [Plotkin, 2008; Fiore, 2008].

**Antibodies against polyribosyl ribitol phosphate (PRP):**

Data from subjects given unconjugated Hib vaccine suggest that, in the absence of induction of immunological memory, a concentration of 0.15 µg/mL is indicative of short-term protection, with 1 µg/mL considered indicative of long-term protection [Kayhty, 1983; Anderson, 1984].

**Antibodies against N. meningitidis serogroups C and Y:**

For MenC, a baseline serum bactericidal titer of ≥1:4 was a strong predictor of protection [Goldschneider, 1969]. To date, no MenY baseline serum bactericidal titer predictive of protection has been published. However, in the absence of a demonstrated correlate of protection for MenY, it has been common practice to extend the 1:4 cut-off to MenY as well. However, during the conduct of the Phase III pivotal study evaluating the Hib-MenCY-TT vaccine, the Food and Drug administration (FDA) has requested to consider the use of a more conservative cut-off (i.e. 1:8) for the hSBA analysis. Therefore, in this study the cut-off of 1:8 will be used for statistical analyses and for determining the list of sub-optimal responders to Hib-MenCY-TT.

**Antibodies against S. pneumoniae serotypes**

The WHO working group has recommended an IgG anticapsular polysaccharide concentration ≥0.35 µg/mL measured by ELISA one month after primary vaccination as the protective threshold [Siber, 2007; Jodar, 2003].

The investigator is encouraged to share the immunological assay results for non-responders with the subjects’ parent(s)/LAR(s).

**Suboptimal responders**

Investigators will be provided with individual listings of sub-optimal responders for those antigens with an accepted correlate of protection. Individual listings of subjects with hSBA-MenC titer < 1:8, hSBA-MenY titer < 1:8 and/or anti-PRP concentration <1.0µg/mL will be provided to the investigator after the vaccination series with that particular antigen is completed. For both groups, anti-HAV concentrations <15mIU/mL post-dose 1 of Havrix (Visit 6) will be provided.
For the study subjects identified as non-responders, it remains the responsibility of the study investigator in charge of the subject’s clinical management to determine the medical need for re-vaccination and to re-vaccinate the subjects as per local/regional practices.

Immunogenicity results and group allocation of all subjects will be provided when the individual listings of the statistical report have been released.

6. STUDY VACCINES AND ADMINISTRATION (AMENDED 16 JUNE 2014)

6.1. Description of study vaccines

The vaccine to be used has been developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each the candidate vaccine are described in separate Quality Assurance documents (e.g. release protocols, certificate of analysis) and the required approvals have been obtained.

The vaccines are labelled and packed according to applicable regulatory requirements.

Commercial vaccines are assumed to comply with the specifications given in the manufacturer’s Summary of Product Characteristics.
<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/product name</th>
<th>Formulation</th>
<th>Presentation</th>
<th>Volume to be administered</th>
<th>number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>PRP=2.5µg TT; PSC=5µg TT; PsY=5µg TT; TT=20µg</td>
<td>Lyophilized monodose vials (white freeze dried pellet). To be reconstituted before use with saline diluent. The reconstituted vaccine is clear and colorless.</td>
<td>0.5 mL</td>
<td>4</td>
</tr>
<tr>
<td>NaCl</td>
<td>NaCl=150mM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotarix</td>
<td>HRV</td>
<td>HRV RIX4144=10⁶.5 CCID₅₀</td>
<td>Single dose vial. The vaccine is a white powder.</td>
<td>1 mL</td>
<td>2</td>
</tr>
<tr>
<td>Rotarix Diluent:</td>
<td>CaCO₃</td>
<td>CaCO₃=60mg</td>
<td>Liquid buffer in pre-filled syringe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Havrix</td>
<td>HAV</td>
<td>HM175 strain hepatitis A virus=720ELU; Al(OH)₃=250µg Al³⁺</td>
<td>Liquid in monodose vials (turbid white suspension)</td>
<td>0.5 mL</td>
<td>2</td>
</tr>
<tr>
<td>Prevnar 13 (Pfizer)</td>
<td>Prevenar 13</td>
<td>PS1=2.2µg CRM197; PS3=2.2µg CRM197; PS4=2.2µg CRM197; PS5=2.2µg CRM197; PS6A=2.2µg CRM197; PS6B=4.4µg CRM197; PS7F=2.2µg CRM197; PS9V=2.2µg CRM197; PS14=2.2µg CRM197; PS18C=2.2µg CRM197; PS19A=2.2µg CRM197; PS19F=2.2µg CRM197; PS23F=2.2µg CRM197; AlPO₄=125µg Al³⁺</td>
<td>Liquid: Single-dose pre-filled syringe containing a white suspension</td>
<td>0.5 mL</td>
<td>4</td>
</tr>
<tr>
<td>PedvaxHIB (Merck)</td>
<td>Pedvax Hib (Merck)</td>
<td>PRP=7.5µg; Neisseria meningitidis OMPC=125µg; AAHSA=225µg</td>
<td>Liquid: monodose vials containing a slightly opaque white suspension</td>
<td>0.5 mL</td>
<td>3</td>
</tr>
<tr>
<td>Pediarix</td>
<td>DTPa-HBV-IPV</td>
<td>DTÆ=30IU; TTÆ=40IU; PT=25µg; FHA=25µg; PRN=8µg; HBsAg=10µg; Inactivated Poliovirus type 1 (Mahoney strain)=40DU; Inactivated Poliovirus type 2 (MEF-1 strain)=8DU; Inactivated Poliovirus type 3 (Saukett)</td>
<td>Pre-filled syringes containing a turbid white suspension</td>
<td>0.5 mL</td>
<td>3</td>
</tr>
</tbody>
</table>
Additionally, the fourth dose of DTaP (Infanrix) will be provided outside of the study by GSK as the CDC recommends DTaP be provided from the same manufacturer and to ensure that all subjects in the study receive the recommended amount of doses of DTaP. A parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.

6.2. Storage and handling of study vaccines

The study vaccines must be stored at the respective label storage temperature conditions in a safe and locked place. Access to the storage space should be limited to authorized study personnel. The storage conditions will be assessed during pre-study activities under the responsibility of the sponsor study contact. The storage temperature should be continuously monitored with calibrated (if not validated) temperature monitoring device(s) and recorded. Refer to the Module on Clinical Trial Supplies in the SPM for more details on storage of the study vaccines.

Temperature excursions must be reported in degree Celsius.

In case of temperature excursion below +2.0°C down to 0.0°C impacting IMP(s) there is no need to report in (e)TDF, but adequate actions must be taken to restore the +2 to +8°C/+36 to +46°F label storage temperature conditions. The impacted IMP(s) may still be administered, but the site should avoid re-occurrence of such temperature excursion. Refer to the Module on Clinical Trial Supplies in the SPM for more details on actions to take.

Refer to the Module on Clinical Trial Supplies in the SPM for details and instructions on the temperature excursion reporting and usage decision process, packaging and accountability of the study vaccines.
Table 14  Dosage and administration for the HbCY group

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment Group</th>
<th>Treatment</th>
<th>Route</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HbCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HbCY</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HbCY</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HbCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HbCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HbCY</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HbCY</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HbCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HbCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HbCY</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HbCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HbCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HbCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HbCY</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 7 months 16-19</td>
<td>1</td>
<td>HbCY</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
</tbody>
</table>

*Any licensed influenza vaccine may be given at any time during the study as per local recommendations (≥6 months of age) but if co-administered with the study vaccines it should be administered intramuscularly in the right lower anterolateral thigh at visits 3 and visit 5. MMR, Varicella and Infanrix should not be given within 30 days of any dose of study vaccine.

1 Oral (O)/ Intramuscular (IM)

N/A = Not applicable

Table 15  Dosage and administration for the PedHIB group

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment Group</th>
<th>Treatment</th>
<th>Route</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>PedHIB</td>
<td>Pedvax</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
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<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
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<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 7 months 16-19</td>
<td>1</td>
<td>PedHIB</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
</tbody>
</table>

*Any licensed influenza vaccine may be given at any time during the study as per local recommendations (≥6 months of age) but if co-administered with the study vaccines it should be administered intramuscularly in the right lower anterolateral thigh at visits 3 and visit 5. MMR, Varicella and Infanrix should not be given within 30 days of any dose of study vaccine.

1 Oral (O)/ Intramuscular (IM)

N/A = Not applicable
Reconstitution of study vaccines

GSK Biological’s HibMenCY-TT vaccine:

Hib-MenCY-TT is to be reconstituted only with the accompanying saline diluents.

Withdraw 0.6 mL of the saline diluent vial (saline) into a graduated syringe and inject into one vial of lyophilised Hib-MenCY-TT vaccine (note: cleanse the stopper of the vial containing the pellet of Hib-MenCY-TT prior to addition of the saline). After addition of the saline solution to the pellet, remove the syringe and needle and shake the vial well. The mixture should be well shaken until the pellet is completely dissolved in the saline solution.

The reconstituted vaccine should be a clear and colorless solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered. After reconstitution, Hib-MenCY-TT should be administered immediately.

Withdraw 0.5 mL of the reconstituted vaccine into the graduated syringe. After withdrawal of the reconstituted vaccine into from the vial, the needle must be changed before injection.

The timing related to reconstitution and vaccination of Hib-MenCY-TT will be recorded in the eCRF.

Refer to the SPM for further information.

GSK Biological’s Rotarix vaccine:

This vaccine is supplied as three components: lyophilised vaccine in glass vial with stopper, liquid diluent (1 mL) in glass prefilled syringe with a plunger stopper and a transfer device for reconstitution.

Remove the plastic cover from the vial containing the lyophilised vaccine and connect the transfer device onto the vial by pushing it downwards until the transfer device is properly and solidly placed. Shake the syringe containing the liquid diluent vigorously. The shaking suspension will appear as a turbid liquid with a slow settling white deposit. Remove the stopper from the syringe and connect the syringe onto the transfer device. Inject the entire contents of the syringe into the vial containing the lyophilised vaccine. Shake the vial and examine for complete dispersal. The reconstituted vaccine will appear more turbid than the suspension alone. Withdraw the entire mixture back into the syringe and remove the syringe from the transfer device. Administer the entire content of the syringe ORALLY (on the inside of the cheek). The child should be seated in a reclining position. If the vaccine is not administered immediately, the syringe containing the reconstituted vaccine should be shaken again before ORAL administration. This vaccine should not be injected.

GSK Biologicals’ Pediarix and Havrix and Pfizer’s Prevnar 13 and Merck & Co’s PedvaxHIB are supplied as liquid vaccines and therefore do not need to be reconstituted.
Intramuscular Injection (all study vaccines except for Rotarix)

In the majority of infants (less than 12 months of age), a 25 mm (1 inch), 22-25 gauge needle is sufficient to penetrate muscle in the infant's anterolateral region of the thigh. The following injection technique is recommended [Groswasser, 1997]:

To avoid injection into subcutaneous tissue, spread the skin of the selected vaccine administration site taut between the thumb and forefinger, isolating the muscle. Another acceptable technique for paediatric patients is to grasp the tissue and 'bunch up' the muscle.

- Insert the needle fully into the muscle at a 90°C angle and inject the vaccine into the tissue.
- Withdraw the needle and apply light pressure to the injection site for several seconds with a dry cotton ball or gauze.
- If injections into the anterolateral thigh are performed in children aged 12 months or above, the needle should be at least 25 mm (1 inch).

6.3. Replacement of unusable vaccine doses

In addition to the vaccine doses provided for the planned number of subjects (including over-randomisation when applicable), at least 15% additional vaccine doses will be supplied to replace those that are unusable.

6.4. Contraindications to subsequent vaccination

The following events constitute absolute contraindications to further administration of Hib-MenCY-TT vaccine; Pediarix, PedvaxHIB, Rotarix, Prevnar 13 and Havrix; if any of events occur during the study, the subject must not receive additional doses of vaccine but may continue other study procedures at the discretion of the investigator (see Section 8.5). The subject must be followed until resolution of the event, as with any AE.

Hib-MenCY-TT, Pediarix, Rotarix, PedvaxHIB, Havrix, and Prevnar 13

Absolute contraindications:

- Anaphylactic reaction following the administration of vaccine or any diphtheria toxoid-containing vaccine (Pediarix and Prevnar 13 only).
- Hypersensitivity reaction to any component of the vaccine or diluent.

GSK Biologicals’ Pediarix

Absolute contraindications:

- Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination, and generally consists of major alterations in consciousness, unresponsiveness, generalized or focal seizures that persist more than a few hours,
with failure to recover within 24 hours. Even though causation by DTaP vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, or progressive encephalopathy. Pertussis vaccine should not be administered to individuals with such conditions until a treatment regimen has been established and the condition has stabilized.

- *Pediari* is available in 2 types of prefilled syringes. One type of prefilled syringe has a tip cap which may contain natural rubber latex and a plunger which does not contain latex. The other type has a tip cap and a rubber plunger which contain dry natural latex rubber. Use of these syringes may cause allergic reactions in latex sensitive individuals.

**Contraindications:**

If the following adverse events occur in temporal relation to *Pediari* administration, the decision to administer additional doses of *Pediari* should be carefully considered:

- Fever ≥40.5°C/104.9°F (rectal temperature) within 48 hours of vaccination not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination.
- Persistent, inconsolable crying lasting >3 hours, occurring within 48 hours of vaccination.
- Seizures with or without fever occurring within 3 days of vaccination.

**GSK Biologicals' Rotarix:**

**Absolute contraindications:**

- Infants who develop symptoms suggestive of hypersensitivity after receiving a dose of *Rotarix* should not receive further doses of *Rotarix*.
- Infants with a history of uncorrected congenital malformation of the gastrointestinal tract (such as Meckel’s diverticulum) that would predispose the infant for intussusception should not receive *Rotarix*.
- Infants with a history of intussusceptions should not receive *Rotarix*. In postmarketing experience, intussusceptions resulting in death following a second dose has been reported following a history of intussusception after the first dose.
- Infants with Severe Combined Immunodeficiency Disease (SCID) should not receive *Rotarix*. Postmarketing reports of gastroenteritis (GE), including severe diarrhoea and prolonged shedding of vaccine virus, have been reported in infants who were administered live, oral rotavirus vaccines and later identified as having SCID.

The following events constitute contraindications to administration of any study vaccine at that point in time; if any of these events occur at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the
protocol (see Section 5.5), or the subject may be withdrawn at the discretion of the investigator (see Section 9.2).

The subject must be followed until resolution of the event, as with any AE:

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. temperature < 38.0°C/100.4°F by any method.

**Specific for Rotarix:**

- GE within 7 days preceding the study vaccine administration.

## 6.5. Warnings and precautions

**Hib-MenCY-TT (MenHibrix)**

Since the Hib capsular polysaccharide antigen is excreted in urine, a false positive urine test for Hib infection can be observed within 1-2 weeks post vaccination. Other tests should be performed in order to confirm Hib infection during this period.

**Pediarix:**

Administration of Pediarix is associated with higher rates of fever relative to separately administered vaccines (i.e. DTaP, HepB and IPV). In one study that evaluated medically attended fever after the first dose of Pediarix or separately administered vaccines, infants who received Pediarix had a higher rate of medical encounters for fever within the first 4 days following vaccination. In some infants, these encounters included the performance of diagnostic studies to evaluate other causes of fever.

The vial stopper is latex-free. The tip cap and the rubber plunger of the needless prefilled syringes contain dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

**Rotarix:**

The tip caps and the rubber plunger may contain natural rubber latex and may cause allergic reactions in latex sensitive individuals.

Administration of Rotarix should be delayed in infants suffering from acute diarrhoea or vomiting.

There are no data on the safety and efficacy of Rotarix in infants with gastrointestinal illnesses. Administration of Rotarix may be considered with caution in such infants when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Safety and effectiveness of Rotarix in immunosuppressed infants, including infants on immunosuppressive therapy, should be based on careful consideration of potential benefits and risks.
Excretion of the vaccine virus in the stools is known to occur after vaccination and lasts for 10 days on average with peak excretion around the 7th day. In clinical trials, cases of transmission of excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptoms. *Rotarix* should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or receiving immunosuppressive therapy. Contacts of recent vaccinees should be advised to observe careful hygiene (including washing their hands) when changing children’s nappies.

The risk of intussusception has been evaluated in a large safety trial (including 63,225 infants) conducted in Latin America and Finland. No increased risk of intussusception was observed in this clinical trial following administration of *Rotarix* when compared with placebo.

However, interim postmarketing safety data from a study indicate a transient increased incidence of intussusception in the 31-day period, mostly within 7 days, following administration of the first dose of *Rotarix*. The overall incidence of intussusceptions remains rare. Whether *Rotarix* affects the overall risk of intussusception has not been established.

Therefore, as a precaution, healthcare professionals should follow-up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever). Parents/guardians should be advised to promptly report such symptoms.

**Prevnar 13:**

Apnea following intramuscular vaccination has been observed in some infants born prematurely. Decisions about when to administer an intramuscular vaccine, including Prevnar 13, to infants born prematurely should be based on consideration of the individual infant’s medical status, and the potential benefits and possible risks of vaccination.

**PedvaxHIB:**

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

Refer to the approved product label/package insert.

**6.6. Concomitant medication/product and concomitant vaccination**

At each study visit/contact, the investigator should question the subject’s parent(s)/LAR(s) about any medication/product taken and vaccination received by the subject.
6.6.1. Recording of concomitant medications/products and concomitant vaccination

The following concomitant medications/products/vaccines must be recorded in the eCRF if administered during the indicated recording period:

- All concomitant medications/products, except vitamins and dietary supplements, administered 30 days following each dose of study vaccine.
- Any concomitant vaccination administered in the period starting 30 days before the dose of study vaccine and ending at the last study visit.
- Prophylactic medication (i.e. medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination).
  E.g. an anti-pyretic is considered to be prophylactic when it is given in the absence of fever and any other symptom, to prevent fever from occurring [fever is defined as temperature ≥38.0°C/100.4°F by any method].
- Any concomitant medications/products/vaccines listed in Section 6.6.2.
- Any concomitant medication/product/vaccine relevant to a SAE* or administered at any time during the study period for the treatment of a SAE*.
  * SAEs that are required to be reported per protocol.
- Any antipyretic administered in the period starting 6 hours before vaccination and ending 12 hours after vaccination.

6.6.2. Concomitant medications/products/vaccines that may lead to the elimination of a subject from ATP analyses

The use of the following concomitant medications/products/vaccines will not require withdrawal of the subject from the study but may determine a subject’s evaluability in the ATP analysis. See Section 10.4 for study cohorts/ data sets to be analysed.

- Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (i.e. more than 14 days) during the study period. For corticosteroids, this will mean ≥0.5 mg/kg/day (for paediatric subjects) or equivalent. Inhaled and topical steroids and topical tacrolimus are allowed.
- A vaccine not foreseen by the study protocol administered during the period starting from 30 days before each dose of study vaccine and ending 30 days after*, with the exception of any licensed inactivated influenza vaccine.
  *In case an emergency mass vaccination for an unforeseen public health threat (e.g.: a pandemic) is organised by the public health authorities, outside the routine immunisation program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its SPC or PI and
according to the local governmental recommendations and provided a written approval of the Sponsor is obtained.

- Measles, mumps, rubella and varicella vaccines are allowed 30 days prior or 30 days after the fourth dose vaccination.

- Administration of vaccination against rotavirus not foreseen by the study protocol since birth and for a period up to 1 month after the 2nd Rotarix vaccination.

- Administration of a Hib, Pneumococcal or meningococcal vaccine not foreseen by the study protocol since birth and for a period up to 1 month after the fourth dose.

- Administration of vaccination against Hepatitis A not foreseen by the study protocol since birth and for a period up to 1 month after the 2nd Havrix vaccination.

- Immunoglobulins and/or any blood products administered during the study period.

6.7. **Intercurrent medical conditions that may lead to elimination of a subject from ATP analyses**

At each study visit subsequent to the vaccination visit, it must be verified if the subject has experienced or is experiencing any intercurrent medical condition. If it is the case, the condition(s) must be recorded in the eCRF.

- Intercurrent *Neisseria meningitidis*, *Haemophilus influenzae* type b, rotavirus, pneumococcal or Hepatitis A infection.

- Subjects may be eliminated from the ATP cohort for immunogenicity if, during the study, they incur a condition that has the capability of altering their immune response.

7. **HEALTH ECONOMICS**

Not applicable.

8. **SAFETY**

The investigator or site staff is/are responsible for the detection, documentation and reporting of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) as provided in this protocol.

Each subject’s parent(s)/LAR(s) will be instructed to contact the investigator immediately should they/the subject manifest any signs or symptoms they perceive as serious.
8.1. Safety definitions

8.1.1. Definition of an adverse event

An AE is any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational vaccine(s)/product(s) administration even though they may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational vaccine(s)/product(s) or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Signs, symptoms temporally associated with vaccine administration.
- Significant failure of expected pharmacological or biological action.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of subject’s previous therapeutic regimen).

AEs to be recorded as endpoints (solicited AEs) are described in Section 8.1.3. All other AEs will be recorded as UNSOLICITED AEs.

Examples of an AE DO NOT include:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE/SAE.
- Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
• Pre-existing conditions or signs and/or symptoms present in a subject prior to the first study vaccination. These events will be recorded in the medical history section of the eCRF.

8.1.2. Definition of a serious adverse event

A serious adverse event is any untoward medical occurrence that:

a. Results in death,

b. Is life-threatening,

Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation,

Note: In general, hospitalisation signifies that the subject has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or in an out-patient setting. Complications that occur during hospitalisation are also considered AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event will also be considered serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious.

Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an AE.

d. Results in disability/incapacity,

Note: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza like illness, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation.
8.1.3. Solicited adverse events

8.1.3.1. Solicited local (injection-site) adverse events

A 4-day follow-up (Day 0 to Day 3) of solicited local adverse events at each injection site will be performed after all vaccinations post-primary and post-fourth dose. Data concerning the following adverse events will be solicited using diary cards provided by the sponsor.

The following local (injection-site) AEs will be solicited:

Table 16 Solicited local adverse events

<table>
<thead>
<tr>
<th>All age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
</tr>
<tr>
<td>Redness at injection site</td>
</tr>
<tr>
<td>Swelling at injection site</td>
</tr>
</tbody>
</table>

8.1.3.2. Solicited general adverse events

A 4-day follow-up (Day 0 to Day 3) of solicited general adverse events will be performed after all vaccinations post-primary and post-fourth dose. Data concerning the following adverse events will be solicited using diary cards provided by the sponsor.

The following general AEs will be solicited:

Table 17 Solicited general adverse events

<table>
<thead>
<tr>
<th>Infant/Toddler</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Irritability/Fussiness</td>
</tr>
<tr>
<td>Loss of appetite</td>
</tr>
</tbody>
</table>

Note: Temperature will be recorded in the evening. Should additional temperature measurements be performed at other times of day, the highest temperature will be recorded in the eCRF.

8.1.4. Clinical laboratory parameters and other abnormal assessments qualifying as adverse events or serious adverse events

In absence of diagnosis, abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. medical imaging) that are judged by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE (refer to Sections 8.1.1 and 8.1.2). Clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen following the start of the study will also be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject’s condition, or that are
present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgement in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.2. Events or outcomes not qualifying as adverse events or serious adverse events

8.2.1. Disease/Population-related events or outcomes not qualifying as serious adverse events

Not applicable

8.3. Detecting and recording adverse events, serious adverse events

8.3.1. Time period for detecting and recording adverse events, serious adverse events

All AEs starting within 30 days following administration of each dose of study vaccine must be recorded into the appropriate section of the eCRF, irrespective of intensity or whether or not they are considered vaccination-related.

The time period for collecting and recording SAEs will begin at the first receipt of study vaccine and will end at Visit 8 following the last blood draw for each subject. See Section 8.4 for instructions on reporting of SAEs.

All AEs/SAEs leading to withdrawal from the study will be collected and recorded from the time of the first receipt of study vaccine.

SAEs that are related to the investigational vaccine will be collected and recorded from the time of the first receipt of study vaccine/placebo/comparator until the subject is discharged from the study.

In addition to the above-mentioned reporting requirements and in order to fulfil international reporting obligations, SAEs that are related to study participation (i.e. protocol-mandated procedures, invasive tests, a change from existing therapy) or are related to a concurrent GSK medication/vaccine or any fatal SAE will be collected and recorded from the time the subject consents to participate in the study until she/he is discharged from the study.

An overview of the protocol-required reporting periods for AEs and SAEs is given in Table 18 and Table 19.
## Table 18 Reporting periods for adverse events and serious adverse events for Epoch 001

<table>
<thead>
<tr>
<th>Study activity</th>
<th>1st vacc</th>
<th>4 days post-vacc1</th>
<th>31 days post-vacc1</th>
<th>2nd vacc</th>
<th>4 days post-vacc2</th>
<th>31 days post-vacc2</th>
<th>3rd vacc</th>
<th>4 days post-vacc3</th>
<th>31 days post-vacc3</th>
<th>ESFU up to the day preceding the start of Epoch 002</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reporting of solicited local and general AEs</strong></td>
<td>Visit 1</td>
<td>Day 0-Day3 post-vacc1</td>
<td></td>
<td>Visit 2</td>
<td>Day 0-Day3 post-vacc2</td>
<td></td>
<td>Visit 3</td>
<td>Day 0-Day3 post-vacc3</td>
<td></td>
<td>Visit 4</td>
</tr>
<tr>
<td><strong>Reporting of unsolicited AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reporting of SAEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reporting of SAEs related to study participation or GSK concomitant products or any fatal SAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

vacc = vaccination; post-vacc = post-vaccination; M= month
31 days = Day 0-Day 30 post-vaccination
**SAEs will be collected throughout the primary phase up to the day preceding the fourth dose vaccination**
### Table 19  Reporting periods for solicited adverse events and serious adverse events for Epoch 002

<table>
<thead>
<tr>
<th>Study activity</th>
<th>4th vacc</th>
<th>4 days post-vacc4</th>
<th>31 days post-vacc</th>
<th>2nd Havrix Vacc. (5th vacc)</th>
<th>4 days post-vacc5</th>
<th>31 days post-vacc5 (end of Epoch 002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting of solicited local and general AEs</td>
<td></td>
<td>Visit 5</td>
<td>Visit 6</td>
<td></td>
<td></td>
<td>Visit 7</td>
</tr>
<tr>
<td>Reporting of unsolicited AEs</td>
<td></td>
<td>Day 0-Day3 post-vacc4</td>
<td></td>
<td></td>
<td></td>
<td>Day 0-Day3 post-vacc5</td>
</tr>
<tr>
<td>Reporting of SAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Visit 8</td>
</tr>
<tr>
<td>Reporting of SAEs related to study participation or GSK concomitant products or any fatal SAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

vacc = vaccination; post-vacc = post-vaccination; M= month
31 days = Day 0-Day 30 post-vaccination
Table 20  Methodology and timing of reporting adverse events during the study

<table>
<thead>
<tr>
<th>Type</th>
<th>Solicited adverse events/ Unsolicited adverse events/ Serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of ‘solicited’ follow-up</td>
<td>Days 0 to 3 after all vaccinations post-primary and post-fourth dose.</td>
</tr>
<tr>
<td>Method of follow-up</td>
<td>Diary cards</td>
</tr>
<tr>
<td>Period of ‘unsolicited’ follow-up</td>
<td>Standard e.g. one month (Day 0 to Day 30) after all vaccinations post-primary and post-fourth dose.</td>
</tr>
<tr>
<td>Period of follow-up for SAEs</td>
<td>Collected throughout the study from Visit 1 (M0) to 8 Months (M8) after the first vaccination.</td>
</tr>
<tr>
<td>Method for reporting SAEs</td>
<td>Electronic screens in the eCRF (RDE) to Oceans</td>
</tr>
</tbody>
</table>

8.3.2.  Post-Study adverse events and serious adverse events

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Table 18 and Table 19. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational vaccine/product, the investigator will promptly notify the Study Contact for Reporting SAEs.

8.3.3.  Evaluation of adverse events and serious adverse events

8.3.3.1.  Active questioning to detect adverse events and serious adverse events

As a consistent method of collecting AEs, the subject’s parent(s)/LAR(s) should be asked a non-leading question such as:

‘Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?’

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE/SAE in the eCRF. The investigator is not allowed to send photocopies of the subject’s medical records to GSK Biologicals instead of appropriately completing the eCRF. However, there may be instances when copies of medical records for certain cases are requested by GSK Biologicals. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to GSK Biologicals.
The investigator will attempt to establish a diagnosis pertaining to the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

**8.3.3.2. Assessment of adverse events**

**8.3.3.2.1. Assessment of intensity (Amended: 16 June 2014)**

The intensity of the following solicited AEs will be assessed as described:

**Table 21 Intensity scales for solicited symptoms in infants/toddlers**

<table>
<thead>
<tr>
<th>Infant/Toddler (0–24 months)</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Minor reaction to touch</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Cries/protests on touch</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Cries when limb is moved/spontaneously painful</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td>Record greatest surface diameter in mm</td>
<td></td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td>Record greatest surface diameter in mm</td>
<td></td>
</tr>
<tr>
<td>Fever*</td>
<td>Record temperature in °F</td>
<td></td>
</tr>
<tr>
<td>Irritability/Fussiness</td>
<td>0</td>
<td>Behaviour as usual</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Crying more than usual/no effect on normal activity</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Crying more than usual/interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Crying that cannot be comforted/prevents normal activity</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>Behaviour as usual</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Drowsiness easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Drowsiness that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Drowsiness that prevents normal activity</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0</td>
<td>Appetite as usual</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Mild: Eating less than usual/no effect on normal activity</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Moderate: Eating less than usual/interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Severe: Not eating at all</td>
</tr>
</tbody>
</table>

*Fever is defined as temperature ≥38.0°C/100.4°F by any method. The preferred route for recording temperature in Epoch 001 will be rectal and axillary in Epoch 002.

Fever will be reported per 0.5°C cumulative increments.

The maximum intensity of local injection site redness/swelling will be scored at GSK Biologicals as follows:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&gt; 0- ≤ 10 mm</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 10 mm- ≤ 30 mm</td>
</tr>
<tr>
<td>3</td>
<td>&gt; 30 mm</td>
</tr>
</tbody>
</table>
The investigator will assess the maximum intensity that occurred over the duration of the event for all unsolicited AEs (including SAEs) recorded during the study. The assessment will be based on the investigator’s clinical judgement.

The intensity should be assigned to one of the following categories:

1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities

(in a young child, such an AE would, for example, prevent attendance at school/kindergarten/a day-care centre and would cause the parent(s)/LAR(s) to seek medical advice. In adults/adolescents, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.)

An AE that is assessed as Grade 3 (severe) should not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. An event is defined as ‘serious’ when it meets one of the pre-defined outcomes as described in Section 8.1.2.

8.3.3.2.2. Assessment of causality

The investigator is obligated to assess the relationship between investigational vaccine/product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative plausible causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational vaccine/product will be considered and investigated. The investigator will also consult the IB and/or PI for marketed products to determine his/her assessment.

There may be situations when a SAE has occurred and the investigator has minimal information to include in the initial report to GSK Biologicals. However, it is very important that the investigator always makes an assessment of causality for every event prior to submission of the SAE report to GSK Biologicals. The investigator may change his/her opinion of causality in light of follow-up information and update the SAE information accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

In case of concomitant administration of multiple vaccines, it may not be possible to determine the causal relationship of general AEs to the individual vaccines administered. The investigator should, therefore, assess whether the AE could be causally related to vaccination rather than to the individual vaccines.
All solicited local (injection site) reactions will be considered causally related to vaccination. Causality of all other AEs should be assessed by the investigator using the following question:

*Is there a reasonable possibility that the AE may have been caused by the investigational vaccine/product?*

**YES** : There is a reasonable possibility that the vaccine(s) contributed to the AE.

**NO** : There is no reasonable possibility that the AE is causally related to the administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.

If an event meets the criteria to be determined as ‘serious’ (see Section 8.1.2), additional examinations/tests will be performed by the investigator in order to determine ALL possible contributing factors for each SAE.

Possible contributing factors include:

- Medical history.
- Other medication.
- Protocol required procedure.
- Other procedure not required by the protocol.
- Lack of efficacy of the vaccines, if applicable.
- Erroneous administration.
- Other cause (specify).

### 8.3.3.3. Assessment of outcomes

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

### 8.3.3.4. Medically attended visits

For each solicited and unsolicited symptom the subject experiences, the subject’s parent(s)/LAR(s) will be asked if the subject received medical attention defined as
hospitalisation, or an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. This information will be recorded in the eCRF.

8.4. Reporting of serious adverse events and other events

8.4.1. Prompt reporting of serious adverse events and other events to GSK Biologicals

SAEs that occur in the time period defined in Section 8.3 will be reported promptly to GSK within the timeframes described in Table 22, once the investigator determines that the event meets the protocol definition of a SAE.

Table 22 Timeframes for submitting serious adverse event and other events reports to GSK Biologicals

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Initial Reports</th>
<th>Follow-up of Relevant Information on a Previous Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Timeframe</td>
<td>Documents</td>
</tr>
<tr>
<td>All SAEs</td>
<td>24 hours*</td>
<td>SAE screen</td>
</tr>
<tr>
<td>Invasive meningococcal disease</td>
<td>24 hours</td>
<td>SAE screen</td>
</tr>
</tbody>
</table>

* Timeframe allowed after receipt or awareness of the information.

8.4.2. Contact information for reporting serious adverse events and other events to GSK Biologicals (Amended: 16 June 2014)

Back-up Study Contact for Reporting SAEs

24/24 hour and 7/7 day availability:

GSK Biologicals Clinical Safety & Pharmacovigilance

Fax: +PPD or +PPD

Please refer to the Study Procedure Manual for the dedicated US Fax Machine number.

8.4.3. Completion and transmission of SAE reports to GSK Biologicals

Once an investigator becomes aware that a SAE has occurred in a study subject, the investigator (or designate) must complete the information in the electronic SAE report WITHIN 24 HOURS. The SAE report will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have all information regarding a SAE, the report should still be completed within 24 hours. Once additional relevant information is received, the report should be updated WITHIN 24 HOURS.

The investigator will always provide an assessment of causality at the time of the initial report.
8.4.3.1. **Back-up system in case the electronic SAE reporting system does not work (Amended: 16 June 2014)**

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours. **Please refer to the Study Procedure Manual for the dedicated US Fax Machine number.**

This back-up system should only be used if the electronic SAE reporting system is not working and NOT if the system is slow. As soon as the electronic SAE reporting system is working again, the investigator (or designate) must complete the electronic SAE report within 24 hours. The final valid information for regulatory reporting will be the information reported through the electronic SAE reporting system.

8.4.4. **Updating of SAE information after freezing of the subject’s eCRF**

When additional SAE information is received after freezing of the subject’s eCRF, new or updated information should be recorded on a paper report, with all changes signed and dated by the investigator. The updated report should be faxed to the GSK Biologicals Clinical Safety and Pharmacovigilance department or to the Study Contact for Reporting SAEs (refer to the Sponsor Information Sheet) within the designated reporting time frames specified in Table 22.

8.4.5. **Regulatory reporting requirements for serious adverse events**

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 8.4.1. GSK Biologicals has a legal responsibility to promptly notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the Study Contact for Reporting SAEs is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

Investigator safety reports are prepared according to the current GSK policy and are forwarded to investigators as necessary. An investigator safety report is prepared for a SAE(s) that is both attributable to the investigational vaccine/product and unexpected. The purpose of the report is to fulfil specific regulatory and GCP requirements, regarding the product under investigation.

8.5. **Follow-up of adverse events and serious adverse events**

8.5.1. **Follow-up during the study**

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide additional relevant information on the subject’s condition to GSK Biologicals (within 24 hours for SAEs; refer to Table 22).
All SAEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the end of the study.

All AEs documented at a previous visit/contact and designated as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until 30 days after the last vaccination.

8.5.1.2. Follow-up after the subject is discharged from the study

The investigator will follow subjects:

- with SAEs, or subjects withdrawn from the study as a result of an AE, until the event has resolved, subsided, stabilised, disappeared, or until the event is otherwise explained, or the subject is lost to follow-up.
- with other non-serious AEs, until study end or they are lost to follow-up.

If the investigator receives additional relevant information on a previously reported SAE, he/she will provide this information to GSK Biologicals using a paper SAE and as applicable.

GSK Biologicals may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a subject dies during participation in the study or during a recognised follow-up period, GSK Biologicals will be provided with any available post-mortem findings, including histopathology.

8.6. Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the subject’s eCRF (refer to Section 6.6).

8.7. Subject card

Study subjects’ parent(s)/LAR(s) must be provided with the address and telephone number of the main contact for information about the clinical study.

The investigator (or designate) must therefore provide a “subject card” to each subject’s parent(s)/LAR(s). In an emergency situation this card serves to inform the responsible attending physician that the subject is in a clinical study and that relevant information may be obtained by contacting the investigator.

Subjects’ parent(s)/LAR(s) must be instructed to keep subject cards in their possession at all times.
9. **SUBJECT COMPLETION AND WITHDRAWAL**

9.1. **Subject completion**

A subject who returns for the concluding visit/is available for the concluding contact foreseen in the protocol is considered to have completed the study.

9.2. **Subject withdrawal**

Withdrawals will not be replaced.

9.2.1. **Subject withdrawal from the study**

From an analysis perspective, a ‘withdrawal’ from the study refers to any subject who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol.

All data collected until the date of withdrawal/last contact of the subject will be used for the analysis.

A subject is considered a ‘withdrawal’ from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

Investigators will make an attempt to contact those subjects who do not return for scheduled visits or follow-up.

Information relative to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a subject from the study was made by the subject’s parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Protocol violation (specify).
- Consent withdrawal, not due to an adverse event*.
- Moved from the study area.
- Lost to follow-up.
- Other (specify).

*In case a subject is withdrawn from the study because he/she/the subject’s parent(s) has withdrawn consent, the investigator will document the reason for withdrawal of consent, if specified by the subject, in the CRF.

Subjects who are withdrawn from the study because of SAEs/AEs must be clearly distinguished from subjects who are withdrawn for other reasons. Investigators will
follow subjects who are withdrawn from the study as result of a SAE/AE until resolution of the event (see Section 8.5.1.2).

9.2.2. **Subject withdrawal from investigational vaccine**

A ‘withdrawal’ from the investigational vaccine refers to any subject who does not receive the complete treatment, i.e. when no further planned dose is administered from the date of withdrawal. A subject withdrawn from the investigational vaccine may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (safety or immunogenicity) if planned in the study protocol.

Information relative to premature discontinuation of the investigational vaccine will be documented on the Vaccine Administration page/screen of the eCRF. The investigator will document whether the decision to discontinue further vaccination/treatment was made by the subject’s parent(s) or LAR(s), or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- Serious adverse event.
- Non-serious adverse event.
- Other (specify).

10. **STATISTICAL METHODS**

10.1. **Primary endpoint(s)**

- Immunogenicity with respect to the components of the co-administered vaccines:
  - Anti-PRP antibody concentrations ≥1.0 µg/mL (1 month post-dose 4 HibCY group, 1 month post-dose 3 PedHIB group).
  - Anti-rotavirus serum IgA GMCs (2 months post-dose 2 of Rotarix)
  - Anti-HAV antibody concentrations ≥15 mIU/mL (1 month post-dose 2 of Havrix)
  - Anti-*S. pneumoniae* GMCs (1 month post-dose 3)
  - Anti-*S. pneumoniae* GMCs (1 month post-dose 4)

10.2. **Secondary endpoint(s)**

**Immunogenicity**

- Immunogenicity with respect to the components of the investigational vaccine:

  - Anti-PRP antibody concentrations ≥0.15 µg/mL and GMCs (2 months post-dose 2 [PedHib group only], 1 month post-dose 3 and 1 month post-dose 4 [HibCY group only]).
  - Anti-PRP antibody concentrations ≥1.0 µg/mL 2 months post-dose 2 (PedHib group only) and 1 month post-dose 3 (HibCY group only).
- hSBA-MenC and hSBA-MenY antibody titers ≥1:4, ≥1:8, ≥1:16, ≥1:32 and GMTs (1 month post-dose 3 and 1 month post-dose 4).

- Immunogenicity with respect to the components of the co-administered vaccines:
  - Anti-rotavirus IgA antibody concentrations ≥20 U/mL (2 months post-dose 2 of Rotarix)
  - Anti-HAV antibodies ≥15 mIU/mL and GMCs (1 month post-dose 1 of Havrix)
  - Anti-HAV GMCs (1 month post-dose 2 of Havrix)
  - *S. pneumoniae* antibody concentrations ≥0.15 μg/mL, ≥0.26 μg/mL and ≥0.35 μg/mL for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F in Prevnar 13 (1 month post-dose 3 and 1 month post-dose 4).

**Safety and Reactogenicity**

- Occurrence of each solicited adverse event 4 days (Day 0 to Day 3) after all vaccines post-primary and post-fourth dose.
  - Local symptoms
  - General symptoms

- Occurrence of unsolicited symptoms 31 days (Day 0 to Day 30) after all vaccines post-primary and post-fourth dose.

- Occurrence throughout the study of SAEs from Day 0 to study end.

### 10.3. Determination of sample size

A total of 600 subjects (300 per group) will be enrolled in this study in order to obtain 450 evaluable subjects (regardless of blood sample availability) for Rotarix Post-dose 2 and for Prevnar Post-dose 3 considering a non-evaluable rate of 25%, and approximately 315 evaluable subjects for Hib (Post-dose 3 for the PedHIB group and Post-dose 4 for the HibCY group), Prevnar Post-dose 4 and Havrix Post-dose 2 considering an additional non-evaluable rate of 30% for subjects completing Epoch 001. Given that not all subjects will have a blood sample at the specified time point, the expected number of subjects evaluable and with a blood sample at each specified time point is shown below:
Table 23  List of non-inferiority objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Timing</th>
<th>Endpoint</th>
<th>Number of subjects evaluable per group</th>
<th>Number of subjects evaluable with blood sample per group</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inferiority</td>
<td>Post-dose 4 (HibCY group); Post-dose 3 (PedHIB group)</td>
<td>Anti-PRP</td>
<td>158 (=225 – 30%)</td>
<td>158</td>
<td>Group difference ≥ - 10%</td>
</tr>
<tr>
<td>Non-inferiority</td>
<td>Post-dose 2</td>
<td>Anti-Rota IgA</td>
<td>225 (=300 – 25%)</td>
<td>150</td>
<td>Group GMC ratio ≥ 0.5</td>
</tr>
<tr>
<td>Non-inferiority</td>
<td>Post-dose 3</td>
<td>Anti- S. pneumoniae</td>
<td>225 (=300 – 25%)</td>
<td>150</td>
<td>Group GMC ratio ≥ 0.5</td>
</tr>
<tr>
<td>Non-inferiority</td>
<td>Post-dose 4</td>
<td>Anti- S. pneumoniae</td>
<td>158 (=225 – 30%)</td>
<td>158</td>
<td>Group GMC ratio ≥ 0.5</td>
</tr>
<tr>
<td>Non-inferiority</td>
<td>Post-dose 2 Hav</td>
<td>Anti-Hav</td>
<td>158 (=225 – 30%)</td>
<td>105</td>
<td>Group difference ≥ - 10%</td>
</tr>
</tbody>
</table>

10.3.1.  Control on type I error

Before concluding on the primary objectives for Rotarix, Prevnar 13, and Havrix a non-inferiority objective regarding Anti-PRP will need to be reached. Further, to maintain the type I error below 2.5% one-sided and be able to conclude independently on the following primary objectives of Epoch 001 (Rotarix and Prevnar13 Post dose 3) and of Epoch 002 (Havrix and Prevnar13 post dose 4), a Bonferroni correction will be used in order to test these primary objectives (1.25% one-sided for Epoch 001 and 1.25% one-sided for Epoch 002). Finally, a hierarchical procedure will be used in order to test the primary hypotheses for each Epoch. For instance, the second primary objective of Epoch 001 can only be reached if the first primary objective of Epoch 001 has been reached. As per the hierarchical procedure, the primary objective about Anti-PRP will first need to be met to be able to conclude on any other primary objective, and within each subsequent arm, the first primary objective will have to be reached to conclude on the second primary objective of that Epoch (see Figure 1).
Non-inferiority of PRP Post-dose 4 in the HibCY group versus Post-dose 3 in the PedHIB group.

The non-inferiority of the HibCY group compared to the PedHIB group will be demonstrated if the non-inferiority criteria specific to anti-PRP (Lower limit of the standardized asymptotic 95% CI for the difference (HibCY group minus the PedHIB group) in the percentage of subjects with anti-PRP concentrations ≥1.0 μg/mL is ≥-10%).
Table 24 Non-inferiority of Hib-MenCY-TT co-administered with Havrix and Prevnar 13 compared to PedvaxHIB co-administered with Havrix and Prevnar 13 with respect to anti-PRP with associated type II error

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Anti-PRP ≥1.0 μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (HibCY vs PedHIB group)</td>
<td>158 vs 158</td>
</tr>
<tr>
<td>Reference value (HibCY vs PedHIB group)</td>
<td>99.2% vs 99.2%</td>
</tr>
<tr>
<td>Non inferiority margin</td>
<td>10%</td>
</tr>
<tr>
<td>Alpha</td>
<td>2.5%</td>
</tr>
<tr>
<td>Type-II error**</td>
<td>0.1%</td>
</tr>
<tr>
<td>Power</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

**PASS 2005, non-inferiority test on two independent proportions, 1-sided, alpha=0.025, margin=10%, power under the alternative hypothesis of equal rates between groups

* Ref: Hib-MenCY-TT-010, percentage of subjects from HibCY group with Anti-PRP ≥1.0 μg/mL 99.2% [97.6%; 99.8%]

Table 24 shows that the probability to reach the non-inferiority criteria is at least 99.9% [= 100% - type II error].

10.3.2. Epoch 001

Primary objective 1: Non-inferiority of Rotarix co-administration Post-dose 2

The non-inferiority of the HibCY group compared to the PedHIB group will be demonstrated if the non-inferiority criteria specific to anti-IgA is met (Lower limit of the two-sided standardized 97.5% CI of the ratio of anti-rotavirus IgA≥0.5 clinical limit for non-inferiority). Table 25 shows that the probability to reach the non-inferiority criteria is at least 93.0% [= 100% - type II error].

Considering that the success of this primary objective is conditional to the success of the primary objective on Anti-PRP, the power associated to this objective is 92.9% [= 100% - type II error from Table 24 - type II error from Table 25].
Table 25  Non-inferiority of Rotarix co-administered with Hib-MenCY-TT compared to Rotarix co-administered with PedvaxHIB with respect to anti-Rota IgA with associated type II error

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Standard deviations for Log10 concentrations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (HibCY vs PedHIB group)</td>
<td>150 vs 150</td>
<td></td>
</tr>
<tr>
<td>Reference value*</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>(HibCY vs PedHIB group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non inferiority margin</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>1.25%</td>
<td></td>
</tr>
<tr>
<td>Type-II error**</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td>93.0%</td>
<td></td>
</tr>
</tbody>
</table>

* Standard deviations references were computed from observed rates in Rota-060 (Rota-IgA) antigen.
Type II error is obtained using PASS 2005, one-sided test for 2 means, under the assumption of equal means & alpha=1.25%

Primary objective 2: Non-inferiority of Prevnar13 co-administration Post-dose 3

The non-inferiority of the HibCY group compared to the PedHIB group with respect to 13 pneumococcal serotypes will be demonstrated if the non-inferiority criteria specific to each serotype are met simultaneously (Lower limit of the two-sided standardized 97.5% CI of the ratio of each anti-pneumococcal antigen ≥0.5 clinical limit for non-inferiority). Table 26 shows that the probability to reach the non-inferiority criteria to the PedHIB group in terms of pneumococcal antigens response is at least 98.7% (= 100% - sum of all type II errors).
## Table 26

Non-inferiority of **Prevnar 13** co-administered with Hib-MenCY-TT compared to **Prevnar 13** co-administered with **PedvaxHIB** with respect to anti- **S. pneumoniae** serotypes post-dose 3 with associated type II errors

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Standard deviations for Log10 concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-1</td>
</tr>
<tr>
<td>Sample size (HibCY vs PedHIB group)</td>
<td>150 vs 150</td>
</tr>
<tr>
<td>Reference value*</td>
<td>0.314</td>
</tr>
<tr>
<td>Non-Inferiority margin</td>
<td>2</td>
</tr>
<tr>
<td>Type-II error**</td>
<td>0.0</td>
</tr>
<tr>
<td>Power</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Reference value corresponds to observed rates in reference studies Hib-MenCY-TT-005 (101858), 10Pn-PD-DiT-011 (107005) and DT Switch-124 for pneumococcal antigens of Prevnar 7 where this is the standard deviation for the Log10 concentration. A lower reference was selected as a worse-case scenario. Reference values for the last 6 antigens in Prevnar 13 correspond to the observed rates in DT Switch-124 was taken.

** Type II error is obtained using PASS 2005, one-sided non-inferiority test for two means, under the alternative of equal means & alpha = 1.25%.
Considering that the success of this second primary objective of Epoch 001 is conditional to meet the primary objectives of Epoch 001, the power associated to this objective is 91.6% (= 100% - type II error from Table 24 - sum of all type II errors from Table 25 – sum of all type II errors from Table 26).

10.3.3. Epoch 002

Primary objective 1: Non-inferiority of *Havrix* co-administration post-dose 2

The non-inferiority of the HibCY group compared to the PedHIB group will be demonstrated if the non-inferiority criteria specific to anti-HAV is met (Lower limit of the two-sided standardized 97.5% CI of the percentage of subjects with anti-HAV concentrations ≥15 mIU/mL is ≥-10% clinical limit for non-inferiority). Table 27 shows that the probability to reach the non-inferiority criteria is at least 98.8% [= 100% - type II error].

Considering that the success of this primary objective is conditional to the success of the primary objective on Anti-PRP, the power associated to this objective is 98.7% [= 100% - type II error from Table 24 - type II error from Table 27].

Table 27 Non-inferiority of *Havrix* co-administered with Hib-MenCY-TT compared to *Havrix* co-administered with *PedvaxHIB* with respect to anti-HAV with associated type II error

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Observed seroprotection rates</th>
<th>Anti-HAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size (HibCY vs PedHIB group)</td>
<td>105 vs 105</td>
<td></td>
</tr>
<tr>
<td>Reference value* (HibCY vs PedHIB group)</td>
<td>99% vs 99%</td>
<td></td>
</tr>
<tr>
<td>Non inferiority margin</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Alpha</td>
<td>1.25%</td>
<td></td>
</tr>
<tr>
<td>Type-II error**</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Power</td>
<td>98.8%</td>
<td></td>
</tr>
</tbody>
</table>

* Reference values are based on observed rates in HAV232 study (HAV-DTaP-Hib group).
Type II error is obtained using PASS 2005, one-sided non-inferiority test for two proportions (Likelihood Score [Miettienen and Nurminen approach]) under the alternative associated to the reference & alpha=1.25%

Primary objective 2: Non-inferiority of *Prevnar13* co-administration post-dose 4

The non-inferiority of the HibCY group compared to the PedHIB group with respect to 13 pneumococcal serotypes will be demonstrated if the non-inferiority criteria specific to each serotype are met simultaneously (Lower limit of the two-sided standardized 97.5% CI of the ratio of each anti-pneumococcal antigen ≥ 0.5 clinical limit for non-inferiority). Table 28 shows that the probability to reach the non-inferiority criteria to the PedHIB group in terms of pneumococcal antigens response is at least 99.1% (= 100% - sum of all type II errors).
Table 28  Non-inferiority of *Prevnar 13* co-administered with Hib-MenCY-TT compared to *Prevnar 13* co-administered with *PedvaxHIB* with respect to anti- *S. pneumoniae* serotypes post-dose 4 with associated type II errors

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Standard deviations for Log10 concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-1</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>(HibCY vs</td>
<td>158 vs</td>
</tr>
<tr>
<td>PedHIB group</td>
<td>158</td>
</tr>
<tr>
<td>Reference</td>
<td>0.314</td>
</tr>
<tr>
<td>value*</td>
<td></td>
</tr>
<tr>
<td>Non-Inferiority margin</td>
<td>2</td>
</tr>
<tr>
<td>Type-II error**</td>
<td>0.0</td>
</tr>
<tr>
<td>Power</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Reference value corresponds to the same used at post-dose 3 so observed rates in reference studies Hib-MenCY-TT-005, 10Pn-PD-DiT-011 (107005) and DT Switch-124 for pneumococcal antigens of *Prevnar 7* where this is the standard deviation for the Log10 concentration. A lower reference was selected as a worse-case scenario. Reference values for the last 6 antigens in *Prevnar 13* in DT Switch-124 was taken.

** Type II error is obtained using PASS 2005, one-sided non-inferiority test for two means, under the alternative of equal means & alpha = 1.25%.
Considering that the success of the second primary objective of Epoch 002 is conditional on meeting the first primary objective of Epoch 002, the power associated to this objective is 97.8% (= 100% - type II error from Table 24 - sum of all type II errors from Table 27– sum of all type II errors from Table 28).

If we consider the first and second primary objectives from Epoch 001 and Epoch 002, the overall power of the study is at least 89.5%.

10.4. Study cohorts/ data sets to be analysed

A total of 12 cohorts are defined for the purpose of analysis. Note that all analyses will be performed per treatment actually administered.

10.4.1. Rota Total vaccinated cohort (post 2nd dose of Rotarix)

The Rota Total Vaccinated cohort will include all vaccinated subjects for whom data are available. Subjects will belong to the Rota Total Vaccinated Cohort if they have received at least one dose of any of the study vaccines: Hib-MenCY-TT, Pediarex, Prevnar 13 or Rotarix. For the Rota Total Vaccinated cohort, the analysis of safety will include all subjects with the vaccine administration documented. For the analysis of immunogenicity, this will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

10.4.2. Rota According-To-Protocol (ATP) cohort for analysis of safety (post 2nd dose of Rotarix)

The Rota ATP cohort for safety will include all subjects:

- who met all inclusion criteria, no exclusion criteria for the study and no elimination criteria
- who have received the 2 doses of study vaccine
- for whom the administration site of study vaccine/comparator is known

10.4.3. Rota According-to-protocol (ATP) cohort for analysis of immunogenicity (post 2nd dose of Rotarix)

The Rota ATP cohort for immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) from the Rota ATP cohort for safety for whom assay results are available for antibodies against at least one study vaccine antigen for the blood sample taken two months after the administration of the second rotavirus vaccination. The interval between Visit 2 and Visit 3 for inclusion in the Rotavirus ATP cohort for immunogenicity will be defined as 56 to 90 days.

10.4.4. First three doses Total Vaccinated cohort (post-dose 3)

The First three doses Total Vaccinated cohort will include all vaccinated subjects for whom data are available. Subjects will belong to the First three doses Total Vaccinated
Cohort if they have received at least one dose of any of the study vaccines: Hib-MenCY-TT, Pediarix, Prevnar 13 or Rotarix. For the First three doses Total Vaccinated cohort, the analysis of safety will include all subjects with the vaccine administration documented. For the analysis of immunogenicity, this will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

10.4.5. First three doses According-to-protocol (ATP) cohort for analysis of safety (post-dose 3)

The ATP cohort for safety will include all subjects:

- who met all inclusion criteria and no exclusion criteria for the study
- who have received 3 doses of study vaccine
- for whom the administration site of study vaccine/comparator is known
- who have not received a vaccine not specified or forbidden in the protocol during the study
- who were not excluded from the Rota ATP cohort for immunogenicity, unless the reason for exclusion was either non-compliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at the post-dose 2 time point.

10.4.6. First three doses According to Protocol (ATP) cohort for analysis of immunogenicity (post-dose 3)

The ATP cohort for immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, and with no elimination criteria during the study) from the First three doses ATP cohort for safety for whom assay results are available for antibodies against at least one study vaccine antigen component for the blood sample taken one month after the 3rd vaccination. The interval between Visit 3 and Visit 4 (Post-dose 3 blood sample) for inclusion in the First three doses ATP cohort for immunogenicity will be defined as 21 to 48 days.

10.4.7. Fourth Dose Total Vaccinated cohort (post-fourth dose)

The Fourth dose Total Vaccinated cohort will include all vaccinated subjects for whom data are available. Subjects will belong to the Fourth dose Total Vaccinated Cohort if they have received at least one dose of any of the study vaccines: Hib-MenCY-TT, Pediarix, Prevnar 13, Rotarix, PedvaxHIB or Havrix. For the Fourth dose Total Vaccinated cohort, the analysis of safety will include all subjects with the vaccine administration documented. For the analysis of immunogenicity, this will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.
10.4.8. **Fourth Dose According to Protocol (ATP) cohort for analysis of safety (post-fourth dose)**

The Fourth dose ATP cohort for safety will include all eligible subjects:

- who met all inclusion criteria and no exclusion criteria for the study
- who have received 3 vaccine doses in the first three doses vaccination course
- who have received the fourth vaccine dose and the first *Havrix* dose
- who have not received a vaccine not specified or forbidden in the protocol during the study
- who were not excluded from the First Three doses ATP cohort for immunogenicity, unless the reason for exclusion was either non-compliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at the post-dose 2 or post-dose 3 time point.

10.4.9. **Fourth Dose According to Protocol (ATP) cohort for analysis of immunogenicity (post-fourth dose)**

The Fourth dose ATP cohort for immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination during the study) from the Fourth dose ATP cohort for safety for whom assay results are available for antibodies against at least one study vaccine antigen for the blood sample taken one month after the administration of the fourth dose vaccine dose. The interval between Visit 5 and Visit 6 for inclusion in the Fourth dose ATP cohort for immunogenicity will be defined as 21 to 48 days.

10.4.10. **Havrix Total Vaccinated cohort (post 2nd dose of Havrix)**

The *Havrix* Total Vaccinated cohort will include all vaccinated subjects for whom data are available. Subjects will belong to the *Havrix* Total Vaccinated Cohort if they have received at least one dose of any of the study vaccines: Hib-MenCY-TT, *Pediarix*, *Prevnar 13*, *Rotarix*, *PedvaxHIB* or *Havrix*. For the *Havrix* Total Vaccinated cohort, the analysis of safety will include all subjects with the vaccine administration documented. For the analysis of immunogenicity, this will include vaccinated subjects for whom data concerning immunogenicity endpoint measures are available.

10.4.11. **Havrix According-To-Protocol (ATP) cohort for analysis of safety (post 2nd dose of Havrix)**

The Fourth dose ATP cohort for safety will include all eligible subjects who:

- who met all inclusion criteria and no exclusion criteria for the study
- who have received 3 vaccine doses in the primary vaccination course
- who have received the fourth dose vaccine dose and the first and second *Havrix* dose
who have not received a vaccine not specified or forbidden in the protocol during the study

- who were not excluded from the First three doses and Fourth dose ATP cohort for immunogenicity, unless the reason for exclusion was either non-compliance with the protocol-defined serum sampling windows or a lack of availability of immunogenicity results at the post-dose 2, post-dose 3 or post-fourth dose timepoints.

10.4.12. **Havrix According-To-Protocol (ATP) cohort for analysis of immunogenicity (post 2\textsuperscript{nd} dose of Havrix)**

The *Havrix* ATP cohort for immunogenicity will include all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) from the *Havrix* ATP cohort for safety for whom assay results are available for antibodies against at least one study vaccine antigen for the blood sample taken one month after the administration of the 2\textsuperscript{nd} *Havrix* vaccination. The interval between Visit 7 and Visit 8 for inclusion in the *Havrix* ATP cohort for immunogenicity will be defined as 21 to 48 days.

10.5. **Derived and transformed data**

- **Immunogenicity:**
  - The cut-off value is defined by the laboratory before the analysis and is described in Section 5.7.3.
  - A seronegative subject is a subject whose antibody concentration or titer is below the cut-off value.
  - A seropositive subject is a subject whose antibody concentration or titer is greater than or equal to the cut-off value.
  - The Geometric Mean Titters/Concentrations (GMTs/GMCs) calculations are performed by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT/GMC calculation.
  - Handling of missing data: for a given subject and a given immunogenicity measurement, missing or non-evaluable measurements will not be replaced. Therefore, an analysis will exclude subjects with missing or non-evaluable measurements.

- **Reactogenicity and Safety:**
  - Handling of missing data: subjects who missed reporting symptoms (solicited/unsolicited or concomitant medications) will be treated as subjects without symptoms (solicited/unsolicited or concomitant medications, respectively). In case of significant non-compliance of study procedures for reporting symptoms, the analysis plan will be reassessed to ensure more accurate reporting of study data by further analysis.
For the analysis of solicited symptom, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the total vaccinated cohort will include only subjects/doses with documented safety data (i.e. symptom screen/sheet completed).

10.6. Analysis of demographics

Demographic characteristics (age at the first dose in weeks, gender, race and height [cm], weight [kg], body mass index [BMI in kg/m²] at first dose), vaccination history, cohort description, withdrawal status will be summarised by group using descriptive statistics:

- Frequency tables will be generated for categorical variable such as race;
- Mean, median and standard error will be provided for continuous data such as age.
- The distribution of subjects enrolled among the study sites will be tabulated as a whole and per group.

Demographic characteristics will be presented by treatment group for the 12 cohorts presented in Section 10.4.

10.7. Analysis of immunogenicity

The primary analysis of immunogenicity will be based on the ATP cohorts for immunogenicity (see Section 10.4 for a description of the immunogenicity cohorts). If, for any vaccine group, the percentage of enrolled subjects with serological results excluded from this ATP cohort is more than 5%, a second analysis based on the Total Vaccinated Cohort will be performed to support the ATP analysis.

In addition, the primary endpoints will be evaluated on the ATP cohorts for immunogenicity post-dose 3 and post-dose 4 and post Havrix dose 2 restricted to subjects who had a blood sample within 30 to 48 days after vaccination.

10.7.1. Within groups assessment

For each treatment group and for each antibody assessed at the corresponding time point:

- Seropositivity rates, percentage of subjects with antibody concentration or titre ≥ cut-off value with exact 95% confidence intervals (CIs) will be calculated.
- Geometric Mean antibody Concentrations or Titers (GMCs or GMTs) with 95% CIs will be tabulated.
- The distribution of concentrations or titers with 95% CI will be tabulated for each antigen as well.
- Antibody concentrations or titers will also be evaluated using reverse cumulative curves for each antibody assessed.
10.7.2. Between groups assessment

Non-inferiority of Hib-MenCY-TT post-dose 4 when co-administered with Prevnar 13 and Havrix compared to PedvaxHIB post-dose 3 co-administered with Prevnar 13 and Havrix with respect to anti-PRP will be evaluated through:

- Computation of the asymptotic standardized 95.0% CIs for the difference in subjects with anti-PRP (HibCY group minus the PedHIB group) 1 months after the 4th dose of Hib-MenCY-TT vaccination and 1 month after the 3rd dose of PedvaxHIB vaccination. Indication of non-inferiority of Hib-MenCY-TT co-administered with Prevnar 13 and Havrix versus PedvaxHIB co-administered with Prevnar 13 and Havrix will be a lower limit of the 95.0% CI greater than or equal to the pre-defined clinical limit of -10%.

Non-inferiority of Rotarix when co-administered with Hib-MenCY-TT compared to Rotarix co-administered with PedvaxHIB with respect to anti-Rota IgA will be evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti-Rota IgA (HibCY group over the PedHIB group) 2 months after the 2nd dose of Rotarix vaccination. Indication of non-inferiority of Rotarix co-administered with Hib-MenCY-TT versus Rotarix co-administered with PedvaxHIB will be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

Non-inferiority of Prevnar 13 when co-administered with Hib-MenCY-TT compared to Prevnar 13 co-administered with PedvaxHIB with respect to anti- S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F will be evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti- S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (HibCY group over the PedHIB group) 1 month after the 3rd dose of Prevnar 13 vaccination. Indication of non-inferiority of Prevnar 13 co-administered with Hib-MenCY-TT versus Prevnar 13 co-administered with PedvaxHIB will be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

Non-inferiority of Havrix when co-administered with Hib-MenCY-TT compared to Havrix co-administered with PedvaxHIB with respect to anti-HAV will be evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the difference in the percentage of subjects with anti-HAV ≥15 mIU/mL (HibCY group rate minus PedHIB group rate) one month after primary vaccination. Indication of non-inferiority of Hib-MenCY-TT will be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of -10%.
Non-inferiority of Prevnar 13 when co-administered with Hib-MenCY-TT compared to Prevnar 13 co-administered with PedvaxHIB with respect to anti- S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F will be evaluated through:

- Computation of the asymptotic standardized 97.5% CIs for the GMC ratio of subjects with anti- S. pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F (HibCY group over the PedHIB group) 1 month after the 4th dose of Prevnar 13 vaccination. Indication of non-inferiority of Prevnar 13 co-administered with Hib-MenCY-TT versus Prevnar 13 co-administered with PedvaxHIB will be a lower limit of the 97.5% CI greater than or equal to the pre-defined clinical limit of 0.5.

One month after the fourth dose of Hib-MenCY-TT and after the third dose of PedvaxHIB, differences in seropositivity/seroprotection and their asymptotic standardized 95% CIs will be calculated for anti-PRP concentrations ≥0.15 and ≥1.0 mg/mL and hSBA-MenC and hSBA-MenY titers ≥1:4, ≥1:8 ≥1:16 and ≥1:32. GMC ratio for Anti-PRP and its 95% CI will also be computed. Note that GMC ratios will be computed for anti-PRP only. No GMT ratio will be computed for hSBA-MenC or hSBA-MenY.

- The 95% CI for geometric mean titers/concentrations (GMTs/GMCs) will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will first be obtained by assuming that log-transformed values were normally distributed with unknown variance. The 95% CI for the GMTs/GMCs will then be obtained by exponential-transformation for the 95% CI for the mean of log transformed concentration/titer.

- The group GMC/GMT ratios will be obtained using an ANOVA model on the logarithm_{10} transformation of the concentrations/titers. The ANOVA model will include the vaccine group and the blood sample sub-cohort as fixed effect.

The primary objectives will be presented for each category of sex, of race and for each center.

10.8. Analysis of safety

The primary analysis will be based on the First three doses Total vaccinated cohort or on the Fourth dose Total vaccinated cohort according to the epoch being considered. A second analysis based on the First three doses/Fourth dose ATP cohort for safety will be performed if, in any vaccine group, the percentage of enrolled subjects excluded from the First three doses/Fourth dose total vaccinated cohort is more than 5%.
For each group (HibCY and PedHIB) the percentage of subjects with at least one local adverse event (solicited and unsolicited), with at least one general adverse event (solicited and unsolicited) and with any adverse event during the 4-day solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall (except after the 2nd Havrix dose). The percentage of doses followed by at least one local adverse event (solicited and unsolicited), by at least one general adverse event (solicited and unsolicited) and by any adverse event will be tabulated, with exact 95% CI. The same computations will be done for grade 3 local, general and any AEs; local, general and any AEs considered related to vaccination; grade 3 local, general, and any AEs considered related to vaccination; and for local, general, and any AEs that resulted in a medically-attended visit.

The percentage of subjects reporting each individual solicited local and general adverse event during the 4-day solicited follow-up period will be tabulated with exact 95% CI after each vaccine dose and overall (except after the 2nd Havrix dose). The percentage of doses followed by each individual solicited local and general adverse event will be tabulated, with exact 95% CI.

Occurrence of fever and related fever will be reported per 0.5°C cumulative increments.

For all solicited symptoms, the same tabulation will be performed for grade 3 adverse events and for general solicited symptoms, the same tabulation will be performed for adverse events with relationship to vaccination (note: all local solicited symptoms are considered related to vaccination).

The verbatim reports of unsolicited AEs will be reviewed by a physician and the signs and symptoms will be coded according to Medical Dictionary for Regulatory Activities (MedDRA). Every verbatim term will be matched with the appropriate Preferred Term. The percentage of subjects with unsolicited AEs occurring within 31 days (Day 0 to Day 30) with exact 95% CI will be tabulated by Preferred Term. Similar tabulation will be done for grade 3 unsolicited AEs, for unsolicited AEs considered related to vaccination and for grade 3 unsolicited AEs considered related to vaccination.

Serious adverse events and withdrawal due to adverse event(s) will be described in detail.

From Dose 1 up to the day preceding the fourth dose, the number and percentage of subjects with SAEs will be tabulated with exact 95% CI.

From the fourth dose through Day 30 after the 2nd Havrix vaccination, the number and percentage of subjects with SAEs will be tabulated with exact 95% CI.

The percentage of subjects given antipyretics and prophylactic antipyretics within 4 days (Day 0 to Day 3) after vaccination will be tabulated (except for the 2nd Havrix dose).

10.9. Interpretation of analyses

Except for analyses addressing criteria specified in the objectives, comparative analyses will be exploratory with the aim to characterise the difference between groups in
immunogenicity. These exploratory analyses should be interpreted with caution since there is no adjustment for multiplicity of endpoints.

With respect to the first and second primary objectives of each Epoch, the interpretation must be done according to a hierarchical procedure accounting for the objective number as described in Section 10.3.

10.10. Conduct of analyses

Any deviation(s) or change(s) from the original statistical plan outlined in this protocol will be described and justified in the final study report.

Note that the statistical analyses will only be performed for the HibCY group and the PedHIB group. No distinction will be made according to the different blood sampling in the sub-cohorts.

10.10.1. Sequence of analyses

The final analyses of the study will be organized according to the following two steps:

- A final analysis of all data up to Visit 5 (i.e. Epoch 001) will be conducted. This analysis will include the final analysis of immunogenicity and the final analysis of solicited and unsolicited AEs for the first three vaccine doses. These analyses will be completed by a listing of SAEs that were reported up to 30 days post-dose 3. These analyses will be reported in a Statistical Report.

- The analyses of the data associated to the fourth dose (i.e. Epoch 002) will be performed in a second step, once these data are available and cleaned. These analyses will be completed with safety and reactogenicity analyses covering the entire study period. Both analyses will be the basis of a CSR and will be made available to the investigators.

10.10.2. Statistical considerations for interim analyses

All analyses will be conducted on final data and therefore no statistical adjustment for interim analyses is required.

11. ADMINISTRATIVE MATTERS

To comply with ICH GCP administrative obligations relating to data collection, monitoring, archiving data, audits, confidentiality and publications must be fulfilled.

11.1. Remote Data Entry instructions

Remote Data Entry (RDE), a validated computer application, will be used as the method for data collection.

In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database.
or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures.

While completed eCRFs are reviewed by a GSK Biologicals’ Site Monitor at the study site, omissions or inconsistencies detected by subsequent eCRF review may necessitate clarification or correction of omissions or inconsistencies with documentation and approval by the investigator or appropriately qualified designee. In all cases, the investigator remains accountable for the study data.

The investigator will be provided with a CD-ROM of the final version of the data generated at the investigational site once the database is archived and the study report is complete and approved by all parties.

11.2. Study Monitoring by GSK Biologicals

GSK will monitor the study to verify that, amongst others, the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits.

Direct access to all study-site related and source data is mandatory for the purpose of monitoring review. The monitor will perform a RDE review and a Source Document Verification (SDV). By SDV we understand verifying RDE entries by comparing them with the source data that will be made available by the investigator for this purpose.

The Source Documentation Agreement Form describes the source data for the different data in the RDE. This document should be completed and signed by the site monitor and investigator and should be filed in the monitor’s and investigator’s study file. Any data item for which the RDE will serve as the source must be identified, agreed and documented in the source documentation agreement form.

For RDE, the monitor will mark completed and approved screens at each visit.

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and GSK procedures.

11.3. Record retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and
secure location. The records must be easily accessible, when needed (e.g. audit or inspection), and must be available for review in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by applicable laws/regulations or institutional policy, some or all of these records can be maintained in a validated format other than hard copy (e.g. microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for making these reproductions.

GSK will inform the investigator/institution of the time period for retaining these records to comply with all applicable regulatory requirements. However, the investigator/institution should seek the written approval of the sponsor before proceeding with the disposal of these records. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by ICH GCP, any institutional requirements, applicable laws or regulations, or GSK standards/procedures; otherwise, the minimum retention period will default to 15 years.

The investigator/institution must notify GSK of any changes in the archival arrangements, including, but not limited to archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

11.4. Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

11.5. Posting of information on publicly available clinical trial registers and publication policy

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

Summaries of the results of GSK interventional studies (phase I-IV) are posted on publicly available results registers within 12 months of the primary completion date for studies of authorised vaccines and 18 months for studies of non-authorised vaccines.

GSK also aims to publish the results of these studies in the searchable, peer reviewed scientific literature. Manuscripts are submitted for publication within 24 months of the last subject’s last visit.
11.6. **Provision of study results to investigators**

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK Biologicals will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

12. **COUNTRY SPECIFIC REQUIREMENTS**

Not Applicable.

13. **REFERENCES**


APPENDIX A  LABORATORY ASSAYS

A minimum of 5 mL of whole venous blood will be collected in pre-specified subsets of subjects at Visits 3, 4, 6 and 8 in 5 mL tubes with serum separator. After blood centrifugation and serum separation, samples will be stored at -20°C or lower until sent to the sponsor. All serological assays will be performed at GSK Biologicals’ central laboratory or in a validated laboratory designated by GSK Biologicals using standardized, validated procedures and adequate controls.

Antibodies against Rotavirus

• Total IgA antibody concentrations to rotavirus will be measured by ELISA and expressed in U/mL. The cut-off of the assay is 20 U/mL.

Antibodies against Hepatitis A

• Total antibody concentrations to Hepatitis A (anti-HAV) will be measured by ELISA and expressed in mIU/mL. The cut-off of the assay is 15 mIU/mL.

Antibodies against PRP

• Total antibody concentrations to the Hib polysaccharide polyribosylribitol phosphate (PRP) will be measured by ELISA and expressed in µg/mL. The cut-off of the assay is 0.15 µg/mL.

Antibodies against N. meningitidis serogroups C and Y

• Functional anti-meningococcal serogroup C and Y activity (hSBA-MenC and hSBA-MenY) will be determined by a serum bactericidal assay based on the CDC protocol [Maslanka, 1997] using human complement. The cut-off of the assay is a dilution of 1:4. Titers will be expressed as the reciprocal of the dilution resulting in 50% killing.

Antibodies against S. pneumoniae serotypes

• S. pneumoniae serotype specific total IgG antibodies (antibodies to 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) will each be measured by ELISA adapted from the method used by the Center for Biologics Evaluation and Research, US Food and Drug Administration (FDA) [Concepcion, 2001]. The antibody concentration will be determined by logistic log comparison of the ELISA curves with a standard reference serum 89-SF available from the FDA [Quartaert, 1995]. The cut-off of the assay for each serotype is 0.15 µg/mL.
## APPENDIX B  CLINICAL LABORATORIES

### Table 29  GSK Biologicals’ laboratories

Following are the addresses of the laboratories where the lab testing will be done:

<table>
<thead>
<tr>
<th>Address</th>
<th>Antigen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Laboratory</td>
<td>GSK Biologicals Vaccine Clinical Laboratory (GVCL) Wavre Nord Noir Epine Avenue Fleming, 20-B-1300 Wavre Belgium hSBA MenC, hSBA MenY, anti-PRP ELISA, Hepatitis A Virus Ab</td>
</tr>
<tr>
<td>GSK Laboratory</td>
<td>GSK Biologicals 525 Cartier Ouest H7V 3S8 Laval (QC), Canada hSBA MenC, hSBA MenY, anti-PRP ELISA</td>
</tr>
</tbody>
</table>

### Table 30  Outsourced laboratories

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Address</th>
<th>Antigen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Goldblatt</td>
<td>Institute of Child Health Dept. of Infection and Immunity 30 Guilford Street London WC1N 1EH</td>
<td>anti- <em>S. pneumoniae</em> serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F</td>
</tr>
</tbody>
</table>
APPENDIX C  AMENDMENTS AND ADMINISTRATIVE CHANGES 
TO THE PROTOCOL

GlaxoSmithKline Biologicals
Clinical Research & Development
Protocol Amendment 1

| eTrack study number and Abbreviated Title | 112931 (HIB-MENCY-TT-016) |
| IND number | 11,706 |
| EudraCT number | 2013-003459-39 |
| Amendment number: | Amendment 1 |
| Amendment date: | 03 September 2013 |
| Co-ordinating author: | PPD, Scientific Writer |

Rationale/background for changes:
Since Havrix and Rotarix are administered in this study, the study falls under Article 46 and per our GUI-BIO-RA-9024 v01 a EudraCT number is needed for trials part of an agreed PIP and for paediatric trials falling into to scope of the Regulation (EC) No. 1901/2006 Article 41 - 45 and 46 no matter where the trial is performed. Therefore, a Eudract number has been issued for this study and included in this Protocol.

Additionally, two typographical errors were identified within the body of the Protocol and corrected:

1) The presentation of Rotarix in the vial was erroneously typed in as a white liquid rather than a powder.

2) The site of administration of the 4th dose of Prevnar 13 was erroneously typed in as in the upper thigh rather than the lower thigh.

3) The product information for the vaccines has been updated to be consistent with the vaccine dictionary definitions.

Amended text has been included in bold italics and deleted text in strikethrough in the following sections:

Contributing authors

*PPD* Global Study Manager, Vaccine Discovery and Development

PPD, Study Development Lead

Title page, Sponsor page and Investigator page:

EudraCT number | 2013-003459-39
**LIST OF ABBREVIATIONS (Amended: 03 September 2013)**

*DTPa-HBV-IPV*  
*Diphtheria and Tetanus Toxoids and Acellular Pertuss Adsorbed Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined*

*HAV*  
*Hepatitis A Vaccine*

*HRV*  
*Human Rotavirus Vaccine*

### 3.0 Study design

#### Table 2  
Epoch 001 study groups and treatment names foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Saline diluent NaCl*</td>
<td>X</td>
</tr>
<tr>
<td>Pediarix</td>
<td>Pediarix DTPa-HBV-IPV</td>
<td>X</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>Prevnar 13 Prevenar 13</td>
<td>X</td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Rotarix</td>
<td>Rotarix HRV</td>
<td>X</td>
</tr>
</tbody>
</table>

*The lyophilized pellet of Hib-MenCY-TT and Rotarix vaccine are to be reconstituted with the supplied saline.*

#### Table 3  
Epoch 002 study groups and treatment names foreseen in the study

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/Product name</th>
<th>Study Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Saline diluent NaCl*</td>
<td>X</td>
</tr>
<tr>
<td>PedvaxHIB</td>
<td>Pedvax Hib (Merck)</td>
<td>X</td>
</tr>
<tr>
<td>Havrix</td>
<td>Havrix HAV</td>
<td>X</td>
</tr>
<tr>
<td>Prevnar 13</td>
<td>Prevnar 13</td>
<td>X</td>
</tr>
</tbody>
</table>

*The lyophilized pellet of Hib-MenCY-TT is to be reconstituted with the supplied saline.*
## 6.0 Study vaccines and Administration

### 6.1 Description of study vaccines

#### Table 13

<table>
<thead>
<tr>
<th>Treatment name</th>
<th>Vaccine/product name</th>
<th>Formulation</th>
<th>Presentation</th>
<th>Volume to be administered</th>
<th>number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib-MenCY-TT</td>
<td>Hib-MenCY-TT</td>
<td>Haemophilus influenzae type polysaccharide (2.5 µg) conjugated to tetanus toxoid 5 to 7 µg; Neisseria meningitidis serogroup C capsular polysaccharide (5 µg) conjugated to tetanus toxoid 5 to 5.5 µg; Neisseria meningitidis serogroup Y capsular polysaccharide (5 µg) conjugated to tetanus toxoid 5 to 7 µg; Tetanus toxoid (total)=18 µg; Tris-HCl, pH 6.8 – 1.6 mM; NaCl 150 mM, Sucrose 42.6 mg PRP=2.5 µg TT; PSC=5 µg TT; PsY=5 µg TT; TT=20 µg</td>
<td>Lyophilized: monodose vials, containing a white freeze dried pellet to be reconstituted before use with the saline diluent. Reconstituted vaccine is clear and colorless. Lyophilized monodose vials (white freeze dried pellet). To be reconstituted before use with saline diluent. The reconstituted vaccine is clear and colorless.</td>
<td>0.5 mL</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Saline-diluent</td>
<td>NaCl=150mM</td>
<td>Liquid in vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotarix</td>
<td>Rotarix HRV</td>
<td>RIX414 HRV-strain 106.5 CCID50, Dulbecco’s Modified Eagle Medium, (DMEM) 3.7 mg, Sucrose 9 mg, Dextran 18 mg, Sorbitol 13.5 mg, Amino acids 9 mg HRV RIX414=10^6.5 CCID₅₀</td>
<td>Single dose vial. The vaccine is a white powder.</td>
<td>1 mL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rotarix Diluent:</td>
<td>Calcium carbonate 60 mg, Xanthane 2.5 mg in Water for injection. CaCO₃ = 60 mg</td>
<td>Liquid buffer in pre-filled syringe</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium carbonate (GSK Biologicals') CaCO₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Havrix</td>
<td>Havrix HAV</td>
<td>Inactivated Hepatitis A viral antigen (720 EL.U.), Aluminum hydroxide 0.25 mg, 2 phenoxethanol 0.5% (w/v), Amino acid supplement 0.3% (w/v), Polysorbate 20 0.05</td>
<td>Liquid in monodose vials (turbid white suspension)</td>
<td>0.5 mL</td>
<td>2</td>
</tr>
<tr>
<td>Treatment name</td>
<td>Vaccine/product name</td>
<td>Formulation</td>
<td>Presentation</td>
<td>Volume to be administered</td>
<td>number of doses</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>--------------</td>
<td>--------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Prevnar 13 (Pfizer)</td>
<td>Prevnar 13</td>
<td>2.2 µg 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F saccharides, 4.4 µg 6B saccharide, 34 µg CRM197, 100 µg polystyrene 80, 295 µg succinate buffer, 125 µg aluminium phosphate adjuvant</td>
<td>Liquid: Single-dose pre-filled syringe containing a white suspension</td>
<td>0.5 mL</td>
<td>4</td>
</tr>
<tr>
<td>PedvaxHIB (Merck &amp; Co., Inc)</td>
<td>Pedvax Hib (Merck)</td>
<td>PRP-7.5 µg; N. meningitidis outer membrane protein complex 125 µg; Aluminum 225 µg; Sodium chloride 0.9%; PRP=7.5µg; Neisseria meningitidis OMPC=125µg; AAHSA=225µg</td>
<td>Liquid: monodose vials containing a slightly opaque white suspension</td>
<td>0.5 mL</td>
<td>3</td>
</tr>
<tr>
<td>Pediarix</td>
<td>DTPa-HBV-IPV</td>
<td>Diphtheria toxoid ≥30 IU (25 Lf), Tetanus toxoid ≥40 IU (10 Lf), PT-25 µg, FHA-25 µg, PRN-8 µg, HBsAg (recombinant) 10 µg, Poliovirus type 1 (Mahoney) 40 D. antigen units, Poliovirus type 2 (MEF-1) 8 D antigen units, Poliovirus type 3 (Saukett) 32 D antigen units, Aluminum adjuvant</td>
<td>Pre-filled syringes containing a turbid white suspension</td>
<td>0.5 mL</td>
<td>3</td>
</tr>
</tbody>
</table>
### Table 14 Dosage and administration for the HibCY group

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment Group</th>
<th>Treatment</th>
<th>Route</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HibCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HibCY</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HibCY</td>
<td>Pediarix</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>HibCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HibCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HibCY</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HibCY</td>
<td>Pediarix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>HibCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HibCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HibCY</td>
<td>Pediarix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>HibCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HibCY</td>
<td>Hib-MenCY-TT</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HibCY</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>HibCY</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 7 months 16-19</td>
<td>1</td>
<td>HibCY</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
</tbody>
</table>

*Any licensed influenza vaccine may be given at any time during the study as per local recommendations (≥6 months of age) but if co-administered with the study vaccines it should be administered intramuscularly in the right lower anterolateral thigh at visits 3 and visit 5. MMR, Varicella and Infanrix should not be given within 30 days of any dose of study vaccine.

1 Oral (O)/ Intramuscular (IM)

N/A = Not applicable
### Table 15  
Dosage and administration for the PedHIB group

<table>
<thead>
<tr>
<th>Type of contact and timepoint</th>
<th>Dose</th>
<th>Treatment Group</th>
<th>Treatment</th>
<th>Route</th>
<th>Site</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 1 days 0</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Rotarix</td>
<td>O</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 2 months 2</td>
<td>1</td>
<td>PedHIB</td>
<td>Pediarix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>PedHIB</td>
<td>Pediarix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 3 months 4</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>PedvaxHIB</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Right</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>Prevnar 13</td>
<td>IM</td>
<td>Lower thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 5 months 10-13</td>
<td>1</td>
<td>PedHIB</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
<tr>
<td>Visit 7 months 16-19</td>
<td>1</td>
<td>PedHIB</td>
<td>Havrix</td>
<td>IM</td>
<td>Upper thigh</td>
<td>Left</td>
</tr>
</tbody>
</table>

*Any licensed influenza vaccine may be given at any time during the study as per local recommendations (≥6 months of age) but if co-administered with the study vaccines it should be administered intramuscularly in the right lower anterolateral thigh at visits 3 and visit 5. MMR, Varicella and Infanrix should not be given within 30 days of any dose of study vaccine.

1Oral (O)/ Intramuscular (IM)
N/A = Not applicable
Protocol Amendment 1 Sponsor Signatory Approval

eTrack study number and Abbreviated Title(s)  112931 (HIB-MENCY-TT-016)

IND number  11,706

EudraCT number (Amended:  2013-003459-39
03 September 2013)

Date of protocol amendment  Amendment 1 Final: 03 September 2013

Detailed Title  A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.

Sponsor signatory  Marie Van Der Wielen, Director, Vaccine Discovery and Development, Neisseria Vaccines

Signature  PPD

Date  06/09/2013

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## Rationale/background for changes:

In order to provide the opportunity for subjects in the control group to receive a meningococcal vaccine, which is not routinely administered in the US to this age group, the protocol has been amended to state that: “...a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by the study sponsor, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.”

Additionally,

- Distribution of a diary card for recording of medications/vaccinations post dose 2 of Havrix has been added.

- Treatment allocation is by component rather than dose.

- Text mentioning that subjects who do not continue in the booster phase will be contacted for safety information via a phone script at the ESFU timepoint has been added.

- The safety contact fax information has been updated.

- There have been a few changes in the contributing authors.
Contributing authors

- PPD, Clinical Research and Development Lead Manager, Vaccine Discovery and Development
- PPD, Study Manager
- PPD, Study Delivery Manager
- PPD, Local Delivery Lead
- PPD, Clinical Medical Affairs
- PPD, Medical Affairs Lead
- PPD, Study Delivery Lead
- PPD, GVCL Project Manager, Vaccine Discovery and Development
- PPD, Project Biostatistician, Vaccine Discovery and Development
- PPD, Director, Statistical Manager
- PPD, Lead Statistician, Vaccine Discovery and Development
- PPD, Study Data Manager, Business and Decision, contractor for GSK Biologicals

Synopsis

Study design

- Vaccination schedule:
  - IM injection of Hib-MenCY-TT at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - IM injection of PedvaxHIB at Day 0, Months 2 and 10-13 (2, 4 and 12-15 months of age).
  - IM injection of Pediarix at Day 0, Months 2 and 4 (2, 4 and 6 months of age).
  - IM injection of Prevnar 13 at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - Oral administration of Rotarix at Day 0 and Month 2 (2 and 4 months of age).
  - IM injection of Havrix at Months 10-13 (12-15 months of age) and 16-19 (18-21 months of age).

Note: The booster dose of Infanrix can be given will be provided by GSK outside of the study and is allowed at any time during the window between Day 30 post-dose 4 and 30 days prior to the administration of the 2nd dose of Havrix. Additionally, a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.
1 Introduction

The dramatic presentation and associated morbidity and mortality of \textit{N. meningitidis} infections have made the development of safe and effective vaccines an important public health priority in the US. \textit{Menactra}® (Sanofi Pasteur Inc. Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) is a quadrivalent meningococcal conjugate vaccine, which is comprised of the polysaccharide capsules of serogroups A, C, Y and W-135 each individually conjugated to diphtheria toxoid. This vaccine was approved by the US Food and Drug Administration (FDA) in January 2005 for use in individuals 11 to 55 years of age to be administered as a single dose. In October 2007, FDA expanded licensure of \textit{Menactra} to include children 2 to 10 years of age. In April 2011, the license for \textit{Menactra} was expanded further to include a two dose schedule for toddlers to be administered at 9 and 12 months of age. In February 2010, a second quadrivalent meningococcal conjugate vaccine, \textit{Menveo}® (Novartis Vaccines and Diagnostics, Inc. Meningococcal Groups A, C, W-135, and Y Polysaccharide CRM\textsubscript{197} Conjugate Vaccine), was licensed in the US for individuals 11-55 years of age, also to be administered as a single dose. In January 2011, FDA expanded licensure of \textit{Menveo} to include children 2-10 years of age \textit{and further expanded to 2 months of age in August 2013}.

3.0 Study Design

- Vaccination schedule:
  - IM injection of Hib-MenCY-TT at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - IM injection of PedvaxHIB at Day 0, Months 2 and 10-13 (2, 4 and 12-15 months of age).
  - IM injection of Pediarix at Day 0, Months 2 and 4 (2, 4 and 6 months of age).
  - IM injection of Prevnar 13 at Day 0, Months 2, 4 and 10-13 (2, 4, 6 and 12-15 months of age).
  - Oral administration of Rotarix at Day 0 and Month 2 (2 and 4 months of age).
  - IM injection of Havrix at Months 10-13 (12-15 months of age) and 16-19 (18-21 months of age).

Note: The booster dose of \textit{Infanrix} can be given \textit{will be provided by GSK} outside of the study and is allowed at any time during the window between Day 30 post-dose 4 and 30 days prior to the administration of the 2nd dose of \textit{Havrix}. \textit{Additionally, a parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.}

5.2.2.2 Treatment allocation to the subject

The treatment numbers will be allocated by \textit{dose component}. 

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5.5 Outline of study procedures

Table 7  List of study procedures, Epoch 001

<table>
<thead>
<tr>
<th>Age</th>
<th>12 – 15 months</th>
<th>13 – 16 months</th>
<th>18 – 21 months</th>
<th>19 – 22 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoch</td>
<td>Epoch 002</td>
<td>VISIT 5</td>
<td>VISIT 6 BLOOD DRAW IMMUNOGENICITY (ALL SUBJECTS) SAFETY (ALL SUBJECTS)</td>
<td>VISIT 7 2ND DOSE OF HAVRIX</td>
</tr>
<tr>
<td>Visit</td>
<td>VISIT 5</td>
<td>VISIT 6 BLOOD DRAW IMMUNOGENICITY (ALL SUBJECTS) SAFETY (ALL SUBJECTS)</td>
<td>VISIT 7 2ND DOSE OF HAVRIX</td>
<td></td>
</tr>
<tr>
<td>Timing</td>
<td>MONTHS 10-13</td>
<td>MONTHS 11-14</td>
<td>MONTHS 16-19</td>
<td>MONTHS 17-20</td>
</tr>
<tr>
<td>Sampling timepoint</td>
<td>Post-Vacc4</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recording of medications/vaccinations Post-dose 2 of Havrix on the diary card</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Return of diary cards (medications/vaccinations Post-dose 2 of Havrix)</td>
<td>●</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary card transcription</td>
<td>○</td>
<td>○</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8  List of study procedures, Epoch 002

5.6.12 Recording of AEs and SAEs

- At each vaccination visits 1, 2, 3 and 5, diary cards will be provided to the subject’s parent(s)/LAR(s). The subject’s parent(s)/LAR(s) will record body (rectal or axillary) temperature and any solicited local/general AEs (i.e. on the day of vaccination and during the next 3 days) or any unsolicited AEs (i.e. on the day of vaccination and during the next 30 days occurring after vaccination. The subject’s parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at the next study visit.

- Collect and verify completed diary cards during discussion with the subject’s parent(s)/LAR(s) on Visits 2, 3, 4, 6 and 8.

- **Diary cards will be provided to the subject’s parent(s)/LAR(s) at Visit 7. The subject’s parent(s)/LAR(s) will record any medications/vaccinations given/received (i.e. on the day of vaccination and during the next 30 days occurring after vaccination, as well as any anti-pyretics administered within 6 hours prior to and 12 hours following vaccination. The subject’s parent(s)/LAR(s) will be instructed to return the completed diary card to the investigator at Visit 8.**
5.6.13 Procedures during the extended safety follow-up period of Epoch 001

If a subject does not return for Visit 5 (Epoch 002), study personnel will review the subject’s electronic medical records and/or contact the subject’s parent/guardian by phone to obtain the subject’s safety information.

5.6.13.1 Epoch 001 study conclusion

Data analysis for safety and immunogenicity will proceed for Epoch 001 when all data has been collected up to study end.

5.6.14 Study conclusion

5.6.14.1 Epoch 001 study conclusion

Data analysis for safety and immunogenicity will proceed for Epoch 001 when all data has been collected up to study end.

5.6.14.2 Epoch 002 study conclusion

The study will be concluded upon the final blood draw at visit 8 of Epoch 002. Data analysis for the safety and immunogenicity for Epoch 002 will proceed when all data collected up to Visit 8 of Epoch 002 have been cleaned and frozen.

6.0 Study vaccines and administration

Additionally, the fourth dose of DTaP (Infanrix) will be provided outside of the study by GSK as the CDC recommends DTaP be provided from the same manufacturer and to ensure that all subjects in the study receive the recommended amount of doses of DTaP. A parent(s)/LAR(s) of a child in the PedvaxHIB control group will be offered the opportunity for their child to be vaccinated with a licensed meningococcal vaccine, which will be provided by GSK, after study end as these subjects did not have the benefit of receiving any meningococcal vaccination during the study.

8.3.3.2.1 Assessment of intensity

The maximum intensity of fever will be scored at GSK Biologicals as follows:

\[
\begin{array}{ccc}
0 & < 100.4^\circ F & < 38.0^\circ C \\
1 & \geq 100.4^\circ F \text{ to } < 102.2^\circ F & \geq 38.0^\circ C \text{ to } < 39.0^\circ C \\
2 & \geq 102.2^\circ F \text{ to } < 104.0^\circ F & \geq 39.0^\circ C \text{ to } < 40.0^\circ C \\
3 & \geq 104.0^\circ F & \geq 40.0^\circ C \\
\end{array}
\]

In addition to the above intensity grade, fever will be reported per 0.5°C cumulative increments.
8.4.2 Contact information for reporting serious adverse events and other events to GSK Biologicals

<table>
<thead>
<tr>
<th>Back-up Study Contact for Reporting SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>24/24 hour and 7/7 day availability:</td>
</tr>
<tr>
<td>GSK Biologicals Clinical Safety &amp; Pharmacovigilance</td>
</tr>
<tr>
<td>Fax: +PPD or +PPD</td>
</tr>
</tbody>
</table>

*Please refer to the Study Procedure Manual for the dedicated US Fax Machine number.*

8.4.3.1 Back-up system in case the electronic SAE reporting system does not work

If the electronic SAE reporting system does not work, the investigator (or designate) must complete, then date and sign a paper SAE report and fax it to the GSK Biologicals Clinical Safety and Pharmacovigilance department within 24 hours. *Please refer to the Study Procedure Manual for the dedicated US Fax Machine number.*
# Protocol Amendment 2 Sponsor Signatory Approval

<table>
<thead>
<tr>
<th>eTrack study number and Abbreviated Title(s)</th>
<th>112931 (HIB-MENCY-TT-016)</th>
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<tbody>
<tr>
<td>IND number</td>
<td>11,706</td>
</tr>
<tr>
<td>EudraCT number</td>
<td>2013-003459-39</td>
</tr>
<tr>
<td>Date of protocol amendment</td>
<td>Amendment 2 Final: 16 June 2014</td>
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<tr>
<td>Detailed Title</td>
<td>A phase IIIb, open, randomized, controlled, multicenter study to assess the co-administration of Rotarix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT (GlaxoSmithKline Biologicals’ Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine) at 2 and 4 months of age, the co-administration of Prevnar 13 (Pfizer) with Hib-MenCY-TT at 2, 4 and 6 months of age and the co-administration of Prevnar 13 and Havrix (GlaxoSmithKline Biologicals’) with Hib-MenCY-TT at 12 to 15 months of age.</td>
</tr>
<tr>
<td>Sponsor signatory</td>
<td>Marie Van Der Wielen, Director, Vaccine Discovery and Development, Neisseria Vaccines</td>
</tr>
<tr>
<td>Signature</td>
<td>PPD</td>
</tr>
<tr>
<td>Date</td>
<td>26 June 2014</td>
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</tbody>
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16-JUN-2014