In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- Information will be excluded in order to protect the privacy of patients and all named persons associated with the study
- Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the GSK Clinical Study Register.
- Aggregate data will be included; with any direct reference to individual patients excluded

*Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered
Final Study Report for Clinical Trial 213501/019
(DTPw-HBV-Hib-019)

Title: Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals’ quadrivalent diphtheria, tetanus, whole cell *Bordetella pertussis*, hepatitis B (DTPw-HBV) and *Haemophilus influenzae* type b conjugate (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with GS Biologicals’ hepatitis B vaccine.

**Study Vaccines:**
- Recombinant hepatitis B vaccine: *Engerix™-B*
- Combined diphtheria-tetanus-whole cell *Bordetella pertussis*-hepatitis B vaccine: *Tritanrix™-HB*
- *Haemophilus influenzae* type b (Hib) vaccine: *Hiberix™*

**CPMS Study No.:**
213501/019 (DTPw-HBV-Hib-019)

**Indication:**
Three-dose immunization course against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b in the first year of life in healthy infants who had previously received a monovalent dose of hepatitis B vaccine at birth.

**Principal Investigator:**
Dr. [Redacted]

**Date of First Visit:**
15 June 2000

**Date of Last Visit:**
9 April 2001

**Coordinating Author:**
[Redacted]
Vice President, Clinical Development

**Other Contributing Authors:**
International
Central Study Co-ordinator
Statistician
Statistician

*The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.*

**Report Date:**
23 April 2002

**Verification and approval**

[Signature]

3/01/02
Date (day/month/year)
Final Study Report for Clinical Trial 213501/019  
(DTPw-HBV-Hib-019)

Title: Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of GlaxoSmithKline (GSK) Biologicals’ quardrivalent diphtheria, tetanus, whole cell Bordetella pertussis, hepatitis B (DTPw-HBV) and Haemophilus influenzae type b conjugate (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with GSK Biologicals’ hepatitis B vaccine.

Study Vaccines: GSK Biologicals’  
- Recombinant hepatitis B vaccine: Engerix™B  
- Combined diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™HB  
- Haemophilus influenzae type b (Hib) vaccine: Hiberix™

CPMS Study No.: 213501/019 (DTPw-HBV-Hib-019)

Indication: Three-dose immunization course against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b in the first year of life in healthy infants who had previously received a monovalent dose of hepatitis B vaccine at birth.

Principal Investigator: Dr. [Name]
Date of First Visit: 15 June 2000
Date of Last Visit: 9 April 2001
Coordinating Author: Vice President, Clinical Development

Other Contributing Authors:  
- Central Study Co-ordinator  
- Statistician  
- Statistician

The trial was performed according to the Good Clinical Practice guidelines in operation at the time of the initiation of the trial.

Report Date: 23 April 2002
**Synopsis of Final Study Report 213501/019 (DTPw-HBV-Hib-019)**

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>GlaxoSmithKline Biologicals, Rixensart, Belgium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Finished Product:</td>
<td><em>Engerix™-B, Tritanrix™-HB and Hiberix™</em></td>
</tr>
<tr>
<td>Name of active substance:</td>
<td>Recombinant hepatitis B surface antigen, diphtheria and tetanus toxoids, whole cell <em>Bordetella pertussis</em> and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP)</td>
</tr>
<tr>
<td>Title of the study:</td>
<td>213501/019 (DTPw-HBV-Hib-019)</td>
</tr>
<tr>
<td>Phase</td>
<td>III</td>
</tr>
<tr>
<td>Study Design:</td>
<td>Open, self-contained study with single group.</td>
</tr>
<tr>
<td>Study Population:</td>
<td>Healthy infants between 6 to 10 weeks of age who had previously received a monovalent dose of GSK Biologicals’ hepatitis B vaccine at birth.</td>
</tr>
<tr>
<td>Number of subjects:</td>
<td>Planned and enrolled: 120  Completed: 116</td>
</tr>
<tr>
<td>Analyzed for According-To-Protocol (ATP) reactogenicity:</td>
<td>117</td>
</tr>
<tr>
<td>Analyzed for ATP immunogenicity:</td>
<td>105</td>
</tr>
<tr>
<td>Diagnosis and criteria for inclusion:</td>
<td>Infants aged between and including 6 and 10 weeks at the time of the first dose of the vaccination course and born after a normal gestation period (between 36 and 42 weeks), who were free of obvious health problems as established by medical history of pregnancy and clinical examination before entering into the study. Written informed consent was obtained from the parent/guardian of the subject prior to study entry.</td>
</tr>
<tr>
<td>Test product, dose, mode of administration, lot No.:</td>
<td>Vaccination schedule/site: Hepatitis B vaccine was administered at birth as a single intramuscular (IM) injection into the left anterolateral thigh. DTPw-HB and Hib vaccines were given according to a 3-dose schedule at 2, 4 and 6 months of age. These two vaccines were mixed extemporaneously and given as a single IM injection in the left anterolateral thigh. Vaccine/composition/dose/lot number: GSK Biologicals’ recombinant hepatitis B vaccine (<em>Engerix™-B</em>) contained per dose of 0.5 ml: 10 mcg of recombinant hepatitis B surface antigen (r-DNA HBsAg), 0.5 mg of aluminium as salts and 25 mcg of thiomersal in a sterile saline solution.</td>
</tr>
</tbody>
</table>

**Publication (reference):** Not published as of 23 April 2002

**Clinical phase:** III

| Principal Investigator: | Dr. |
| Study Center: | Colombia |
| Study period: | Date of first visit: 15 June 2000  Date of last visit: 9 April 2001 |

**Synopsis page 1 of 5**
Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium
Name of Finished Product: Engerix™B, Tritanrix™-HB and Hiberix™
Name of active substance: Recombinant hepatitis B surface antigen, diphtheria and tetanus toxoids, whole cell Bordetella pertussis and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP)
solution (150 mM NaCl). Lot no.: ENG2814A2/M.

GSK Biologicals’ combined quadrivalent diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine (Tritanrix™-HB) contained per dose of 0.5 ml: not less than 30 IU (7.5 Lf) of diphtheria toxoid, not less than 60 IU (3.25 Lf) of tetanus toxoid, not less than 2 IU (15 OU) of Bordetella pertussis (killed), 10 mcg of r-DNA HBsAg, 0.5 mg of aluminium (as salts) and 50 mcg of 2-phenoxyethanol in a sterile saline solution (150 mM NaCl). Lot no.: 15776A2/M.

GSK Biologicals’ Haemophilus influenzae type b conjugate vaccine (Hiberix™) contained per dose: 10 mcg of conjugate of Hib capsular polysaccharide (PRP), 20 to 40 mcg of tetanus toxoid and 12.6 mg of lactose. Lot no.: Hib273A47/M.

Duration of treatment: Approximately 7 months for each subject.

Reference therapy, dose and mode of administration, batch number: NA

Criteria for evaluation:
Primary endpoint: Percentage of infants with anti-HBs antibody titers ≥ 10 mIU/ml at the time of the second dose of DTPw-HBV/Hib vaccine, i.e., at 4 months of age
Secondary endpoints:
- At each blood sampling time point, the serum antibody titers for anti-HBs, anti-PRP, anti-B. pertussis (anti-BPT), anti-tetanus and anti-diphtheria antibodies.
- Occurrence of any solicited local and/or general symptoms within 4 days after each dose of vaccines.
- Occurrence of unsolicited symptoms within 30 days after each dose of vaccines.
- Occurrence of Serious Adverse Events (SAEs) over the course of the study (beginning with first study procedure at birth up to and including 30 days following the third dose of DTPw-HBV/Hib vaccine).

Statistical methods:
Analysis of demographics: Demographic characteristics (age and gender) of each study cohort was tabulated. The mean age (plus range and standard deviation) by gender of the enrolled subjects was calculated.

Analysis of immunogenicity: Analysis was performed on two cohorts: total and according-to-protocol (ATP) cohorts. The analysis on ATP cohort was considered the primary analysis. Seropositivity/seroprotection rates (percentage of subjects with titer ≥ assay cut-off) and Geometric Mean Titers (GMT) for antibodies against all vaccine antigens were calculated with 95% Confidence Interval (95% CI), at each blood sampling time point. The percentage of subjects with protective levels of anti-HBs antibodies (i.e., titers ≥ 10 mIU/ml), anti-diphtheria and anti-tetanus toxoid antibodies (i.e., titers ≥ 0.1 IU/ml) was determined at each blood sampling time point. The percentage of subjects with a serum antibody concentration of anti-PRP antibodies ≥ 0.15 mcg/ml (generally accepted as short-term seroprotection) and ≥ 1.0 mcg/ml (generally accepted as long-term seroprotection), with anti-BPT antibody titer ≥ the assay cut-off of 15 EL.U/ml were tabulated. The GMT calculations were performed by taking the anti-log of the mean of the log titer transformations. Vaccine response to whole-cell pertussis was calculated with 95% CI at Month 7 and was defined as:
- the presence of antibodies (titer ≥ cut-off) in subjects seronegative at pre-vaccination or
- post-vaccination antibody titers ≥ pre-vaccination titers, in subjects seropositive at pre-vaccination.

Analysis of reactogenicity: Analysis was performed on only one cohort, as the ATP reactogenicity cohort was the same as the total cohort. Incidence of symptoms was calculated on the number of symptom sheets completed (per-dose analysis) and on the number of subjects reporting symptoms (per-subject analysis). The percentage of doses followed by a report of any
symptom (solicited or unsolicited) and percentage of doses followed by at least one local or general symptom during the 4-day follow-up period after vaccination was determined. The incidence and intensity of each solicited symptom during the 4-day follow-up period was reported. The relationship of solicited general symptoms to vaccination was tabulated. The incidence, relationship to vaccination and intensity of unsolicited symptoms was tabulated. Serious adverse events and discontinuation due to adverse events were described in detail.

**SUMMARY-CONCLUSIONS:**

Demography:
The mean age of the total cohort at the time of DTPw-HBV/Hib vaccine dose (i.e., at Month 2) was 7.6 weeks with a standard deviation of 0.91 weeks. The male to female ratio was 1.2: 1 (64/53)

**Immunological results:**

Immunological data at all blood sampling time points for anti-HBs antibodies (primary endpoint) and pre- and post-vaccination (i.e., at Month 7) time points for antibodies to all other vaccine antigens are presented for the ATP immunogenicity cohort in the table below.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>N</th>
<th>S+ %</th>
<th>95% CI LL</th>
<th>GMT</th>
<th>95% CI UL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PIV (M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-HBs ≥ 10 mIU/ml</td>
<td>Pre (P17)</td>
<td>103</td>
<td>4</td>
<td>3.9</td>
<td>1.1</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>104</td>
<td>85</td>
<td>81.7</td>
<td>72.9</td>
<td>88.6</td>
</tr>
<tr>
<td></td>
<td>PII (M4)</td>
<td>105</td>
<td>104</td>
<td>99.0</td>
<td>94.8</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PIII (M6)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PIV (M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-PRP ≥ 0.15 mcg/ml</td>
<td>Pre (P17)</td>
<td>105</td>
<td>74</td>
<td>70.5</td>
<td>60.8</td>
<td>79.0</td>
</tr>
<tr>
<td>(short-term seroprotect)</td>
<td>PIV (M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-PRP ≥ 1 mcg/ml</td>
<td>Pre (P17)</td>
<td>105</td>
<td>33</td>
<td>31.4</td>
<td>22.7</td>
<td>41.2</td>
</tr>
<tr>
<td>(long-term seroprotect)</td>
<td>PIV (M7)</td>
<td>105</td>
<td>104</td>
<td>99.0</td>
<td>94.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Anti-diphtheria ≥ 0.1 IU/ml</td>
<td>Pre (P17)</td>
<td>105</td>
<td>91</td>
<td>86.7</td>
<td>78.6</td>
<td>92.5</td>
</tr>
<tr>
<td></td>
<td>PIV (M7)</td>
<td>105</td>
<td>101</td>
<td>98.1</td>
<td>93.2</td>
<td>99.8</td>
</tr>
<tr>
<td>Anti-tetanus ≥ 0.1 IU/ml</td>
<td>Pre (P17)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PIV (M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-vacc status</th>
<th>N</th>
<th>R+ %</th>
<th>95% CI LL</th>
<th>95% CI UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-BPT vaccine response at Month 7</td>
<td>S+ * 19</td>
<td>19</td>
<td>100.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Se * 86</td>
<td>86</td>
<td>100.0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
</tr>
</tbody>
</table>

All subjects received Engerix™B at birth + DTPw-HBV /Hib at 2, 4 and 6 months of age

N: Number of subjects tested; 95% CI, LL, UL: 95% confidence interval, lower and upper limits

S+ (%): Number (percentage) of subjects seropositive for the respective antibodies

SP (%): Number (percentage) of subjects seroprotected for the respective antibodies

Pre: At Month 0; PII (M4): Two months after first dose of DTPw-HBV/Hib

PIII (M6): Two months after second dose of DTPw-HBV/Hib

PIV (M7): One month after third dose of DTPw-HBV/Hib

R+ (%): Number (percentage) of responders (i.e., subjects who showed a vaccine response)

*S-/S+: Subjects seronegative/seropositive for anti-BPT antibodies at pre-vaccination

In the ATP immunogenicity cohort,

- A total of 81.7 % subjects were seroprotected for anti-HBs antibodies. There was an 11.5-fold increase in anti-HBs GMTs from pre-vaccination to Month 4.

One month after the full vaccination course (i.e., at Month 7), in the ATP cohort:

- All subjects were seroprotected for anti-HBs antibodies and there was a 263-fold increase in anti-HBs GMTs from pre-vaccination to Month 7.
**Name of Company:** GlaxoSmithKline Biologicals, Rixensart, Belgium  
**Name of Finished Product:** Enferix™B, Tritanrix™HB and Hiberix™  
**Name of active substance:** Recombinant hepatitis B surface antigen, diphtheria and tetanus toxoids, whole cell Bordetella pertussis and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP)  

---

### Reactogenicity Results

Reactogenicity results for the ATP cohort were as follows:

<table>
<thead>
<tr>
<th>Local/ general symptoms (solicited/ unsolicited)</th>
<th>N</th>
<th>n (%)</th>
<th>Any %</th>
<th>95% CI</th>
<th>n (%)</th>
<th>Any %</th>
<th>95% CI</th>
<th>n (%)</th>
<th>Any %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth dose of Enferix™B</td>
<td>117</td>
<td>26</td>
<td>22.2</td>
<td>15.1</td>
<td>30.8</td>
<td>13</td>
<td>11.1</td>
<td>6.1</td>
<td>18.3</td>
<td>19</td>
</tr>
<tr>
<td>Dose 1 of DTPw-HBV/Hib</td>
<td>116</td>
<td>76</td>
<td>65.5</td>
<td>56.1</td>
<td>74.1</td>
<td>63</td>
<td>54.3</td>
<td>44.8</td>
<td>63.6</td>
<td>62</td>
</tr>
<tr>
<td>Dose 2 of DTPw-HBV/Hib</td>
<td>116</td>
<td>57</td>
<td>49.1</td>
<td>39.7</td>
<td>58.6</td>
<td>50</td>
<td>43.1</td>
<td>33.9</td>
<td>52.6</td>
<td>40</td>
</tr>
<tr>
<td>Dose 3 of DTPw-HBV/Hib</td>
<td>116</td>
<td>54</td>
<td>46.6</td>
<td>37.2</td>
<td>56.0</td>
<td>45</td>
<td>38.8</td>
<td>29.9</td>
<td>48.3</td>
<td>44</td>
</tr>
<tr>
<td>Overall/dose</td>
<td>465</td>
<td>213</td>
<td>45.8</td>
<td>41.2</td>
<td>50.5</td>
<td>171</td>
<td>36.8</td>
<td>32.4</td>
<td>41.3</td>
<td>165</td>
</tr>
<tr>
<td>Overall/subject</td>
<td>117</td>
<td>90</td>
<td>76.9</td>
<td>68.2</td>
<td>84.2</td>
<td>86</td>
<td>73.5</td>
<td>64.5</td>
<td>81.2</td>
<td>74</td>
</tr>
</tbody>
</table>

---

### According to per-dose analysis:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>Birth dose of Enferix™B (N = 117)</th>
<th>Dose 1 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th>Dose 2 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th>Dose 3 of DTPw-HBV/Hib vaccine (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Any %</td>
<td>95% CI</td>
<td>LL</td>
<td>UL</td>
</tr>
<tr>
<td>Pain</td>
<td>Sor</td>
<td>7</td>
<td>6.0</td>
<td>2.4</td>
<td>11.9</td>
</tr>
<tr>
<td>Grade &quot;3&quot;</td>
<td>Sor</td>
<td>4</td>
<td>3.9</td>
<td>1.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Redness</td>
<td>Sor</td>
<td>13</td>
<td>11.1</td>
<td>6.1</td>
<td>18.3</td>
</tr>
<tr>
<td>Swelling</td>
<td>Sor</td>
<td>25</td>
<td>4.4</td>
<td>3.0</td>
<td>6.1</td>
</tr>
</tbody>
</table>

---

All subjects received Enferix™B at birth + DTPw-HBV/Hib at 2, 4 and 6 months of age

95% CI, LL, UL: Exact 95% confidence interval, lower and upper limits

**For each dose and overall per-subject:**

N: Number of subjects with at least one documented dose

n (%): Number (percentage) of doses followed by a given type of symptom

For overall / dose:

N: Number of documented doses

n (%) per dose: Number (percentage) of doses followed by a given type of symptom

Fever: axillary temperature >39 °C or rectal temperature ≥ 38.0°C

Grade "3" pain: Cried when limb was moved/spontaneously painful

Grade "3" irritability: Crying that could not be comforted/ prevented normal activity

Grade "3" loss of appetite: Not eating at all

Grade "3" fever: axillary temperature >39 °C or rectal temperature >39.5 °C
For the ATP reactogenicity cohort, any symptom (solicited/unsolicited): The incidence of symptoms (local/general, solicited/unsolicited) reported during the 4-day follow-up after vaccination, decreased with subsequent doses.

Solicited local symptoms: Redness at injection site was the most reported solicited local symptom following birth dose of HBV vaccine and pain at injection site was the most reported solicited local symptom following DTPw-HBV/Hib vaccination. All grade “3” solicited local symptoms reported (58 symptoms) were pain at injection site and resolved within the 4-day follow-up period except for one symptom, which resolved on Day 6 after vaccination.

Solicited general symptoms: Fever was the most reported solicited general symptom and irritability was the most reported grade “3” solicited general symptom. All solicited general symptoms were considered by the investigator to have a ‘probable’ (‘PB’) or ‘suspected’ (‘SU’) relationship to the study vaccines. Only one case of grade “3” fever was reported. All grade “3” symptoms resolved within the 4-day follow-up period after vaccination.

Unsolicited symptoms: A total of 52 doses were followed by at least one report of unsolicited symptom classified by WHO Preferred Terms, during the 30-day follow-up period after vaccination. Of these, 8 (1.7%) doses were followed by grade “3” symptoms. Of the 52 doses, 11 (2.4%) doses were followed by unsolicited symptoms that were considered by the investigator to have a ‘PB’/’SU’ relationship to study vaccines. Of these symptoms that had a ‘PB’/’SU’ relationship to study vaccines, two unsolicited symptoms were of intensity grade “3”. All unsolicited symptoms resolved within the 30-day follow-up period after vaccination.

Serious Adverse Events:

Conclusions:

- The seroprotection rate of anti-HBs antibodies at Month 4 (i.e., two months after the second dose of HBsAg) was 81.7%, at Month 6 (i.e., two months after third dose of HBsAg) was 99% and at Month 7 (i.e., one month after the fourth dose of HBsAg) was 100%.
- One month after the full vaccination course (i.e., at Month 7), all subjects had anti-PRP antibody titers ≥ 0.15 mcg/ml (generally accepted as short-term seroprotection), 99% subjects had anti-PRP antibody titers ≥ 1 mcg/ml (generally accepted as long-term seroprotection) and all subjects showed a vaccine response to whole cell pertussis. Also, all subjects were seroprotected for anti-tetanus antibodies and 98.1% of subjects were seroprotected for anti-diphtheria antibodies.
- The incidence of symptoms (local/general, solicited/unsolicited) reported during the 4-day follow-up after vaccination decreased with subsequent doses of DTPw-HBV/Hib. No increase in the incidence of symptoms could be observed following the fourth dose of HBsAg. Few grade “3” solicited symptoms were reported and all (except one) grade “3” solicited symptoms resolved within the 4-day follow-up period after vaccination. Only one SAE was reported, which was considered by the investigator to be ‘not related’ to the vaccination.
- Therefore, within the limitations of this study, the immunogenicity and safety profile of DTPw-HBV/Hib vaccine given at 2, 4 and 6 months following a birth dose of hepatitis B vaccine was found to be good.

Date of report: 23 April 2002
CONTENTS: TEXT

1. INTRODUCTION/RATIONALE ........................................................................................................ 15

2. STUDY OBJECTIVES .................................................................................................................. 16
   2.1 PRIMARY OBJECTIVE ............................................................................................................. 16
   2.2 SECONDARY OBJECTIVES .................................................................................................... 16

3. METHODOLOGY ........................................................................................................................ 16
   3.1 STUDY DESIGN ....................................................................................................................... 16
   3.2 INVESTIGATOR AND TRIAL CENTER ..................................................................................... 17
   3.3 ETHICS .................................................................................................................................... 17
       3.3.1 Protocol amendments/modifications ............................................................................ 17
   3.4 SELECTION OF STUDY POPULATION .................................................................................... 17
       3.4.1 Number of subjects ....................................................................................................... 17
       3.4.2 Inclusion criteria ........................................................................................................... 18
       3.4.3 Exclusion criteria ......................................................................................................... 18
       3.4.4 Elimination criteria .................................................................................................... 19
       3.4.5 Contraindications to vaccination .............................................................................. 19
   3.5 STUDY VACCINES AND ADMINISTRATION ......................................................................... 20
       3.5.1 Study vaccines composition ....................................................................................... 20
       3.5.2 Dosage and administration ....................................................................................... 22
   3.6 TREATMENT ALLOCATION AND RANDOMIZATION ............................................................ 22
   3.7 BLINDING ................................................................................................................................ 22
   3.8 STUDY PROCEDURES ............................................................................................................. 22
   3.9 SUBJECT COMPLETION AND DROP-OUT ........................................................................... 23
   3.10 ASSESSMENT OF IMMUNOGENICITY VARIABLES ............................................................. 24
       3.10.1 Intervals between study visits ..................................................................................... 24
       3.10.2 Laboratory assays and time points ............................................................................. 24
   3.11 ASSESSMENT OF REACTOGENICITY VARIABLES ............................................................ 26
       3.11.1 Biochemical assays ..................................................................................................... 31
       3.11.2 Pregnancy ................................................................................................................... 31
       3.11.3 Prior and concomitant medication ............................................................................ 31
   3.12 DATA QUALITY ASSURANCE ............................................................................................. 31
   3.13 STATISTICAL METHODS ....................................................................................................... 31
       3.13.1 Primary endpoint ......................................................................................................... 31
       3.13.2 Secondary endpoints .................................................................................................. 32
       3.13.3 Target sample size ...................................................................................................... 32
       3.13.4 Study cohorts/data sets analysed .............................................................................. 32
       3.13.5 Analysis of demographics .......................................................................................... 33
       3.13.6 Analysis of immunogenicity ....................................................................................... 33
       3.13.7 Analysis of reactogenicity ........................................................................................... 34
   3.14 CHANGES IN PLANNED ANALYSES ..................................................................................... 34
4. STUDY POPULATION........................................................................................................ 35

4.1 STUDY DATES...................................................................................................................... 35

4.2 SUBJECT ELIGIBILITY AND ATTRITION FROM STUDY.................................................. 35

  4.2.1 Number and distribution of subjects ......................................................................... 35

  4.2.2 Study completion and drop-out ............................................................................... 35

  4.2.3 Eligibility for analysis ............................................................................................. 36

  4.2.4 Compliance with protocol specified procedures ..................................................... 37

4.3 DEMOGRAPHIC CHARACTERISTICS.................................................................................... 37

  4.3.1 Total cohort ............................................................................................................. 37

  4.3.2 Subjects included in the ATP analysis of immunogenicity ...................................... 38

5. ANALYSIS OF IMMUNOGENICITY .................................................................................... 38

5.1 DATA SETS ANALYSED...................................................................................................... 39

5.2 ACCORDING-TO-PROTOCOL ANALYSIS......................................................................... 39

  5.2.1 Anti-HBs antibody response ................................................................................... 39

  5.2.2 Anti-PRP antibody response ................................................................................... 40

  5.2.3 Anti-BPT antibody response ................................................................................... 40

  5.2.4 Anti-diphtheria and anti-tetanus antibody response ............................................... 41

5.3 ANALYSIS OF TOTAL COHORT ....................................................................................... 42

6. ANALYSIS OF REACTOGENICITY ..................................................................................... 43

6.1 OVERALL INCIDENCE OF SYMPTOMS ............................................................................. 43

6.2 SOLICITED LOCAL SIGNS AND SYMPTOMS ................................................................. 44

6.3 SOLICITED GENERAL SIGNS AND SYMPTOMS ........................................................... 46

6.4 UNSOLICITED SYMPTOMS .............................................................................................. 47

6.5 CONCOMITANT MEDICATIONS/ VACCINATIONS .......................................................... 49

6.6 BIOCHEMICAL ANALYSES ............................................................................................ 49

6.7 PREGNANCY .................................................................................................................. 50

6.8 SERIOUS ADVERSE EVENTS ......................................................................................... 50

7. DISCUSSION ....................................................................................................................... 51

8. OVERALL CONCLUSIONS................................................................................................. 52

9. REFERENCES....................................................................................................................... 53

GSK BIOLOGICALS VACCINES CLINTRIAL ELIMINATION CODES ................................. 64

NOTES TO APPENDIX TABLES............................................................................................ 66
CONTENTS: REPORT TABLES AND FIGURES

TABLE 1 OUTLINE OF STUDY PROCEDURES ................................................................. 23
TABLE 2 INTERVALS BETWEEN STUDY VISITS .......................................................... 24
TABLE 3 SEROLOGICAL ASSAYS .................................................................................. 25
TABLE 4 SOLICITED ADVERSE EVENTS ........................................................................ 27
TABLE 5 ASSESSMENT OF INTENSITY ......................................................................... 28
TABLE 6 REASONS FOR DROP-OUT ............................................................................. 35
TABLE 7 THE NUMBER OF SUBJECTS, ENROLLED INTO THE STUDY AS WELL AS THE NUMBER EXCLUDED FROM ANALYSES .................................................................................. 37
TABLE 8 DEMOGRAPHICS: TOTAL COHORT AT MONTH 2 .............................................. 38
TABLE 9 DEMOGRAPHICS: ATP IMMUNOGENICITY COHORT ........................................ 38
TABLE 10 SEROPROTECTION RATE AND GMTs OF ANTI-HBs ANTIBODIES (ATP IMMUNOGENICITY COHORT) .............................................................................................................................. 39
TABLE 11 PERCENTAGE OF SUBJECTS WITH TITERS ≥0.15 MCG/ML AND ≥1.0 MCG/ML AND GMTs OF ANTI-PRP ANTIBODIES (ATP IMMUNOGENICITY COHORT) .............................................................................................................................. 40
TABLE 12 SEROPOSITIVITY RATES AND GMTs OF ANTI-BPT ANTIBODIES (ATP IMMUNOGENICITY COHORT) .............................................................................................................................. 41
TABLE 13 VACCINE RESPONSE TO WHOLE CELL PERTUSSIS AT MONTH 7 (ATP IMMUNOGENICITY COHORT) .............................................................................................................................. 41
TABLE 14 SEROPROTECTION RATES AND GMT OF ANTI-DIPHTHERIA AND ANTI-TETANUS ANTIBODIES (ATP IMMUNOGENICITY COHORT) .............................................................................................................................. 42
TABLE 15 NUMBER AND PERCENTAGE OF SUBJECTS WHO RECEIVED VACCINATION (TOTAL COHORT) .............................................................................................................................. 43
TABLE 16 INCIDENCE OF SYMPTOMS (SOLICITED/UNSOLICITED) REPORTED DURING THE 4-DAY FOLLOW-UP PERIOD AFTER EACH DOSE OF DTPw-HBV/Hib AND ENGERIX™-B VACCINES AND OVERALL (ATP REACTOGENICITY COHORT) .............................................................................................................................. 44
TABLE 17 INCIDENCE OF SOLICITED LOCAL SYMPTOMS AND THOSE GRADED “3” IN INTENSITY REPORTED DURING THE 4-DAY FOLLOW-UP PERIOD AFTER ENGERIX™-B VACCINE DOSE AT BIRTH (ATP REACTOGENICITY COHORT) .............................................................................................................................. 45
TABLE 18 INCIDENCE OF SOLICITED LOCAL SYMPTOMS (ANY/ GRADE “3”), REPORTED DURING THE 4-DAY FOLLOW-UP PERIOD AFTER EACH OF THE THREE DOSES OF DTPw-HBV/Hib VACCINE (ATP REACTOGENICITY COHORT) .............................................................................................................................. 46
TABLE 19 INCIDENCE OF SOLICITED GENERAL SYMPTOMS (ANY AND GRADE “3”) REPORTED DURING THE 4-DAY FOLLOW-UP PERIOD AFTER EACH VACCINE DOSE (ATP REACTOGENICITY COHORT) .............................................................................................................................. 47
TABLE 20 NUMBER OF DOSES FOLLOWED BY AT LEAST ONE REPORT OF UNSOLICITED SYMPTOM CLASSIFIED BY WHO PREFERRED TERM AND DETERMINED BY THE INVESTIGATOR TO HAVE ‘PROBABLE’ OR ‘SUSPECTED’ RELATIONSHIP TO THE VACCINATION, REPORTED DURING THE 30-DAY FOLLOW-UP PERIOD (ATP REACTOGENICITY COHORT) .............................................................................................................................. 49
CONTENTS: SUPPLEMENTARY TABLES

<table>
<thead>
<tr>
<th>SUPPLEMENTARY TABLE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEMOGRAPHICS: RACIAL AND GENDER COMPOSITION (TOTAL COHORT)</td>
</tr>
<tr>
<td>2</td>
<td>DEMOGRAPHICS: RACIAL AND GENDER COMPOSITION (ATP IMMUNOGENICITY COHORT)</td>
</tr>
<tr>
<td>3</td>
<td>SEROPROTECTION RATE AND GMTS OF ANTI-HBs ANTIBODIES (TOTAL COHORT)</td>
</tr>
<tr>
<td>4</td>
<td>PERCENTAGE OF SUBJECTS WITH TITERS ≥ 0.15 MCG/ML AND ≥ 1.0 MCG/ML AND GMTS OF ANTI-PRP ANTIBODIES (TOTAL COHORT)</td>
</tr>
<tr>
<td>5</td>
<td>SEROPOSITIVITY RATES AND GMTS OF ANTI-BPT ANTIBODIES (TOTAL COHORT)</td>
</tr>
<tr>
<td>6</td>
<td>VACCINE RESPONSE TO WHOLE CELL PERTUSSIS ANTIGEN AT MONTH 7 (TOTAL COHORT)</td>
</tr>
<tr>
<td>7</td>
<td>SEROPROTECTION RATES AND GMT OF ANTI-DIPHTHERIA AND ANTI-TETANUS ANTIBODIES (TOTAL COHORT)</td>
</tr>
<tr>
<td>8</td>
<td>VACCINE RESPONSE TO WHOLE CELL PERTUSSIS ANTIGEN AT MONTH 7 (TOTAL COHORT)</td>
</tr>
<tr>
<td>9</td>
<td>OVERALL INCIDENCE OF SOLICITED LOCAL SYMPTOMS (ANY AND GRADE “3”) REPORTED DURING THE 4-DAY FOLLOW-UP PERIOD AFTER ALL FOUR VACCINE DOSES (ENERIX™-B AND DTPw-HBV/Hib), ACCORDING TO PER-DOSE AND PER-SUBJECT ANALYSES (ATP REACTOGENICITY COHORT)</td>
</tr>
<tr>
<td>10</td>
<td>OVERALL INCIDENCE OF SOLICITED LOCAL SYMPTOMS (ANY AND GRADE “3”) REPORTED FOLLOWING THE THREE DOSES OF DTPw-HBV/Hib VACCINE, ACCORDING TO PER-DOSE AND PER-SUBJECT ANALYSES (ATP REACTOGENICITY COHORT)</td>
</tr>
<tr>
<td>11</td>
<td>OVERALL INCIDENCE OF SOLICITED GENERAL SYMPTOMS (ANY AND GRADE “3”) REPORTED FOLLOWING THE THREE DOSES OF DTPw-HBV/Hib VACCINE, ACCORDING TO PER-DOSE AND PER-SUBJECT ANALYSES (ATP REACTOGENICITY COHORT)</td>
</tr>
<tr>
<td>12</td>
<td>OVERALL INCIDENCE OF SOLICITED GENERAL SYMPTOMS (ANY AND GRADE “3”) REPORTED FOLLOWING THE THREE DOSES OF DTPw-HBV/Hib VACCINE, ACCORDING TO PER-DOSE AND PER-SUBJECT ANALYSES (ATP REACTOGENICITY COHORT)</td>
</tr>
<tr>
<td>13</td>
<td>NUMBER OF DOSES FOLLOWED BY AT LEAST ONE REPORT OF UNSOLICITED SYMPTOM CLASSIFIED BY WHO PREFERRED TERMS REPORTED DURING THE 30-DAY FOLLOW-UP PERIOD AFTER VACCINATION (ATP REACTOGENICITY COHORT)</td>
</tr>
</tbody>
</table>
APPENDICES

APPENDICES: INDIVIDUAL LISTINGS

I  A  ELIMINATION CODES
    B  DEMOGRAPHY
    C  DATES OF BIRTH, VACCINATION AND BLOOD SAMPLING VISITS
    D  GENERAL MEDICAL HISTORY - PHYSICAL EXAMINATION
    E  STUDY CONCLUSION

II A  SOLICITED LOCAL ADVERSE EVENTS
     B  SOLICITED GENERAL ADVERSE EVENTS
     Ci  UNSOLICITED ADVERSE EVENTS WITHIN 30 DAYS POST VACCINATION
     Cii UNSOLICITED ADVERSE EVENTS STARTED MORE THAN 30 DAYS POST VACCINATION
     Di  MEDICATION
     Dii CONCOMITANT VACCINATION

III A  IMMUNOGENICITY

APPENDICES: SERIOUS ADVERSE EVENTS

     −  CIOMS
     −  SERIOUS ADVERSE EVENTS TABLE

APPENDICES: STUDY INFORMATION

     −  PROTOCOL
     −  REPRESENTATIVE SUBJECT INFORMATION SHEET
     −  RELEVANT PAGES OF CRF (UNIQUE PAGES ONLY)
     −  RANDOMIZATION LIST
     −  ONE PAGE CV FOR PRINCIPAL INVESTIGATOR(S)
     −  PUBLICATIONS REFERENCED IN THE REPORT
List of Abbreviations and Definitions of Terms

anti-BPT    antibody to *Bordetella pertussis*
anti-HBs    antibody to hepatitis B surface antigen
anti-PRP    antibody to polyribosylribitol phosphate
ATP         According-To-Protocol
*B. pertussis* *Bordetella pertussis*
CI           Confidence Interval
CRF          Case Report Form
CVI          Children’s Vaccine Initiative
DTPw         Diphtheria, Tetanus, Whole Cell Pertussis vaccine
DTPw-HBV     Combined Diphtheria, Tetanus, Whole Cell Pertussis and Hepatitis B Vaccine
ELISA       Enzyme-Linked Immunosorbent Assay
EL.U        ELISA Units
EL.U/ml     ELISA Units per milliliter
GSK Biologicals  GlaxoSmithKline Biologicals
HBsAg       Hepatitis B surface Antigen
HBV         Hepatitis B Virus
Hib         *Haemophilus influenzae* type b
IU           International Units
IU/ml       International Units per milliliter
LF           Limit Flocculation
mcg         micrograms
mIU         milli-International Units
mIU/ml      milli-International Units per milliliter
ml           milliliter
mM           milli-Moles
OU           Opacity Units
PRP          Polyribosyl-Ribitol-Phosphate: polysaccharide component of the Hib bacterium capsule
r-DNA       Recombinant Deoxyribonucleic Acid
RIA          Radioimmunoassay
SAGE         Scientific Advisory Group of Experts
WHO          World Health Organization
Glossary of Terms

**Adverse Event:** An adverse event included any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory detected changes occurring in any phase of the clinical study whether associated with the study vaccine, active comparator or placebo and whether or not considered vaccination related. This included an exacerbation of pre-existing conditions or events, intercurrent illnesses, or vaccine or drug interaction.

**ATP immunogenicity cohort:** The ATP cohort for analysis of immunogenicity included all subjects for whom differential treatment effects on immunogenicity was likely (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol) and for whom data concerning immunogenicity endpoints were available. This included subjects for whom assay results were available for at least one study vaccine antigen component after vaccination.

**ATP reactogenicity cohort:** The ATP cohort for analysis of reactogenicity included all subjects who received the study vaccine, who had sufficient data to perform an analysis of reactogenicity, who did not receive a vaccine forbidden in the protocol and for whom administration site of study vaccine was known.

**Case Report Form:** Hard copy standardized form for recording individual subject data.

**Completed:** Subjects who completed at least the last study visit

**Conjugated vaccine:** Vaccine in which the pathogenic antigen is linked to a more immunogenic ‘protein carrier’.
Diary-card: Individual card provided by the sponsor for parents/guardians of each vaccinee (after the vaccine dose), designed to document the presence of solicited local and general adverse events as well as any other sign/symptom the vaccinee might experience during the four days after vaccination (days 0 to 3).

Documented dose: Any dose with at least one symptom sheet completed and/or at least one unsolicited symptom reported.

Drop-out: Subjects who did not come back at least for the last study visit.

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

Evaluable: Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis.

Subject(s): Term used throughout the report to denote the enrolled individual(s).

Symptom sheet: Symptom sheets are the specific pages in the individual case report forms onto which the investigator transcribed diary card documentation on solicited symptoms reported by the subject.

Total cohort: The total cohort included all subjects enrolled in the study for whom data was available.

Whole-cell pertussis vaccine: Vaccine which consisted of killed whole *Bordetella pertussis* bacteria.
1. Introduction/Rationale

Hepatitis B infection continues to be a major health concern all around the globe. Given the worldwide prevalence of hepatitis B and the availability of efficacious vaccines for its prevention, mass immunization would be an important step towards global control of hepatitis B infection. GlaxoSmithKline (GSK) Biologicals’ recombinant hepatitis B vaccine, Engerix™-B, was first registered in 1986 and was approved for commercial use in Colombia in 1989 and is universally accepted as a vaccine for administration to neonates at birth.

The Scientific Advisory Group of Experts (SAGE) of the Children’s Vaccine Initiative (CVI) recommended in 1992 the development of hepatitis B combination vaccines based on the well-established and accepted diphtheria-tetanus-whole cell pertussis (DTPw) vaccine. GSK Biologicals developed the first DTPw-Hepatitis B combination (DTPw-HBV) vaccine, Tritanrix™-HB. Studies have shown it to be safe and effective following a three dose primary course \(^1, 2, 3\) . It has been commercially available in Europe since 1996 after approval by centralized procedure and was approved for commercial use in Colombia in June 1998.

Another infection which has gained focus of attention is Haemophilus influenzae type b (Hib), a leading cause of invasive bacterial illness such as meningitis and pneumonia among infants and children worldwide. GSK Biologicals’ Hib conjugate vaccine (Hiberix™) was first registered for commercial use in April 1997 and has been registered in Colombia since May 1998.

Results of clinical studies performed in healthy neonates vaccinated with GSK Biologicals’ combined quadrivalent Tritanrix™-HB and Haemophilus influenzae type b (Hiberix™) vaccine mixed as a pentavalent vaccine in a single injection have proven that the combination of the DTPw-HBV and Hib vaccines had no negative impact on the immune response to vaccination against any of the 5 disease antigens nor on the reactogenicity profile \(^5, 6, 7, 8\) . The combined use of the pentavalent DTPw-HBV (Tritanrix™-HB) with Hib (Hiberix™) is licensed by centralized procedure in European countries. With this pentavalent combination, children will be protected against 5 diseases with 3 injections, whereas in the past 9 injections were needed to reach this goal.

This study assessed the immunogenicity, safety and reactogenicity of syringe-mixing of GSK Biologicals’ DTPw-HBV and Hib conjugate vaccines in infants previously primed with a monovalent dose of GSK Biologicals’ hepatitis B vaccine at birth. The rationale for this study was to assess the kinetics of antibody response to the recombinant hepatitis B surface antigen administered according to
the present study regimen (birth dose of Engerix™ B and a 3-dose vaccination schedule of DTPw-HBV-Hib vaccine given at 2, 4 and 6 months of age).

2. Study Objectives

2.1 Primary objective

To assess the antibody response to the recombinant hepatitis B surface antigen.

2.2 Secondary objectives

- To assess the antibody response to all other vaccine antigens: diphtheria and tetanus toxoids, whole cell Bordetella pertussis and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP).
- To assess the safety and reactogenicity of the vaccines.

3. Methodology

3.1 Study design

- Experimental design: Open study with a single group.
- Indication: Three-dose immunization course against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b in the first year of life in infants who had previously received a monovalent dose of GSK Biologicals’ hepatitis B vaccine at birth.
- Control: None.
- Treatment allocation: All subjects received GSK Biologicals’ combined DTPw-HBV and Hib conjugate vaccines extemporaneously mixed and administered as a single injection at 2, 4 and 6 months of age subsequent to a birth dose of GSK Biologicals’ hepatitis B vaccine.
- The study was self-contained, i.e., the study was not designed as an extension of one or more existing protocols nor was it planned to be combined with other protocols for a joint analysis.
- No randomization was done as this study had only one group.
- For each subject, the duration of the study was approximately 7 months.
- Data collection: Hard copy Case Report Form (CRF).
3.2 Investigator and trial center

The study was conducted in one center. The principal investigator for this study was Dr.  and the study center was Colombia.

The curriculum vitae of the investigator can be found in the report appendices for study information.

3.3 Ethics

The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki as amended in Somerset West, Republic of South Africa, October 1996. The protocol dated 23 November 1999, and statement of informed consent was approved by on 1 December 1999 prior to study initiation. Written informed consent was obtained from each parent/guardian prior to entry into the study.

CRFs were provided for each subject’s data to be recorded. The subject information sheet and unique pages of the individual CRF used in the study can be found in the report appendices for study information.

3.3.1 Protocol amendments/modifications

The protocol was amended on 31 May 2000. The protocol specified that cord blood sample obtained at birth would be used for antibody determination. It was amended to allow for either cord or peripheral blood sample to be used for pre-vaccination serological analysis. The amendment was approved by on 13 June 2000.

3.4 Selection of study population

3.4.1 Number of subjects

A total of 120 eligible subjects were planned to be enrolled at birth to ensure a minimum of 100 eligible healthy male and female infants between and including 6 to 10 weeks of age at the time of the first dose of the three-dose vaccination course. Enrolment was terminated when 120 subjects were enrolled at birth. Drop-outs were not replaced.
3.4.2 Inclusion criteria

Inclusion criteria for enrolment at birth

All subjects satisfied the following criteria at birth:

- Written informed consent obtained from the parent or guardian of the subject before entering into the study.
- Born after a normal gestation period (between 36 and 42 weeks).
- Free of obvious health problems as established by medical history of pregnancy and clinical examination before entering into the study.

Inclusion criteria for administration of DTPw-HBV/Hib vaccine

All subjects enrolled satisfied the following criteria at Month 2:

- A male or female between and including 6 and 10 weeks of age at the time of the first dose of the three-dose course of vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.

3.4.3 Exclusion criteria

Exclusion criteria for enrolment at birth

The following criteria were checked at birth. If any applied, the subject was not considered for enrolment:

- A family history of congenital or hereditary immunodeficiency.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- Major congenital defects.

Exclusion criteria for administration of DTPw-HBV/Hib vaccine

The following criteria were checked at Month 2 (before administration of DTPw-HBV/Hib vaccine). If any applied, the subject was not included in the study:

- Use of any investigational or non-registered drug or vaccine other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune modifying drugs since birth.
- Any chronic drug therapy to be continued during the study period.
- Planned administration/administration of a vaccine except oral polio vaccine (OPV) or Bacille Calmette-Guérin (BCG) vaccine during the period starting from 30 days before each dose of vaccines and ending 30 days after.
- Previous vaccination against diphtheria, tetanus, pertussis or Haemophilus influenzae type b disease.
• History of, or intercurrent, diphtheria, tetanus, pertussis, hepatitis B and/or Hib disease.
• Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
• A family history of congenital or hereditary immunodeficiency.
• History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
• Serious chronic illness.
• History of any neurologic disorders or seizures.
• Acute disease at the time of enrolment (Acute disease was defined as the presence of a moderate or severe illness with or without fever).
• Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.

3.4.4 Elimination criteria

The following criteria were checked at each visit subsequent to the first visit of the three-dose immunization course. If any became applicable during the study, the subject was not required to discontinue the study but could be eliminated from the ATP analyses.

• Use of any investigational or non-registered drug or vaccine other than the study vaccines during the study period.
• Administration of chronic immunosuppressants or other immune modifying drugs.
• Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of vaccines and ending 30 days after, with the exception of OPV or BCG vaccine.
• Administration of immunoglobulins and/or any blood products during the study period.

3.4.5 Contraindications to vaccination

The following adverse events constituted contraindications to administration of Engerix™-B and DTPw-HBV/Hib vaccine at that point in time; if any one of these adverse events occurred at the time scheduled for vaccination, the subject could be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator. The subject was followed until resolution of the event as with any adverse event.

• Acute disease at the time of vaccination.
• Axillary temperature of ≥ 37.5 °C at the time of vaccination.

The following adverse events constituted absolute contraindications to further administration of Engerix™-B and DTPw-HBV/Hib vaccine; if any of these
adverse events occurred during the study, the subject was withdrawn and was followed until resolution of the event, as with any adverse event.

- Anaphylactic reaction following the administration of vaccines.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.

The following adverse events associated with DTP vaccination constituted absolute contraindications to further administration of DTP; if any of these adverse events occurred during the study, the subject was withdrawn and was followed until resolution of the event, as with any adverse event.

**Absolute contraindications:**

Encephalopathy (not due to another identifiable cause). This was defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination, and generally consisting 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 if causation by DTP vaccine could not be established, no subsequent doses of pertussis vaccine were to be given.

*Precautions:*

- Fever $\geq 40 ^\circ C$ (axillary 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 $\geq 3$ hours occurring within 48 hours of vaccination.
- Seizures with or without fever which occurred within 3 days of vaccination.

### 3.5 Study vaccines and administration

#### 3.5.1 Study vaccines composition

All study vaccines used in this study were developed and manufactured by GSK Biologicals.

The Quality Control Standards and Requirements for each study vaccine are described in separate release protocols and the required approvals were obtained. Commercial vaccines were assumed to comply with the specifications given in the manufacturer's Summary of Product Characteristics. The vaccine release protocol is archived in the study file and is available upon request.
3.5.1.1 **GlaxoSmithKline Biologicals’ recombinant hepatitis B vaccine: Engerix™-B**

Each vaccine dose of 0.5 ml contained:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant hepatitis B surface antigen (r-DNA HBsAg)</td>
<td>10 mcg</td>
</tr>
<tr>
<td>Aluminium as salts</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Thiomersal</td>
<td>25 mcg</td>
</tr>
<tr>
<td>Sterile saline solution</td>
<td>150 mM NaCl</td>
</tr>
<tr>
<td>Lot number</td>
<td>ENG2814A2/M</td>
</tr>
</tbody>
</table>

The vaccine was supplied in monodose vials.

3.5.1.2 **GlaxoSmithKline Biologicals’ combined quadrivalent diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™-HB**

Each vaccine dose of 0.5 ml contained:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria toxoid</td>
<td>not less than 30 IU (7.5 Lf)</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>not less than 60 IU (3.25 Lf)</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em>, killed</td>
<td>not less than 2 IU (15 OU)</td>
</tr>
<tr>
<td>Recombinant hepatitis B surface antigen (r-DNA HBsAg)</td>
<td>10 mcg</td>
</tr>
<tr>
<td>Aluminium (as salts)</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>2-phenoxyethanol</td>
<td>50 mcg</td>
</tr>
<tr>
<td>Sterile saline solution</td>
<td>150 mM NaCl</td>
</tr>
<tr>
<td>Lot number</td>
<td>15776A2/M</td>
</tr>
</tbody>
</table>

The vaccine was supplied as a whitish liquid in monodose vials.

3.5.1.3 **GlaxoSmithKline Biologicals’ Haemophilus influenzae type b conjugate vaccine: Hiberix™**

Each vaccine dose contained:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugate of <em>Haemophilus influenzae</em> type b capsular polysaccharide (polyribosyl-ribitol-phosphate; PRP)</td>
<td>10 mcg</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>20 to 40 mcg</td>
</tr>
<tr>
<td>Lactose</td>
<td>12.6 mg</td>
</tr>
<tr>
<td>Lot number</td>
<td>Hib273A47/M</td>
</tr>
</tbody>
</table>

This vaccine was supplied as a white freeze dried pellet in monodose vials to be reconstituted before use with the liquid DTPw-HBV vaccine (*Tritanrix™-HB*).
3.5.2 Dosage and administration

Hepatitis B administration at birth

One dose, consisting of 0.5 ml of the hepatitis B vaccine (Engerix™-B) was administered by intramuscular (IM) injection into the left anterolateral thigh.

Extemporaneous mixing of the DTPw-HBV and Hib vaccines

The full content of the DTPw-HBV vaccine vial was extracted and injected into the vial containing the lyophilized Hib conjugate vaccine. The vial was agitated until the lyophilized Hib vaccine pellet had completely dissolved. The reconstituted DTPw-HBV/Hib vaccine was used promptly after reconstitution (within 30 minutes). In order to ensure proper IM injection of the study vaccines in the upper lateral quadrant of the thigh, a needle of at least 1 inch (2.54 cm) length and 25 gauge was used.

The vaccinees were observed closely for at least 15 minutes after vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

3.6 Treatment allocation and randomization

No randomization was done as this study had only one group. Subjects received a study number in the order in which they were enrolled into the study at birth. The study number served as subject identifier for all data collected under the study.

3.7 Blinding

This was an open study as all subjects enrolled received the same vaccination course.

3.8 Study procedures

Table 1 presents the flow sheet that summarizes the procedures, including assessments that were performed at each time point throughout the study.
### Table 1: Outline of study procedures

<table>
<thead>
<tr>
<th>Age</th>
<th>Visit Timing</th>
<th>Birth Visit 1 Day 0 Pre</th>
<th>6-10 weeks Visit 2 Month 2</th>
<th>4 months Visit 3 Month 4 Post-vacc 2</th>
<th>6 months Visit 4 Month 6 Post-vacc 3</th>
<th>7 months Visit 5 Month 7 Post-vacc 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood sampling time point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Written informed consent from parents/guardians</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of inclusion criteria for eligibility at birth</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of exclusion criteria for eligibility at birth</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical examination</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of inclusion criteria for 3-dose DTPw-HBV/Hib vaccine course</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of exclusion criteria for 3-dose DTPw-HBV/Hib vaccine course</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of elimination criteria</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check of contraindications</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical history</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pre-vaccination assessment of adverse events</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood sampling for antibody determination (3 ml)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaccination</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily post-vaccination recording of solicited symptoms (Days 0–3) by parents/guardians</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recording of unsolicited adverse events occurring one month (30 days) post-vaccination, by investigator</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Return of diary cards</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diary card transcription</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recording medication</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reporting of any serious adverse events (SAEs) occurring at any time from birth up to and including 30 days after the last dose of DTPw-HBV/Hib vaccine</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study Conclusion</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

*GSK Biologicals’ hepatitis B vaccine (Engerix™-B)

** GSK Biologicals’ DTPw-HBV (Tritanrix™HB) and Hib (Hiberix™) vaccines mixed extemporaneously and administered as a single injection

● is used to indicate a study procedure, which required documentation in the individual CRF

### 3.9 Subject completion and drop-out

From an analysis perspective, a ‘drop-out’ was any subject who did not come back at least for the concluding visit foreseen in the protocol. A subject who returned at least for the concluding visit foreseen in the protocol was considered to have
completed the study. Investigators made an attempt to contact the parents/guardians of those subjects who did not return for scheduled visits or follow-up.

Information gathered was described on the study conclusion page of the CRF and on medication/adverse event forms. The possible reasons for the subject to have dropped out from the study were as follows:

- Serious adverse event
- Non-serious adverse event
- Protocol violation (to be specified)
- Consent withdrawal, not due to an adverse event
- Migration from the study area
- Lost to follow-up
- Other (to be specified)

### 3.10 Assessment of immunogenicity variables

#### 3.10.1 Intervals between study visits

To adequately assess the immune response elicited by the vaccines, the time intervals that were to be respected between visits were specified in the protocol. However, the adapted intervals served as the absolute criterion for the exclusion of subjects from the ATP analyses. Table 2 summarizes both protocol-defined and adapted intervals between the study visits.

#### Table 2 Intervals between study visits

<table>
<thead>
<tr>
<th>Interval</th>
<th>Protocol-defined</th>
<th>Adapted</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOB → Visit 1 (Birth dose of Engerix™ B)</td>
<td>0 days (At birth)</td>
<td>0-5 days</td>
</tr>
<tr>
<td>Visit 1 → Visit 2 (First dose of DTPw-HBV/Hib vaccine)</td>
<td>6-10 weeks</td>
<td>6-10 weeks</td>
</tr>
<tr>
<td>Visit 2 → Visit 3 (Second dose of DTPw-HBV/Hib vaccine)</td>
<td>56-70 days</td>
<td>56-70 days</td>
</tr>
<tr>
<td>Visit 3 → Visit 4 (Third dose of DTPw-HBV/Hib vaccine)</td>
<td>56-70 days</td>
<td>56-70 days</td>
</tr>
<tr>
<td>Visit 4 → Visit 5 (Post-vacc blood sampling)</td>
<td>30-35 days</td>
<td>30-35 days</td>
</tr>
</tbody>
</table>

Note: The date of the previous visit is the reference date. DOB: date of birth

#### 3.10.2 Laboratory assays and time points

Blood samples were taken at Months 0, 4, 6 and 7. The blood samples at birth could be cord blood sample or peripheral blood sample. The separated pre- and post-vaccination serum samples were stored at temperatures below −20°C until transferred to GSK Biologicals. All the serological assays were performed at GSK Biologicals’ central laboratory or in a validated laboratory designated by GSK.
Biologics using standardized, validated procedures with adequate controls. Details of the serological assays are summarized in Table 3.

Table 3 Serological assays

<table>
<thead>
<tr>
<th>Marker</th>
<th>Assay method</th>
<th>Test Kit/ Manufacturer</th>
<th>Assay unit</th>
<th>Assay cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HBs</td>
<td>Radioimmuno- assay (RIA) and Enzyme-Linked Immunosorbent Assay (ELISA)</td>
<td>AUSAB, Abbott (RIA) and in-house assay (ELISA)</td>
<td>mIU/ml</td>
<td>10 mIU/ml</td>
</tr>
<tr>
<td>Anti-PRP</td>
<td>ELISA</td>
<td>In-house assay</td>
<td>mcg/ml</td>
<td>0.15 mcg/ml</td>
</tr>
<tr>
<td>Anti-BPT</td>
<td>ELISA</td>
<td>IgG EIA test kit, Labsystems</td>
<td>EL.U/ml</td>
<td>15 EL.U/ml</td>
</tr>
<tr>
<td>Anti-diphtheria and anti-tetanus</td>
<td>ELISA</td>
<td>In-house assay</td>
<td>IU/ml</td>
<td>0.1 IU/ml</td>
</tr>
</tbody>
</table>

Note: The protocol defined that anti-HBs antibodies would be analysed by RIA, using 10 mIU/ml as the assay cut-off. However, the anti-HBs antibodies were analysed by enzyme-linked immunosorbent assay (ELISA) kits, using 10 mIU/ml as the assay cut-off. Initially some pre-vaccination samples in this study were analysed with RIA and the rest were analysed with ELISA. However, those pre-vaccination blood samples that were tested by RIA were re-tested using ELISA.

Serology plan

Pre- (Month 0) and post-vaccination (Month 4, 6 and 7) serum samples were tested in all subjects for antibodies against all vaccine antigens (HBsAg, PRP and pertussis antigen and diphtheria and tetanus toxoids).

In case of insufficient blood sample volume to perform assays for all antibodies, they were analysed according to the following priority ranking:

- anti-HBs
- anti-PRP
- anti-BPT
- anti-tetanus
- anti-diphtheria

Sub-optimal response

An additional dose of licensed vaccines were planned to be offered to subjects who, after the three dose primary series demonstrated a sub-optimal response to any of the antigens contained in the vaccines.
Sub-optimal response was defined as follows:

Anti-HBs antibody titer < 10 mIU/ml
Anti-PRP antibody titer < 0.15 mcg/ml
Anti-BPT antibody titer < 15 EL.U/ml
Anti-tetanus antibody titer < 0.1 IU/ml
Anti-diphtheria antibody titer < 0.1 IU/ml

Since booster immunizations were not generally provided for hepatitis B (until 4 to 6 years of age), subjects who demonstrated a sub-optimal response to either of these vaccines were offered an additional dose of hepatitis B vaccine.

For subjects who demonstrated a sub-optimal response to the Hib conjugate vaccine after the primary series and who had not yet received a booster dose of Hib vaccine, their parents/guardians were contacted and were requested to present their child/ward early for an additional dose of vaccine. For subjects who demonstrated a sub-optimal response to the Hib conjugate vaccine after receiving primary and booster doses, no additional vaccination was offered.

Subjects who demonstrated a sub-optimal response to one or more antigens in the DTP vaccine after the primary series received their booster dose of licensed DTP at 12-18 months, as was routine.

3.11 Assessment of reactogenicity variables

On the day of vaccination, diary cards were distributed by the investigator to the parent/guardian of the subjects to record local and general signs and symptoms or illnesses (both solicited and unsolicited) occurring during the 4-day follow-up period after vaccination. Parent/guardian of subjects were instructed to return the completed diary card at the next visit and to contact the investigator immediately if the subject manifested any signs or symptoms they perceived as serious. Diary cards were checked by the investigator at the subsequent visit and data transcribed into the appropriate sections of the CRFs, i.e., symptom sheets or adverse event sections. Table 4 presents the adverse events solicited during the study.
Table 4 Solicited Adverse Events

<table>
<thead>
<tr>
<th>Local (injection site) adverse events</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>

<table>
<thead>
<tr>
<th>General adverse events</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>

The protocol mentioned that fever would be measured via the axillary route. However temperature was recorded by axillary/rectal route. Temperature measurement was usually recorded in the evening, but if temperature measurement was additionally performed at another time of day, the highest temperature was recorded.

Assessment of intensity

The intensity of the symptoms that occurred in this study is described in Table 5. The intensity of all symptoms except redness and swelling at the injection site and fever were assessed by the investigator. For redness and swelling, the investigator recorded the largest surface diameter in mm and for fever, the investigator recorded the axillary/rectal temperature in °C. These symptoms were then scored for intensity at GSK Biologicals.
Table 5: Assessment of intensity

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>0 Absent</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>1 Minor reaction to touch</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>2 Cried/protested on touch</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>3 Cried when limb was moved/spontaneously painful</td>
<td>Parameter</td>
</tr>
<tr>
<td>Redness at injection site*</td>
<td>Greatest surface diameter recorded in mm</td>
<td>Parameter</td>
</tr>
<tr>
<td>Swelling at injection site*</td>
<td>Greatest surface diameter recorded in mm</td>
<td>Parameter</td>
</tr>
<tr>
<td>Fever*</td>
<td>Fever recorded in °C (defined as axillary temperature ≥ 37.5°C or rectal temperature ≥ 38.0°C)</td>
<td>Parameter</td>
</tr>
<tr>
<td>Irritability/Fussiness</td>
<td>0 Behaviour as usual</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>1 Crying more than usual/ no effect on normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>2 Crying more than usual/ interferes with normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>3 Crying that could not be comforted/ prevented normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0 Behaviour as usual</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>1 Drowsiness easily tolerated</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>2 Drowsiness that interfered with normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>3 Drowsiness that prevented normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0 Normal</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>1 Eating less than usual/ no effect on normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>2 Eating less than usual/ interferes with normal activity</td>
<td>Parameter</td>
</tr>
<tr>
<td></td>
<td>3 Not eating at all</td>
<td>Parameter</td>
</tr>
</tbody>
</table>

*The intensity of redness/swelling at injection site and fever was scored at GSK Biologicals prior to analysis as follows:
Redness and swelling: 0: absent; 1: > 0 mm and ≤ 5mm; 2: > 5 mm and ≤ 20 mm; 3: > 20 mm
Fever (axillary): 0: < 37.5 °C; 1: ≥ 37.5 °C and ≤ 38.0 °C; 2: > 38.0 °C and ≤ 39.0 °C; 3: > 39 °C.
Fever (rectal): 0: < 38.0 °C; 1: ≥ 38.0 °C and ≤ 38.5 °C; 2: > 38.5 °C and ≤ 39.5 °C; 3: > 39.5 °C.
For each solicited symptom, parents/guardians of the subjects were asked if they sought medical advice (i.e. contact with a member of medical personnel) for this symptom.

For all other adverse events, maximum intensity was assigned to one of the following categories:
0: No adverse event.
1: An adverse event which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which was sufficiently discomfoting to interfere with normal everyday activities.
3: An adverse event which prevented normal, everyday activities.

Assessment of causality

Every effort was made by the investigator to explain each adverse event and assess its causal relationship, if any, to administration of the study vaccines.

In case of concomitant administration of multiple vaccines, it was not possible to determine causal relationship of general adverse events to the individual vaccines administered. The investigator, therefore, assessed whether the adverse event could be causally related to vaccination rather than to the individual vaccines.
All solicited local (injection site) reactions were considered causally related to vaccination. Causality of all other adverse events were assessed by the investigator using the following categories: not related, unlikely, suspected (reasonable possibility), probable.

NR: Not related The adverse event was definitely not causally related to administration of the study vaccines.

UL: Unlikely There were other, more likely causes and administration of the study vaccines was not suspected as a cause.

SU: Suspected (reasonable possibility) A direct cause and effect relationship between administration of the study vaccines and the adverse event had not been demonstrated but there was a reasonable possibility that the event was caused by administration of the study vaccines.

PB: Probable There probably was a direct cause and effect relationship between the adverse event and administration of the study vaccines.

**Follow-up of adverse events**

Investigators followed-up subjects with serious adverse events until the event had subsided (disappeared) or until the condition had stabilized. Investigators followed-up subjects with non-serious adverse events until study conclusion for that subject. Reports relative to the subsequent course of an adverse event noted for any subject was to be submitted to the Study Monitor.

**Assessment of outcome**

Outcome was assessed for unsolicited symptoms and serious adverse events as
1: Recovered
2: Recovered with sequelae
3: Ongoing at subject study conclusion
4: Died
5: Unknown

**Serious adverse events**

A serious adverse event was any untoward medical occurrence that resulted in death, was life threatening*, resulted in persistent or significant disability/ incapacity†, required in-patient hospitalization or prolongation of existing hospitalization or was a congenital anomaly/birth defect in the offspring of a study subject. In addition, important medical events that may have jeopardized the patient or may have required intervention to prevent one of the other outcomes
listed above was considered serious. Although not considered as ‘serious adverse events’, pregnancies and cancers were reported in the same way as serious adverse events.

*Life threatening—definition: An adverse event was life threatening if the subject was at risk of death at the time of the event; it did not refer to an event, which hypothetically might have caused death, if it were more severe.

†Disabling/incapacitating—definition: An adverse event was incapacitating or disabling if the event resulted in a substantial disruption of the subject's ability to carry out normal life functions. This definition was not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma.

Hospitalization: In general, hospitalization signified that the subject had been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician’s office or out-patient setting.

Hospitalization for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalization for “social” reasons) that are not the result of an adverse event need not have been considered as adverse events and was therefore not serious adverse events.

¶Routine Clinical Procedure—definition: One which was defined as a procedure which took place during the study period and did not interfere with the study vaccine administration or any of the ongoing protocol specific procedures.

N.B. If anything untoward was reported during an elective procedure, that occurrence was reported as an adverse event, either ‘serious’ or ‘non-serious’ according to the usual criteria.

When in doubt as to whether ‘hospitalization’ occurred or was necessary, the adverse event was considered serious.

Any serious adverse events which occurred during the period starting from the day of administration of the birth dose of hepatitis B vaccine to each subject and ending within one month (maximum 30 days) of administration of the last dose of DTPw-HBV/Hib vaccine for that subject, whether or not considered to be related to the study vaccine, was reported by the investigator to the GSK Biologicals monitoring personnel by fax or telephone within 24 hours. Instances of death, cancer or congenital abnormality in offspring if brought to the attention of the investigator at any time after cessation of study medication and suspected by the investigator to be related to study medication, was reported to the Study Monitor.
3.11.1 Biochemical assays

None.

3.11.2 Pregnancy

Not applicable.

3.11.3 Prior and concomitant medication

Concomitant medication—including any vaccine other than the study vaccines, and any other medication relevant to the protocol, including any specifically contraindicated—administered during the period starting from one week before each dose and ending one month (maximum 30 days) after was recorded in the CRF with trade name and/ or generic name of the medication, medical indication, start and end dates of treatment. It was also recorded whether the medication was given

- prophylactically in anticipation of reaction to the vaccination (coded as ‘P’ in the CRF).
- as therapy for an existing symptom (coded as ‘T’ in the CRF).
- neither of the above (coded as ‘N’ in the CRF).

Medications, which weren’t needed to be recorded, included any homeopathic remedies, vitamins, minerals and any other dietary supplements.

3.12 Data quality assurance

To ensure that study procedures conformed across all investigator sites, the protocol, CRF and reactogenicity reporting were reviewed with the investigator and his personnel responsible for the conduct of the study by the Company representative(s) at the investigator site.

Adherence to the protocol requirements and verification of data generation accuracy was achieved through monitoring visits to each investigator site. All procedures were performed according to methodologies detailed in GSK Standard Operating Procedures (SOPs).

No study specific audits were performed for this study.

3.13 Statistical methods

3.13.1 Primary endpoint

Percentage of infants with anti-HBs antibody titers ≥ 10 mIU/ml at the time of the second dose of DTPw-HBV/Hib vaccine, i.e., at 4 months of age.
3.13.2 Secondary endpoints

- At each blood sampling time point
  - anti-HBs antibody titers.
  - anti-PRP antibody titers.
  - anti-BPT antibody titers.
  - anti-tetanus antibody titers.
  - anti-diphtheria antibody titers.

- Occurrence of any solicited local and/or general symptoms within 4 days after each dose of vaccines.

- Occurrence of unsolicited symptoms within 30 days after each dose of vaccines.

- Occurrence of Serious Adverse Events (SAEs) over the course of the study (beginning with first study procedure at birth up to and including 30 days following the third dose of DTPw-HBV/Hib vaccine).

3.13.3 Target sample size

A sample size of 100 eligible subjects was planned to provide enough confidence on seroprotection rate for anti-HBs antibodies (i.e., percentage of subjects with anti-HBs antibody titer $\geq 10$ mIU/ml) after each vaccination.

3.13.4 Study cohorts/data sets analysed

Total cohort

The total cohort included all enrolled (i.e., vaccinated with DTPw-HBV/Hib vaccine) subjects for whom data were available. The total cohort analysis of reactogenicity included all vaccinated subjects for whom reactogenicity data were available. The total cohort analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

According-To-Protocol (ATP) cohort for analysis of reactogenicity

The ATP cohort for analysis of reactogenicity included all subjects
- who received at least one dose of DTPw-HBV/Hib vaccine.
- with sufficient data to perform an analysis of reactogenicity.
- who had not received a vaccine forbidden in the protocol.
- for whom administration site of study vaccine is known.

ATP cohort for analysis of immunogenicity

The ATP cohort for analysis of immunogenicity included all subjects for whom differential treatment effects on immunogenicity was likely (i.e., those meeting all
eligibility criteria complying with the procedures defined in the protocol) and for whom data concerning immunogenicity endpoints were available. This included subjects for whom assay results were available for at least one study vaccine antigen component after vaccination.

3.13.5 Analysis of demographics

Demographic characteristics (age, gender) of each study cohort was tabulated. The mean age (plus range and standard deviation) by gender of the enrolled subjects was calculated.

3.13.6 Analysis of immunogenicity

Analysis of immunogenicity was performed on two cohorts: the total cohort and the ATP cohort. The ATP cohort served as the cohort of primary interest in this study. Immunogenicity of the vaccine, i.e. antibody response, was the measure of vaccine efficacy. Analysis of immunogenicity was as follows:

The seropositivity/seroprotection rates and Geometric Mean Titers (GMTs) for antibodies against all vaccine antigens were calculated with 95% confidence interval (95% CI), at each blood sampling time point. Seropositivity rate was the percentage of seropositive subjects, i.e., subjects with antibody titers ≥ the assay cut-off. A seronegative subject was a subject whose titer was below the cut-off value. A seropositive subject was a subject whose titer was greater than or equal to the cut-off value.

The GMT calculations were performed for all antibodies to all vaccine antigen components by taking the anti-log of the mean of the log titer transformations. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMT calculation.

The percentage of subjects with protective levels of anti-HBs antibodies (i.e., titers ≥ 10 mIU/ml) with 95% CI was determined at each blood sampling time point. Since the assay cut-off used was 10 mIU/ml in this study, the seropositivity rate equaled seroprotection rate.

The percentage of subjects with anti-PRP serum antibody concentration ≥ 0.15 mcg/ml (generally accepted as short-term seroprotection) and ≥ 1.0 mcg/ml (generally accepted as long-term seroprotection) and the corresponding 95% CI were tabulated.

The percentage of subjects with anti-*Bordetella pertussis* (anti-BPT) antibody titer ≥ the assay cut-off of 15 EL.U/ml with 95% CI were tabulated. Vaccine response to whole cell pertussis vaccine with 95% CI was also tabulated. Vaccine response to whole cell pertussis vaccine was defined as follows:
− the presence of antibodies (titer $\geq$ cut-off) in subjects seronegative at pre-vaccination or
− post-vaccination antibody titers $\geq$ pre-vaccination titers, in subjects seropositive at pre-vaccination.

This vaccine response definition took into consideration the expected decrease in maternal antibody titers. The half-life for decay of maternal pertussis antibodies was approximately 6 weeks.

The percentage of subjects with anti-diphtheria and anti-tetanus toxoid antibody titers $\geq 0.1$ IU/ml (considered to be seroprotection rate) with 95% CI were tabulated.

### 3.13.7 Analysis of reactogenicity

Analysis was performed on one cohort. Total cohort was equal to ATP cohort as symptom sheets were not completed for any dose for three subjects.

Incidence of symptoms was calculated per-dose (i.e., on number of symptom sheets completed) and per-subject (i.e., on the number of subjects reporting symptoms). The overall incidence of local, general and both local and general symptoms were calculated with exact 95% CI. The same incidence analyses were presented for symptoms of intensity Grade “3”. The incidence, intensity and relationship to vaccination of individual solicited symptoms over the entire follow-up period (4 days) after each vaccine dose was calculated with 95% CI.

The verbatim reports of unsolicited symptoms was reviewed by a physician and the signs and symptoms were coded according to the World Health Organization’s (WHO) Dictionary for Adverse Reaction Terminology; every verbatim term was matched to the appropriate WHO preferred term. The number of doses and subjects who reported at least one unsolicited symptom, classified by WHO preferred terms, were tabulated in addition to relationship.

Serious adverse events and discontinuation due to adverse events was described in detail.

### 3.14 Changes in planned analyses

None.
4. Study Population

4.1 Study dates

The first volunteer was enrolled in the study on 15 June 2000 and the last study visit was on 9 April 2001. Individual subject data on study dates can be found in Appendix Table IC.

4.2 Subject eligibility and attrition from study

4.2.1 Number and distribution of subjects

A total of 120 subjects were enrolled at a single centre in Colombia.

4.2.2 Study completion and drop-out

Of the 120 subjects enrolled, four subjects dropped out of the study. The reasons were as follows:

- Three subjects migrated from the study area.
- Lost to follow-up (subject with incomplete vaccination course)

Hence a total of 116 subjects completed the study. Table 6 gives the details about the study completion and drop out.

<table>
<thead>
<tr>
<th>Table 6 Reasons for drop-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects enrolled</td>
</tr>
<tr>
<td>Number of subjects completed</td>
</tr>
<tr>
<td>Number of subjects dropped-out</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for drop-out:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migration from study area</td>
</tr>
<tr>
<td>Lost to follow-up (subject with incomplete vaccination course)</td>
</tr>
</tbody>
</table>

Individual subject data on study conclusion can be found in Appendix Table IE.

All subjects received Engerix™B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

Enrolled: Number of subjects who where enrolled in the study
Completed: Number of subjects who came back for at least the last study visit
Dropped-out: Number of subjects who did not come back at least for the last visit
Individual subject data on study conclusion can be found in Appendix Table IE.

### 4.2.3 Eligibility for analysis

Table 7 presents the number of subjects enrolled in the study as well as the subjects excluded from ATP analyses with reasons for exclusion.

Of the 120 subjects enrolled, three subjects were eliminated from the ATP reactogenicity analysis. Hence they were given the elimination code 1080 for essential reactogenicity data missing.

Of the 117 subjects included in the ATP reactogenicity cohort, 12 subjects were eliminated from the ATP immunogenicity analysis. The reasons were as follows:

- 
- 
- 

Hence, 105 subjects were included in the ATP immunogenicity cohort.
Table 7 The number of subjects, enrolled into the study as well as the number excluded from analyses

<table>
<thead>
<tr>
<th>Title</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects planned and enrolled</td>
<td>120</td>
<td>100.0</td>
</tr>
<tr>
<td>Essential data missing (code 1080)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Number of subjects in the ATP cohort for reactogenicity</td>
<td>117</td>
<td>97.5</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Essential serological data missing (code 2100)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of subjects in the ATP cohort for immunogenicity</td>
<td>105</td>
<td>87.5</td>
</tr>
</tbody>
</table>

Individual subject data on elimination codes can be found in Appendix Table IA. All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

Subjects may have one or more elimination code(s) assigned in which case the lowest code number is listed in the figure. Codes were given based on a ranking order. The code number listed in the figure are presented in order of ranking; therefore, for example, code 2080 was assigned preferentially to 2090 when the subject was eligible for elimination on both counts.

4.2.4 Compliance with protocol specified procedures

For 469 doses administered in the total cohort, symptom sheets for local and general symptoms were completed for 465 doses, for a compliance of 99.1%.

4.3 Demographic characteristics

4.3.1 Total cohort

Table 8 presents the demographic profile of the total cohort.

Hence the demographics of the ATP reactogenicity cohort was the same as the total cohort.

The mean age of the total cohort at the time of the first DTPw-HBV/Hib vaccine dose (i.e., at Month 2) was 7.6 weeks with a standard deviation of 0.91 weeks. The male to female ratio was 1.2: 1 (64/53).
Table 8 Demographics: Total cohort at Month 2

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>Mean age (weeks)</th>
<th>SD</th>
<th>Min. age (weeks)</th>
<th>Max. age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>53</td>
<td>7.6</td>
<td>0.94</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>7.7</td>
<td>0.89</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>7.6</td>
<td>0.91</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB
All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age
N: Number of subjects with documentation on age and gender
SD: Standard deviation
Min., Max. age: Minimum, maximum age

Supplementary Table 1 presents the racial and gender composition for the total cohort. Individual subject data on demographics can be found in Appendix Table IB.

4.3.2 Subjects included in the ATP analysis of immunogenicity

The demographic profile of the ATP immunogenicity cohort is presented in Table 9.

The mean age of the ATP immunogenicity cohort at the time of the first DTPw-HBV/Hib vaccine dose (i.e., at Month 2) was 7.7 weeks with a standard deviation of 0.88 weeks. The male to female ratio was 1.1:1 (54/51).

Table 9 Demographics: ATP immunogenicity cohort

<table>
<thead>
<tr>
<th>Gender</th>
<th>N</th>
<th>Mean Age (weeks)</th>
<th>SD</th>
<th>Min. age (weeks)</th>
<th>Max. age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>51</td>
<td>7.7</td>
<td>0.90</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>7.7</td>
<td>0.87</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>7.7</td>
<td>0.88</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB
All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age
N: Number of subjects with documentation on age and gender
SD: Standard deviation
Min., Max. age: Minimum, maximum age

Supplementary Table 2 presents the racial and gender composition for the ATP immunogenicity cohort. Individual subject data on demographics can be found in Appendix Table IB.

5. Analysis of immunogenicity

Individual subject data on immunogenicity can be found in Appendix table IIIA.
5.1 Data sets analysed

Immunogenicity analysis was performed on two cohorts: total and ATP cohorts, where ATP cohort analysis was the primary analysis (see Section 3.13.4 for details about the cohort definitions).

5.2 According-To-Protocol analysis

Data from 105 subjects were included in this ATP immunogenicity analysis.

5.2.1 Anti-HBs antibody response

Table 10 details the seroprotection rates and GMTs of anti-HBs antibodies for the ATP immunogenicity cohort.

- At Month 4 (i.e., two months after the second dose of HBsAg), the seroprotection rate for anti-HBs antibodies was 81.7%. There was an 11.5-fold increase in anti-HBs GMTs from pre-vaccination to Month 4.

- At Month 7 (i.e., one month after the completion of DTPw-HBV/Hib vaccination course), all subjects were seroprotected for anti-HBs antibodies and there was a 263-fold increase in anti-HBs GMTs from pre-vaccination to Month 7.

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>SP</th>
<th>95% CI</th>
<th>GMT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
<td>(ll, ul)</td>
<td>(mIU/ml)</td>
<td>(ll, ul)</td>
</tr>
<tr>
<td>Pre</td>
<td>103</td>
<td>4</td>
<td>3.9</td>
<td>6.1</td>
<td>4.9</td>
</tr>
<tr>
<td>PII(M4)</td>
<td>104</td>
<td>85</td>
<td>81.7</td>
<td>70.1</td>
<td>49.9</td>
</tr>
<tr>
<td>PIII(M6)</td>
<td>105</td>
<td>104</td>
<td>99.0</td>
<td>612.2</td>
<td>492.9</td>
</tr>
<tr>
<td>PIV(M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>1603.8</td>
<td>1334.9</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested
SP: Seroprotection for anti-HBs antibodies (i.e., titers ≥ 10 mIU/ml)
n (%): Number (percentage) of subjects seroprotected for anti-HBs antibodies
Pre: At Month 0
PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine
PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine
PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit
GMT: Geometric Mean Titer
5.2.2 Anti-PRP antibody response

Table 11 details the seropositivity rates and GMTs of anti-PRP antibodies for ATP immunogenicity cohort.

One month after the full vaccination course (i.e., at Month 7),

- All subjects had anti-PRP antibody titers \( \geq 0.15 \) mcg/ml (generally accepted as short-term seroprotection) and all except one (99%) had anti-PRP antibody titers \( \geq 1 \) mcg/ml (generally accepted as long-term seroprotection).
- There was a 58.7-fold increase in anti-PRP GMTs from pre-vaccination to Month 7.

Table 11 Percentage of subjects with titers \( \geq 0.15 \) mcg/ml and \( \geq 1.0 \) mcg/ml and GMTs of anti-PRP antibodies (ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>( \geq 0.15 ) mcg/ml</th>
<th>( \geq 1.0 ) mcg/ml</th>
<th>GMT mcg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% 95% CI</td>
<td>n % 95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>UL</td>
<td>LL  UL</td>
<td>LL UL</td>
</tr>
<tr>
<td>Pre</td>
<td>105</td>
<td>74 70.5 60.8 79.0</td>
<td>33 31.4 22.7 41.2</td>
<td>0.475 0.347 0.650</td>
</tr>
<tr>
<td>PII(M4)</td>
<td>104</td>
<td>67 64.4 54.4 73.6</td>
<td>26 25.0 17.0 34.4</td>
<td>0.358 0.264 0.485</td>
</tr>
<tr>
<td>PIII(M6)</td>
<td>105</td>
<td>103 98.1 93.3 99.8</td>
<td>90 85.7 77.5 91.8</td>
<td>9.098 6.465 12.802</td>
</tr>
<tr>
<td>PIV(M7)</td>
<td>105</td>
<td>105 100.0 96.5 100.0</td>
<td>104 99.0 94.8 100.0</td>
<td>27.888 22.618 34.386</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received Engerix™B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested

n (%): Number (percentage) of subjects with anti-PRP antibody titers \( \geq 0.15 \) mcg/ml (short-term seroprotection) or 1 mcg/ml (long-term seroprotection)

Pre: At Month 0
PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine
PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine
PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit

GMT: Geometric Mean Titer

5.2.3 Anti-BPT antibody response

Table 12 details the seropositivity rates and GMTs of anti-BPT antibodies for ATP immunogenicity cohort. Table 13 details the vaccine response to whole cell pertussis, for the ATP immunogenicity cohort.

One month after the full vaccination course (i.e., at Month 7),

- All subjects showed a vaccine response to whole cell pertussis.
- There was a 9.1-fold increase in anti-BPT GMTs from pre-vaccination to Month 7.
Table 12 Seropositivity rates and GMTs of anti-BPT antibodies (ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI</th>
<th>GMT (EL.U/ml)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
<td>UL</td>
<td>LL</td>
</tr>
<tr>
<td>Pre</td>
<td>105</td>
<td>19</td>
<td>18.1</td>
<td>11.3 - 26.8</td>
<td>9.339</td>
</tr>
<tr>
<td>PII(M4)</td>
<td>104</td>
<td>0</td>
<td>0.0</td>
<td>0.0 - 3.5</td>
<td>7.500</td>
</tr>
<tr>
<td>PIII(M6)</td>
<td>105</td>
<td>54</td>
<td>51.4</td>
<td>41.5 - 61.3</td>
<td>14.882</td>
</tr>
<tr>
<td>PIV(M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5 - 100.0</td>
<td>85.029</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA.

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

N: Number of subjects tested
S+: Seropositivity for anti-BPT antibodies (i.e., titers ≥ 15 EL.U/ml)
n (%): Number (percentage) of subjects seropositive for anti-BPT antibodies
Pre: At Month 0
PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine
PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine
PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit
GMT: Geometric Mean Titer

Table 13 Vaccine response to whole cell pertussis at Month 7 (ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Prevacc. status</th>
<th>N</th>
<th>R+</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>19</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>86</td>
<td>86</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>105</td>
<td>100</td>
<td>96.5 - 100</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA.

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

N: Number of subjects with both pre-and post-vaccination results available
R+ (%): Number (percentage) of responders (i.e., subjects who showed a vaccine response)
Vaccine response was defined as:
- The presence of anti-BPT antibodies in subjects seronegative at pre-vaccination or
- Post-vaccination antibody titers ≥ pre-vaccination titers in subjects who were seropositive at pre-vaccination
S−/S+: Seronegative/seropositive subjects at pre vaccination (i.e., birth dose of Engerix™-B)
Total: Subjects either seropositive or seronegative at pre-vaccination
95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit

5.2.4 Anti-diphtheria and anti-tetanus antibody response

Table 14 shows the seroprotection (SP) rates and GMT of anti-diphtheria and anti-tetanus antibody titers for the ATP immunogenicity cohort.

One month after the full vaccination course (i.e., at Month 7),

- All subjects except four (98.1%) were seroprotected for anti-diphtheria antibodies and all subjects were seroprotected for anti-tetanus antibodies.
• There was a 1.75-fold increase in anti-diphtheria antibody GMTs from pre-vaccination to Month 7.

• Anti-tetanus antibody GMTs at post-vaccination blood sampling time points were lower than that at pre-vaccination, which could be probably due to high levels of maternal antibodies at pre-vaccination.

Table 14 Seroprotection rates and GMT of anti-diphtheria and anti-tetanus antibodies (ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>N</th>
<th>SP n</th>
<th>SP %</th>
<th>95% CI LL</th>
<th>95% CI UL</th>
<th>GMT (IU/ml)</th>
<th>95% CI LL</th>
<th>95% CI UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diphtheria</td>
<td>Pre</td>
<td>105</td>
<td>91</td>
<td>86.7</td>
<td>78.6</td>
<td>92.5</td>
<td>1.042</td>
<td>0.751</td>
<td>1.445</td>
</tr>
<tr>
<td></td>
<td>PII(M4)</td>
<td>104</td>
<td>48</td>
<td>46.2</td>
<td>36.3</td>
<td>56.2</td>
<td>0.116</td>
<td>0.095</td>
<td>0.142</td>
</tr>
<tr>
<td></td>
<td>PIII(M6)</td>
<td>105</td>
<td>64</td>
<td>61.0</td>
<td>50.9</td>
<td>70.3</td>
<td>0.188</td>
<td>0.145</td>
<td>0.243</td>
</tr>
<tr>
<td></td>
<td>PIV(M7)</td>
<td>105</td>
<td>101</td>
<td>98.1</td>
<td>93.2</td>
<td>99.8</td>
<td>1.826</td>
<td>1.456</td>
<td>2.290</td>
</tr>
<tr>
<td>Anti-tetanus</td>
<td>Pre</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
<td>6.052</td>
<td>5.022</td>
<td>7.294</td>
</tr>
<tr>
<td></td>
<td>PII(M4)</td>
<td>104</td>
<td>98</td>
<td>94.2</td>
<td>87.9</td>
<td>97.9</td>
<td>0.441</td>
<td>0.364</td>
<td>0.535</td>
</tr>
<tr>
<td></td>
<td>PIII(M6)</td>
<td>105</td>
<td>103</td>
<td>98.1</td>
<td>93.3</td>
<td>99.8</td>
<td>0.528</td>
<td>0.432</td>
<td>0.645</td>
</tr>
<tr>
<td></td>
<td>PIV(M7)</td>
<td>105</td>
<td>105</td>
<td>100.0</td>
<td>96.5</td>
<td>100.0</td>
<td>4.517</td>
<td>3.727</td>
<td>5.474</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received Engerix™B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested
SP: Seroprotection for anti-diphtheria/ anti-tetanus antibodies (i.e., titers ≥ 0.1 IU/ml)
n(%): Number (percentage) of subjects seroprotected for anti-diphtheria / anti-tetanus antibodies
Pre: At Month 0
PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine
PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine
PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine
95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit
GMT: Geometric Mean Titer

5.3 Analysis of total cohort

Supplementary Table 3 presents the seroprotection rates and GMTs of anti-HBs antibodies for the total cohort. Supplementary Table 4 presents the seroprotection rates and GMTs of anti-PRP antibodies for the total cohort. Supplementary Table 5 presents the seropositivity rates and GMTs of anti-BPT antibodies for the total cohort. Supplementary Table 6 presents the vaccine response to anti-BPT antibodies for the total cohort. Supplementary Table 7 presents seroprotection rates and GMT of anti-diphtheria and anti-tetanus antibody titers for the total cohort.

The results of total cohort analysis are consistent with those obtained from the ATP cohort analysis.
6. Analysis of reactogenicity

Analysis was performed on only one cohort, as the ATP reactogenicity cohort was the same as the total cohort. Data are available for 117 subjects, as the symptom sheets were not completed for any dose for three subjects.

In the ATP reactogenicity cohort, 465 symptom sheets were completed for 466 doses that were administered for a compliance of 99.8%. Symptom sheets are the specific pages in the individual CRFs onto which the investigator transcribed diary card documentation and any other symptom(s) reported by the subject.

Table 15 presents the number of subjects vaccinated in the total cohort.

<table>
<thead>
<tr>
<th>Total number of doses received</th>
<th>N = 120</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>116</td>
<td>96.7</td>
</tr>
<tr>
<td>Any</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects included in the ATP analysis of reactogenicity
n (%): Number (percentage) of subjects who received 1, 2, 3 or any doses
1 dose: Number of subjects who received only 1 dose (i.e., birth dose of Engerix™-B)
2 doses: Number of subjects who received only 2 doses (i.e., birth dose of Engerix™-B and 1 dose of DTPw-HBV/Hib vaccine)
3 doses: Number of subjects who received only 3 doses (i.e., birth dose of Engerix™-B and 2 doses of DTPw-HBV/Hib vaccine)
4 doses: Number of subjects who received all 4 doses (i.e., birth dose of Engerix™-B and 3 doses of DTPw-HBV/Hib vaccine)
Any: At least one dose

The occurrence and intensity of solicited local and general signs and symptoms recorded on the day of each vaccination and for the three following days and unsolicited symptoms occurring within 30 days after a vaccine dose, are tabulated in Appendix Tables II A, B and C.

6.1 Overall incidence of symptoms

Table 16 details the incidence of both solicited and unsolicited (local/ general) reported during the 4-day follow-up period (Days 0 to 3) after each vaccine dose and overall, for the ATP reactogenicity cohort.
• According to per-dose analysis: The incidence of symptoms (local/ general, solicited/ unsolicited) reported during the 4-day follow-up after DTPw-HBV/Hib vaccine, decreased with subsequent doses.

Table 16 Incidence of symptoms (solicited/unsolicited) reported during the 4-day follow-up period after each dose of DTPw-HBV/Hib and Engerix™-B vaccines and overall (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Vaccine dose</th>
<th>N</th>
<th>Any Symptom n (%)</th>
<th>General Symptoms n (%)</th>
<th>Local Symptoms n (%)</th>
<th>Overall/dose</th>
<th>Overall/subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any Symptom 95% CI</td>
<td>General Symptoms 95% CI</td>
<td>Local Symptoms 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LL UL</td>
<td>LL UL</td>
<td>LL UL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth dose of Engerix™-B vaccine</td>
<td>117</td>
<td>26 22.2 15.1 30.8</td>
<td>13 11.1 63 54.3 6.1 18.3</td>
<td>19 16.2 62 53.4 10.1 24.2</td>
<td>465</td>
<td>117</td>
</tr>
<tr>
<td>Dose 1 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>76 65.5 56.1 74.1</td>
<td>63 54.3 44.8 63.6</td>
<td>62 53.4 44.0 62.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 2 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>57 49.1 39.7 58.6</td>
<td>50 43.1 33.9 52.6</td>
<td>40 34.5 25.9 43.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 3 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>54 46.6 37.2 56.0</td>
<td>45 38.8 29.9 48.3</td>
<td>44 37.9 29.1 47.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall/dose</td>
<td>465</td>
<td>213 45.8 41.2 50.5</td>
<td>171 36.8 32.4 41.3</td>
<td>165 35.5 31.1 40.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall/subject</td>
<td>117</td>
<td>90 76.9 68.2 84.2</td>
<td>86 73.5 64.5 81.2</td>
<td>74 63.2 53.8 72.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data on solicited/ unsolicited symptoms can be found in Appendix Tables IIA-C. All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

For each dose and overall per-subject:
N: Number of subjects with at least one documented dose
n (%): Number (percentage) of subjects presenting at least one type of symptom during the 4-day follow-up period

For overall / dose:
N: Number of documented doses
n (%) per dose: Number (percentage) of doses followed by a given type of symptom
95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Supplementary Table 8 details the incidence of symptoms (solicited and unsolicited) reported during the 4-day follow-up period (Days 0 to 3) for the three doses of DTPw-HBV/Hib vaccine and overall for the ATP reactogenicity cohort. Individual subject data on solicited/ unsolicited symptoms can be found in Appendix Tables IIA-C.

6.2 Solicited local signs and symptoms

• All local symptoms were considered to be causally related to vaccination

Table 17 presents the incidence of solicited local symptoms and those graded “3” in intensity reported during the 4-day follow-up period following Engerix™-B vaccine dose at birth, for the ATP reactogenicity cohort.
Following Engerix™-B at birth:

- Redness at injection site was the most reported (11.1%) solicited local symptom.

- Five cases of grade “3” solicited local symptoms were reported, all of which were pain at injection site.

Table 17 Incidence of solicited local symptoms and those graded “3” in intensity reported during the 4-day follow-up period after Engerix™-B vaccine dose at birth (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>N = 117</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL</td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>7</td>
<td>6.0</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>5</td>
<td>4.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>13</td>
<td>11.1</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>5</td>
<td>4.3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Individual subject data on solicited local symptoms can be found in Appendix Table IIA

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects with at least one symptom sheet completed for local symptoms

n (%): Number (percentage) of subjects reporting a specified symptom

Any: Any solicited local symptom (irrespective of intensity grade)

Grade “3” pain: Cried when limb was moved/ spontaneously painful

Grade “3” redness or swelling: redness or swelling ≥20mm at the injection site

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Table 18 presents the incidence of solicited local symptoms and those graded “3” in intensity, reported during the 4-day follow-up period after each of the three doses of DTPw-HBV/Hib for the ATP reactogenicity cohort.

Following DTPw-HBV/Hib vaccine doses:

- Pain at injection site was the most reported solicited local symptom.

- All cases of grade “3” solicited local symptoms reported (a total of 53 symptoms) were pain at injection site. All grade “3” symptoms resolved within the 4-day follow-up period.
Table 18 Incidence of solicited local symptoms (any/grade “3”), reported during the 4-day follow-up period after each of the three doses of DTPw-HBV/Hib vaccine (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>Dose 1 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th></th>
<th>Dose 2 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th></th>
<th>Dose 3 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>53 45.7 36.4 55.2</td>
<td>32 27.6 19.7 36.7</td>
<td>39 33.6 25.1 43.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>28 24.1 16.7 33.0</td>
<td>10 8.6 4.2 15.3</td>
<td>15 12.9 7.4 20.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>36 31.0 22.8 40.3</td>
<td>23 19.8 13.0 28.3</td>
<td>26 22.4 15.2 31.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 0.0</td>
<td>0 0.0 0.0 0.0</td>
<td>0 0.0 0.0 0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>20 17.2 10.9 25.4</td>
<td>13 11.2 6.1 18.4</td>
<td>17 14.7 8.8 22.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 0.0</td>
<td>0 0.0 0.0 0.0</td>
<td>0 0.0 0.0 0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data on solicited local symptoms can be found in Appendix Table IIA.

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

N: Number of doses for which at least one symptom sheet was completed for local symptoms.

n (%): Number (percentage) of doses with reports of a specified symptom.

Any: Any solicited local symptom (irrespective of intensity grade).

Grade “3” pain: Cried when limb was moved/ spontaneously painful.

Grade “3” redness or swelling: redness or swelling >20mm at the injection site.

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

Supplementary Table 9 details the overall incidence of solicited local symptoms (any/grade “3”) reported during the 4-day follow-up period after the three doses of DTPw-HBV/Hib vaccine, according to per-dose and per-subject analyses for the ATP reactogenicity cohort.

Supplementary Table 10 details the overall incidence of solicited local symptoms (any and grade “3”) reported during the 4-day follow-up period after all four vaccine doses (Engerix™-B and DTPw-HBV/Hib), according to per-dose and per-subject analyses, for the ATP reactogenicity cohort.

Individual subject data on solicited local symptoms can be found in Appendix Table IIA.

6.3 Solicited general signs and symptoms

Table 19 presents the incidence of solicited general symptoms (any and grade “3”) reported during the 4-day follow-up period after each vaccine dose, for the ATP reactogenicity cohort.

Following all four vaccine doses,

- Fever was the most reported solicited general symptom and irritability was the most frequently reported Grade “3” symptom.
• All solicited general symptoms reported were considered by the investigator to have a ‘probable’ (‘PB’) or ‘suspected’ (‘SU’) relationship to vaccination.

• All grade “3” solicited general symptoms reported resolved within the 4-day follow-up period after vaccination.

Table 19 Incidence of solicited general symptoms (any and grade “3”) reported during the 4-day follow-up period after each vaccine dose (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>Birth dose of Engerix™B (N = 117)</th>
<th>Dose 1 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th>Dose 2 of DTPw-HBV/Hib vaccine (N = 116)</th>
<th>Dose 3 of DTPw-HBV/Hib vaccine (N = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Any</td>
<td></td>
<td>6 5.1 1.9 10.8</td>
<td>25 21.6 14.5 30.1</td>
<td>19 16.4 10.2 24.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td></td>
<td>1 0.9 0.0 4.7</td>
<td>5 4.3 1.4 9.8</td>
<td>5 4.3 1.4 9.8</td>
</tr>
<tr>
<td>Irritability</td>
<td>Any</td>
<td></td>
<td>3 2.6 0.5 7.3</td>
<td>35 30.2 22.0 39.4</td>
<td>23 19.8 13.0 28.3</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td></td>
<td>2 1.7 0.2 6.0</td>
<td>13 11.2 6.1 18.4</td>
<td>4 3.4 0.9 8.6</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Any</td>
<td></td>
<td>3 2.6 0.5 7.3</td>
<td>25 21.6 14.5 30.1</td>
<td>17 14.7 8.8 22.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td></td>
<td>1 0.9 0.0 4.7</td>
<td>5 4.3 1.4 9.8</td>
<td>6 5.2 1.9 10.9</td>
</tr>
<tr>
<td>Fever</td>
<td>Any</td>
<td></td>
<td>1 0.9 0.0 4.7</td>
<td>41 35.3 26.7 44.8</td>
<td>32 27.6 19.7 36.7</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td></td>
<td>0 0.0 0.0 3.1</td>
<td>0 0.0 0.0 3.1</td>
<td>1 0.9 0.0 4.7</td>
</tr>
</tbody>
</table>

Individual subject data on solicited general symptoms can be found in Appendix Table IIB.

All subjects received Engerix™B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

Any: Incidence of solicited general symptom regardless of intensity or relationship.

N: Number of doses for which the symptom sheet was completed for solicited general symptoms.

n (%): Number (percentage) of doses followed by a specified symptom.

Grade “3” drowsiness: Drowsiness that prevented normal activity.

Grade “3” irritability: Crying that could not be comforted/ prevented normal activity.

Grade “3” loss of appetite: Not eating at all.

Grade “3” fever: axillary temperature >39 °C or rectal temperature >39.5 °C.

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

Supplementary Table 11 presents the incidence of solicited general symptoms (any/grade “3”) following the three doses of DTPw-HBV/Hib vaccine, according to per-dose and per-subject analysis for the ATP reactogenicity cohort.

Supplementary Table 12 presents the overall incidence of solicited general symptoms (any and grade “3”) following all four doses (Engerix™B and DTPw-HBV/Hib), according to per-dose and per-subject analyses, for the ATP reactogenicity cohort.

Individual subject data on solicited general symptoms can be found in Appendix Table II B.

6.4 Unsolicited symptoms

In addition to the solicited symptoms reported, any other symptoms that were reported to the investigator were documented under “others” in the case report form. Symptoms designated as solicited in diary cards are also included under unsolicited symptoms if they started outside the protocol specified follow-up
period for solicited symptoms. Unsolicited signs and symptoms were coded by use of the World Health Organization’s (WHO) Dictionary for Adverse Reaction Terminology; every verbatim term was matched to the appropriate WHO Preferred Term. The count of WHO Preferred Terms may not necessarily correspond to the number of subjects having developed an adverse event. Indeed, a person may have developed the same sign and symptom at different time periods, or a person may have developed different signs and symptoms coded to different WHO body system classes.

Table 20 presents the number of doses followed by at least one report of unsolicited symptom classified by WHO Preferred Term and determined by the investigator to have ‘probable’ or ‘suspected’ relationship to the vaccination, reported during the 30-day follow-up period, for the ATP reactogenicity cohort.

- A total of 30 subjects reported at least one unsolicited symptom classified by WHO Preferred Term during the 30-day follow-up period after vaccination.
- A total of 52 doses were followed by at least one report of unsolicited symptom classified by WHO preferred terms, during the 30-day follow-up period after vaccination.
- Of these 52 doses,
  - Eleven (2.4%) doses were followed by at least one unsolicited symptom that was considered by the investigator to have a ‘PB’/‘SU’ relationship to the vaccination, during the 30-day follow-up period after vaccination.
  - Eight doses (1.7%) were followed by at least one unsolicited symptom of intensity “3”, during the 30-day follow-up period after vaccination. Of these eight doses, two doses were followed by unsolicited symptoms that were considered by the investigator to have a ‘suspected’ relationship to the vaccination. All other grade “3” unsolicited symptoms were considered by the investigator to be ‘not related’ to the vaccination.
- All unsolicited symptoms reported resolved within the 30-day follow-up period after vaccination.
Table 20 Number of doses followed by at least one report of unsolicited symptom classified by WHO Preferred Term and determined by the investigator to have ‘probable’ or ‘suspected’ relationship to the vaccination, reported during the 30-day follow-up period (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>WHO Body System (CODE)</th>
<th>WHO Preferred Term (CODE)</th>
<th>d</th>
<th>%</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one symptom</td>
<td></td>
<td></td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a whole general (1810)</td>
<td></td>
<td></td>
<td>465</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (0725)</td>
<td></td>
<td>3</td>
<td>0.6</td>
<td>0.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Malaise (0728)</td>
<td></td>
<td>3</td>
<td>0.6</td>
<td>0.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Gastrointestinal system (600)</td>
<td></td>
<td></td>
<td>465</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea (0205)</td>
<td></td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Tenesmus (0231)</td>
<td></td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Psychiatric (500)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insomnia (0183)</td>
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<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
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<tr>
<td>Respiratory system (1100)</td>
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<td></td>
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</tr>
<tr>
<td>Coughing (0513)</td>
<td></td>
<td>2</td>
<td>0.4</td>
<td>0.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Individual subject data on unsolicited symptoms can be found in Appendix Table II C.

All subjects received Engerix™B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

At least one symptom: At least one symptom experienced (without taking into account the Preferred Term)

D: Total number doses

Individual subject data on unsolicited symptoms can be found in Appendix Table II C.

6.5 Concomitant medications/ vaccinations

A total of 65 subjects included in the ATP analysis of reactogenicity were given at least one medication during the study course. Of these 65 subjects, 11 subjects received concomitant medication prophylactically (of these, 9 subjects received Acetaminophen for fever or pain).

Please refer Appendix Table IID for individual subject data on concomitant medication.

6.6 Biochemical analyses

Not applicable.
6.7 Pregnancy

Not applicable.

6.8 Serious adverse events

The investigator considered the event as ‘not related’ to the vaccination. The subject received the subsequent doses of DTPw-HBV/Hib vaccine.

Suspect Adverse Reaction Reports (SARR) and the SAE Table for the SAE are included in report appendix for serious adverse events.
7. Discussion

This study was conducted to assess the immunogenicity and reactogenicity of GSK Biologicals' DTPw-HBV/Hib vaccine, given as a three-dose immunization course at 2, 4 and 6 months of age, to infants who had previously received a monovalent dose of GSK Biologicals’ hepatitis B (Engerix™-B) vaccine at birth.

In Columbia, the routinely used schedule for hepatitis B vaccine is 0, 1, 6 months. In this study where a 2, 4, 6 month schedule of hepatitis B vaccine was employed, along with a birth dose of hepatitis B vaccine, it was observed that after 2 doses, over 80% of the subjects were seroprotected against hepatitis B. WHO recommends that the HB component of a DTP-HB combination vaccine should be able to induce an anti-HBs antibody response of at least 10 mIU/ml in ≥ 95% of vaccinees after 3 doses\(^{10}\). In this study, 99% seroprotection rate was observed after 3 doses and all subjects were seroprotected one month after the fourth dose.

The anti-diphtheria and anti-tetanus antibody titers observed at pre-vaccination were very high (86.7% were seroprotected for anti-diphtheria and all subjects were seroprotected for anti-tetanus antibodies). This could be probably due to high levels of maternal antibodies at pre-vaccination, as in most countries it is a practice to vaccinate pregnant mothers against tetanus. However, the seroprotection rates were higher (than those at pre-vaccination) or maintained one month after the full vaccination course.

The immune response for anti-PRP and anti-BPT antibodies was good. The high anti-PRP antibody titers at pre-vaccination could be due to maternal antibodies. The vaccine response for whole cell pertussis one month after last dose of vaccination was 100%.

There have been questions raised about the safety of increased number of hepatitis B vaccine doses for fear of triggering an increase in reactogenicity. The results of this study show that the reactogenicity after three doses of DTPw-HBV/Hib vaccine, did not increase with the fourth dose of hepatitis B antigen when compared to another study\(^{11}\) in which DTPw-HBV and Hib vaccines were given according to a 2, 4, 6 month schedule to subjects who were not given a birth dose of hepatitis B.
8. Overall Conclusions

- The seroprotection rate of anti-HBs antibodies at Month 4 (i.e., two months after the second dose of HBsAg) was 81.7%, at Month 6 (i.e., two months after third dose of HBsAg) was 99% and at Month 7 (i.e., one month after the fourth dose of HBsAg) was 100%.

- One month after the full vaccination course (i.e., at Month 7), all subjects had anti-PRP antibody titers ≥ 0.15 mcg/ml (generally accepted as short-term seroprotection), 99% subjects had anti-PRP antibody titers ≥ 1 mcg/ml (generally accepted as long-term seroprotection) and all subjects showed a vaccine response to whole cell pertussis. Also, all subjects were seroprotected for anti-tetanus antibodies and 98.1% of subjects were seroprotected for anti-diphtheria antibodies.

- The incidence of symptoms (local/ general, solicited/ unsolicited) reported during the 4-day follow-up after vaccination decreased with subsequent doses of DTPw-HBV/Hib. No increase in the incidence of symptoms could be observed following the fourth dose of HBsAg. Few grade “3” solicited symptoms were reported and all (except one) grade “3” solicited symptoms resolved within the 4-day follow-up period after vaccination. Only one SAE was reported, which was considered by the investigator to be ‘not related’ to the vaccination.

- Therefore, within the limitations of this study, the immunogenicity and safety profile of DTPw-HBV/Hib vaccine given at 2, 4 and 6 months following a birth dose of hepatitis B vaccine was found to be good.
9. References


11 Interim clinical study report 213501/008 (DTPw-HBV-Hib-008). Multicentric open randomized clinical study to assess the immunogenicity and reactogenicity of the co-administration of GSK Biologicals’ DTPw-HBV vaccine and Hib vaccine, either mixed in one syringe or given in two separate injections, to healthy infants at the age 2, 4 and 6 months and as a booster at 18 months.
### Supplementary Table 1 Demographics: racial and gender composition (total cohort)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameters or Categories</th>
<th>N = 120 Value or n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in weeks</td>
<td>Mean</td>
<td>7.6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.91</td>
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<tr>
<td></td>
<td>Median</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>67</td>
<td>55.8</td>
</tr>
<tr>
<td></td>
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<td>44.2</td>
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<tr>
<td>Race</td>
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<td>41</td>
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<td></td>
<td>Black</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Oriental</td>
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<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>71</td>
<td>59.2</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB
All subjects received *Engerix*™ B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects with documentation on age and gender

Value/n (%): Value for parameters of age/number (percentage) of subjects of subjects in a given category

%: n / Number of subjects with available results x 100

SD: Standard deviation

### Supplementary Table 2 Demographics: racial and gender composition (ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parameters or Categories</th>
<th>N = 105 Value or n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in weeks</td>
<td>Mean</td>
<td>7.7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.88</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Minimum</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Maximum</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>54</td>
<td>51.4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>51</td>
<td>48.6</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>33</td>
<td>31.4</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>8</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>Oriental</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>64</td>
<td>61.0</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB
All subjects received *Engerix*™ B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects with documentation on age and gender

%: Percentage calculated using N as denominator

Value/n (%): Value for parameters of age/number (percentage) of subjects of subjects in a given category

SD: Standard deviation
**Supplementary Table 3** Seroprotection rate and GMTs of anti-HBs antibodies  
*(Total cohort)*

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>SP</th>
<th>95% CI</th>
<th>GMT</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
<td>UL</td>
<td>LL</td>
</tr>
<tr>
<td>Pre</td>
<td>118</td>
<td>5</td>
<td>4.2</td>
<td>1.4</td>
<td>9.6</td>
</tr>
<tr>
<td>PII(M4)</td>
<td>114</td>
<td>94</td>
<td>82.5</td>
<td>74.2</td>
<td>88.9</td>
</tr>
<tr>
<td>PIII(M6)</td>
<td>116</td>
<td>115</td>
<td>99.1</td>
<td>95.3</td>
<td>100.0</td>
</tr>
<tr>
<td>PIV(M7)</td>
<td>116</td>
<td>116</td>
<td>100.0</td>
<td>96.9</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA.  
All subjects received *Engerix™* B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.  

**N:** Number of subjects tested  
**SP:** Seroprotection for anti-HBs antibodies (i.e., titers ≥ 10 mIU/ml)  
**n (%):** Number (percentage) of subjects seroprotected for anti-HBs antibodies  
**Pre:** Month 0 (birth dose of *Engerix™* B)  
**PII (M4):** Two months after first dose of DTPw-HBV/Hib vaccine  
**PIII (M6):** Two months after second dose of DTPw-HBV/Hib vaccine  
**PIV (M7):** One month after third dose of DTPw-HBV/Hib vaccine  
**95% CI:** 95% confidence interval; **LL:** Lower Limit; **UL:** Upper Limit  
**GMT:** Geometric Mean Titer

**Supplementary Table 4** Percentage of subjects with titers ≥ 0.15 mcg/ml and ≥ 1.0 mcg/ml and GMTs of anti-PRP antibodies  
*(Total cohort)*

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>≥ 0.15 mcg/ml</th>
<th>95% CI</th>
<th>≥ 1.0 mcg/ml</th>
<th>95% CI</th>
<th>GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
<td>%</td>
<td>LL</td>
<td>LL</td>
</tr>
<tr>
<td>Pre</td>
<td>120</td>
<td>84</td>
<td>70.0</td>
<td>61.0</td>
<td>78.0</td>
<td>0.494</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>32.5</td>
<td>24.2</td>
<td>4.2</td>
<td>41.7</td>
<td>0.362</td>
</tr>
<tr>
<td></td>
<td>114</td>
<td>73</td>
<td>63.2</td>
<td>53.6</td>
<td>72.0</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>24.6</td>
<td>17.0</td>
<td>0.1</td>
<td>33.5</td>
<td>0.255</td>
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<tr>
<td></td>
<td>116</td>
<td>113</td>
<td>97.4</td>
<td>92.6</td>
<td>99.5</td>
<td>8.869</td>
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<tr>
<td></td>
<td>100</td>
<td>86.2</td>
<td>78.6</td>
<td>9.9</td>
<td>91.9</td>
<td>6.392</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>99.1</td>
<td>95.3</td>
<td>96.9</td>
<td>100.0</td>
<td>29.494</td>
</tr>
<tr>
<td></td>
<td>116</td>
<td>100.0</td>
<td>100.0</td>
<td>96.9</td>
<td>100.0</td>
<td>24.176</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA.  
All subjects received *Engerix™* B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.  

**N:** Number of subjects tested  
**n (%):** Number (percentage) of subjects with anti-PRP antibody titers ≥ 0.15 mcg/ml (short-term seroprotection) or 1 mcg/ml (long-term seroprotection)  
**Pre:** Month 0 (birth dose of *Engerix™* B)  
**PII (M4):** Two months after first dose of DTPw-HBV/Hib vaccine  
**PIII (M6):** Two months after second dose of DTPw-HBV/Hib vaccine  
**PIV (M7):** One month after third dose of DTPw-HBV/Hib vaccine  
**95% CI:** 95% confidence interval; **LL:** Lower Limit; **UL:** Upper Limit  
**GMT:** Geometric Mean Titer
### Supplementary Table 5 Seropositivity rates and GMTs of anti-BPT antibodies
**(Total cohort)**

<table>
<thead>
<tr>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI</th>
<th>GMT (EL.U/ml)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>LL</td>
<td>UL</td>
<td>LL</td>
</tr>
<tr>
<td>Pre</td>
<td>120</td>
<td>24</td>
<td>20.0</td>
<td>13.3</td>
<td>28.3</td>
</tr>
<tr>
<td>PII(M4)</td>
<td>114</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>3.2</td>
</tr>
<tr>
<td>PIII(M6)</td>
<td>116</td>
<td>60</td>
<td>51.7</td>
<td>42.3</td>
<td>61.1</td>
</tr>
<tr>
<td>PIV(M7)</td>
<td>116</td>
<td>116</td>
<td>100.0</td>
<td>96.9</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received *Engerix™-B* (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested

S+: Seropositivity for anti-BPT antibodies (i.e., titers ≥ 15 EL.U/ml)

n (%): Number (percentage) of subjects seropositive for anti-BPT antibodies

Pre: Month 0 (birth dose of *Engerix™-B*)

PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine

PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine

PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine

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

### Supplementary Table 6 Vaccine response to whole cell pertussis antigen at Month 7 (Total cohort)

<table>
<thead>
<tr>
<th>Prevacc. status</th>
<th>N</th>
<th>R+</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL</td>
</tr>
<tr>
<td>S+</td>
<td>22</td>
<td>22</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>S−</td>
<td>94</td>
<td>94</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>116</td>
<td>116</td>
<td>100</td>
<td>96.9</td>
</tr>
</tbody>
</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received *Engerix™-B* (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested

R+ (%): Number (percentage) of responders (i.e., subjects who showed a vaccine response)

Vaccine response was defined as:

- The presence of anti-BPT antibodies in subjects seronegative at pre-vaccination or
- Post-vaccination antibody titers ≥ pre-vaccination titers in subjects who were seropositive at pre-vaccination

S−/S+: Seronegative/seropositive subjects at pre vaccination (i.e., birth dose of *Engerix™-B*)

Total: Subjects either seropositive or seronegative at pre vaccination

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit
### Supplementary Table 7 Seroprotection rates and GMT of anti-diphtheria and anti-tetanus antibodies (Total cohort)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Timing</th>
<th>N</th>
<th>SP</th>
<th>95% CI</th>
<th>GMT (IU/ml)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Diphtheria</td>
<td>Pre</td>
<td>120</td>
<td>105</td>
<td>87.5</td>
<td>80.2 92.8</td>
<td>1.110</td>
</tr>
<tr>
<td></td>
<td>PII(M4)</td>
<td>114</td>
<td>55</td>
<td>48.2</td>
<td>38.8 57.8</td>
<td>0.116</td>
</tr>
<tr>
<td></td>
<td>PIII(M6)</td>
<td>116</td>
<td>70</td>
<td>60.3</td>
<td>50.8 69.3</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>PIV(M7)</td>
<td>116</td>
<td>112</td>
<td>98.2</td>
<td>93.8 99.8</td>
<td>1.919</td>
</tr>
<tr>
<td>Anti-Tetanus</td>
<td>Pre</td>
<td>120</td>
<td>120</td>
<td>100.0</td>
<td>97.0 100.0</td>
<td>6.241</td>
</tr>
<tr>
<td></td>
<td>PII(M4)</td>
<td>114</td>
<td>108</td>
<td>94.7</td>
<td>88.9 98.0</td>
<td>0.457</td>
</tr>
<tr>
<td></td>
<td>PIII(M6)</td>
<td>116</td>
<td>114</td>
<td>98.3</td>
<td>93.9 99.8</td>
<td>0.534</td>
</tr>
<tr>
<td></td>
<td>PIV(M7)</td>
<td>116</td>
<td>116</td>
<td>100.0</td>
<td>96.9 100.0</td>
<td>4.671</td>
</tr>
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</table>

Individual subject data on immunogenicity can be found in Appendix table IIIA

All subjects received **Engerix™ B** (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

N: Number of subjects tested

SP: Seroprotection for anti-diphtheria/anti-tetanus antibodies (i.e., titers ≥ 0.1 IU/ml)

n(%) : Number (percentage) of subjects seroprotected for anti-diphtheria/anti-tetanus antibodies

Pre: At Month 0

PII (M4): Two months after first dose of DTPw-HBV/Hib vaccine

PIII (M6): Two months after second dose of DTPw-HBV/Hib vaccine

PIV (M7): One month after third dose of DTPw-HBV/Hib vaccine

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

GMT: Geometric Mean Titer

### Supplementary Table 8 Incidence of symptoms (solicited and unsolicited) reported during the 4-day follow-up period for the three doses of DTPw-HBV/Hib vaccine and overall (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Any Symptom n (%)</th>
<th>95% CI</th>
<th>General Symptoms n (%)</th>
<th>95% CI</th>
<th>Local Symptoms n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>76 65.5</td>
<td>56.1 74.1</td>
<td>63 54.3</td>
<td>44.8 63.6</td>
<td>62 53.4</td>
<td>44.0 62.8</td>
</tr>
<tr>
<td>Dose 2 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>57 49.1</td>
<td>39.7 58.6</td>
<td>50 43.1</td>
<td>33.9 52.6</td>
<td>40 34.5</td>
<td>25.9 43.9</td>
</tr>
<tr>
<td>Dose 3 of DTPw-HBV/Hib vaccine</td>
<td>116</td>
<td>54 46.6</td>
<td>37.2 56.0</td>
<td>45 38.8</td>
<td>29.9 48.3</td>
<td>44 37.9</td>
<td>29.1 47.4</td>
</tr>
<tr>
<td>Overall/dose</td>
<td>348</td>
<td>187 53.7</td>
<td>48.3 59.1</td>
<td>158 45.4</td>
<td>40.1 50.8</td>
<td>146 42.0</td>
<td>36.7 47.3</td>
</tr>
<tr>
<td>Overall/subject</td>
<td>116</td>
<td>90 77.6</td>
<td>68.9 84.8</td>
<td>86 74.1</td>
<td>65.2 81.8</td>
<td>73 62.9</td>
<td>53.5 71.7</td>
</tr>
</tbody>
</table>

Individual subject data on solicited/unsolicited symptoms can be found in Appendix Tables IIA-C

All subjects received **Engerix™ B** (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

For each dose and overall per-subject:

N: Number of subjects with at least one documented dose

n (%): Number (percentage) of subjects presenting at least one type of symptom during the 4-day follow-up period

For overall / dose:

N: Number of documented doses

n (%): Number (percentage) of doses followed by a given type of symptom

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit
Supplementary Table 9 Overall incidence of solicited local symptoms (any/ grade “3”) reported during the 4-day follow-up period after the three doses of DTPw-HBV/Hib vaccine, according to per-dose and per-subject analyses (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>All/Dose</th>
<th>All/Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 348)</td>
<td>(N = 116)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n % 95% CI</td>
<td>n % 95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LL UL</td>
<td>LL UL</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>124 35.6 30.6 40.9</td>
<td>70 60.3 50.8 69.3</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>53 15.2 11.6 19.4</td>
<td>38 32.8 24.3 42.1</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>85 24.4 20.0 29.3</td>
<td>48 41.4 32.3 50.9</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 1.1</td>
<td>0 0.0 0.0 3.1</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>50 14.4 10.9 18.5</td>
<td>32 27.6 19.7 36.7</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 1.1</td>
<td>0 0.0 0.0 3.1</td>
</tr>
</tbody>
</table>

Individual subject data on solicited local symptoms can be found in Appendix Table IIA
All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

For overall per-dose:
N: Number of doses for which at least one symptom sheet was completed for local symptoms
n (%): Number (percentage) of documented doses with at least one symptom reported

For overall per-subject:
N: Number of subjects with at least one documented dose
n (%) per subject: Number (percentage) of subjects presenting at least one type of symptom
Any: Any solicited local symptom (irrespective of intensity grade)
Grade “3” pain: Cried when limb was moved/ spontaneously painful
Grade “3” redness or swelling: redness or swelling >20mm at the injection site
95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit
Supplementary Table 10 Overall incidence of solicited local symptoms (any and grade “3”) reported during the 4-day follow-up period after all four vaccine doses (Engerix™-B and DTPw-HBV/Hib), according to per-dose and per-subject analyses (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
<th>All/Dose (N = 465)</th>
<th>All/Subject (N = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n (%) 95% CI LL UL</td>
<td>n (%) 95% CI LL UL</td>
</tr>
<tr>
<td>Pain</td>
<td>Any</td>
<td>131 28.2 24.1 32.5</td>
<td>71 60.7 51.2 69.6</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>58 12.5 9.6 15.8</td>
<td>42 35.9 27.2 45.3</td>
</tr>
<tr>
<td>Redness</td>
<td>Any</td>
<td>98 21.1 17.5 25.1</td>
<td>49 41.9 32.8 51.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 0.8</td>
<td>0 0.0 0.0 3.1</td>
</tr>
<tr>
<td>Swelling</td>
<td>Any</td>
<td>55 11.8 9.0 15.1</td>
<td>34 29.1 21.0 38.2</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>0 0.0 0.0 0.8</td>
<td>0 0.0 0.0 3.1</td>
</tr>
</tbody>
</table>

Individual subject data on solicited local symptoms can be found in Appendix Table IIA
All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

For overall per-dose:
N: Number of doses for which at least one symptom sheet was completed for local symptoms
n (%): Number (percentage) of documented doses with at least one symptom reported

For overall per-subject:
N: Number of subjects with at least one documented dose
n (% per subject): Number (percentage) of subjects presenting at least one type of symptom
Any: Any solicited local symptom (irrespective of intensity grade)
Grade “3” pain: Cried when limb was moved/ spontaneously painful
Grade “3” redness or swelling: redness or swelling >20mm at the injection site
95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit
**Supplementary Table 11 Overall incidence of solicited general symptoms (any and grade “3”) reported following the three doses of DTPw-HBV/Hib vaccine, according to per-dose and per-subject analyses (ATP reactogenicity cohort)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Intensity</th>
<th>All/Dose (N = 348)</th>
<th></th>
<th>All/Subject (N = 116)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>LL</td>
<td>UL</td>
<td></td>
<td>LL</td>
<td>UL</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Any</td>
<td>64</td>
<td>18.4</td>
<td>14.5</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>14</td>
<td>4.0</td>
<td>2.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Irritability</td>
<td>Any</td>
<td>82</td>
<td>23.6</td>
<td>19.2</td>
<td>28.4</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>23</td>
<td>6.6</td>
<td>4.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Any</td>
<td>55</td>
<td>15.8</td>
<td>12.1</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>12</td>
<td>3.4</td>
<td>1.8</td>
<td>5.9</td>
</tr>
<tr>
<td>Fever</td>
<td>Any</td>
<td>110</td>
<td>31.6</td>
<td>26.8</td>
<td>36.8</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>1</td>
<td>0.3</td>
<td>0.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Individual subject data on solicited general symptoms can be found in Appendix Table IIB

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

Any: Incidence of solicited general symptom regardless of intensity or relationship

N: Number of doses for which the symptom sheet was completed for general symptoms

n (%): Number (percentage) of doses followed by a specified symptom

Grade “3” drowsiness: Drowsiness that prevented normal activity

Grade “3” irritability: Crying that could not be comforted/prevented normal activity

Grade “3” loss of appetite: Not eating at all

Grade “3” fever: axillary temperature >39 °C or rectal temperature >39.5 °C

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit

Note: All solicited general symptoms had a ‘PB’/‘SU’ relationship to vaccination
**Supplementary Table 12** Overall incidence of solicited general symptoms (any and grade “3”) reported following all four vaccine doses (Engerix™-B and DTPw-HBV/Hib), according to per-dose and per-subject analyses (ATP reactogenicity cohort)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Intensity</th>
<th>All/Dose (N = 465)</th>
<th>All/Subject (N = 117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N = 465)</td>
<td>%</td>
<td>95% CI LL UL</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>Any</td>
<td>70</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>15</td>
<td>3.2</td>
</tr>
<tr>
<td>Irritability</td>
<td>Any</td>
<td>85</td>
<td>18.3</td>
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<tr>
<td></td>
<td>Grade “3”</td>
<td>25</td>
<td>5.4</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>Any</td>
<td>58</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>13</td>
<td>2.8</td>
</tr>
<tr>
<td>Fever</td>
<td>Any</td>
<td>111</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td>Grade “3”</td>
<td>1</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Individual subject data on solicited general symptoms can be found in Appendix Table IIB.

All subjects received Engerix™-B (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age.

Any: Incidence of solicited general symptom regardless of intensity or relationship.

N: Number of doses for which the symptom sheet was completed for general symptoms.

n (%): Number (percentage) of doses followed by a specified symptom.

Grade “3” drowsiness: Drowsiness that prevented normal activity.

Grade “3” irritability: Crying that could not be comforted/ prevented normal activity.

Grade “3” loss of appetite: Not eating at all.

Grade “3” fever: axillary temperature >39 °C or rectal temperature >39.5 °C.

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit.
**Supplementary Table 13 Number of doses followed by at least one report of unsolicited symptom classified by WHO Preferred Terms reported during the 30-day follow-up period after vaccination (ATP reactogenicity cohort)**

<table>
<thead>
<tr>
<th>WHO Body System (CODE)</th>
<th>WHO Preferred Term (CODE)</th>
<th>(d)</th>
<th>(%)</th>
<th>95% CI</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one symptom</td>
<td></td>
<td>38</td>
<td>8.2</td>
<td>5.8</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Body as a whole general (1810)</td>
<td>Fever (0725)</td>
<td>6</td>
<td>1.3</td>
<td>0.5</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Malaise (0728)</td>
<td>4</td>
<td>0.9</td>
<td>0.2</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system (600)</td>
<td>Abdominal pain (0268)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia (0165)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation (0204)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea (0205)</td>
<td>2</td>
<td>0.4</td>
<td>0.1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gingivitis (1083)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hiccup (0300)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenesmus (0231)</td>
<td>2</td>
<td>0.4</td>
<td>0.1</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vomiting (0228)</td>
<td>3</td>
<td>0.6</td>
<td>0.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Psychiatric (500)</td>
<td>Insomnia (0183)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Resistance mechanism (1830)</td>
<td>Infection bacterial (0738)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection viral (0740)</td>
<td>8</td>
<td>1.7</td>
<td>0.7</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection (0543)</td>
<td>3</td>
<td>0.6</td>
<td>0.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Respiratory system (1100)</td>
<td>Bronchitis (0805)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coughing (0513)</td>
<td>10</td>
<td>2.2</td>
<td>1.0</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhinitis (0539)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Skin and appendages (100)</td>
<td>Rash (0027)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash erythematous (0028)</td>
<td>1</td>
<td>0.2</td>
<td>0.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Vision (431)</td>
<td>Conjunctivitis (0238)</td>
<td>3</td>
<td>0.6</td>
<td>0.1</td>
<td>1.9</td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data on unsolicited symptoms can be found in Appendix Table II C

All subjects received *Engerix™ B* (ENG2814A2/M) at birth + DTPw-HBV (15776A2/M)/Hib (Hib273A47/M) at 2, 4 and 6 months of age

At least one symptom: at least one symptom experienced (without taking into account the Preferred Term)

D: Total number doses

d (\%): Number (percentage) of doses followed by a specified symptom

95% CI: Exact 95% confidence interval; LL: Lower Limit; UL: Upper Limit
GSK BIOLOGICALS VACCINES CLINTRIAL
ELIMINATION CODES

Elimination from safety and serology analysis

1010 Subject or vaccine number not allocated
   Vaccine not administered at all
   No subject allocated to the randomization number

1030 Study vaccine dose not administered but subject number allocated
   Vaccine dose not administered at all
   At least one dose not administered

1040 Administration of vaccine(s) forbidden in the protocol

1050 Randomization failure
   Wrong vaccine vial given

1060 Randomization code broken at the investigator site

1070 Study vaccine dose not administered according to protocol
   Side, site or route of study vaccine administration unknown
   Side, site or route of study vaccine administration wrong

1080 Essential data missing
   Date of vaccination unknown
   Any data which prevent the analysis

Elimination from serology analysis

2010 Protocol violation
   Demographics:
   Too young
   Too old
   Unknown age, gender
   Gender not according to the protocol
   Others

2020 Initially seropositive or unknown antibody status
   Preliminary lab results not according to protocol
   Abnormal value

2030 Biochemistry, haematology and other laboratory values outside range
   before any vaccination

2040 Administration of any medication forbidden by the protocol

2050 Underlying medical condition forbidden by the protocol

2060 Concomitant infection related to the vaccine which may influence
   immune response
   Infection related to any of the vaccine components

2070 Concomitant infection not related to the vaccine which may influence
   immune response

2080 Non compliance with vaccination schedule (including wrong and
   unknown dates)
2090  Non compliance with blood sampling schedule (including wrong and unknown dates)
2100  Essential serological data missing
      Blood sample lost
      Blood sample unable to test (hemolysis, insufficient volume, etc)
      Absence of parallelism
2110  Blood sample available but not yet tested (interim analysis)
2120  Obvious incoherence or abnormality or error in data
      Wrong labelling in BS
      Abnormal serology evolution
2130  Subject not planned to be bled for all blood sampling visits
2500  Others
Notes to Appendix Tables

Sub. No. : subject number
Elig : eligibility
Elim : eliminated from analysis (es)
I : elimination from immunogenicity analysis
E : elimination from safety analysis
F : female
M : male

Appendix table IC

Pre: pre-vaccination blood sample
Post: post-vaccination blood sample obtained 1 month after the vaccine dose

Appendix table ID

past : medical history
current : present at the physical examination

Appendix table IIA

P? : According to protocol? Y / N: Yes / No
L? : Any solicited local symptom reported? Y / N: Yes / No
Site : site of vaccination
Side : Left / Right
Exp : adverse event: Y / N: Yes / No
Out : Outcome :
  1 = recovered
  2 = recovered with sequelae
  3 = ongoing
  4 = died
  5 = unknown

Cor : Corrective therapy
PA : Pain: scored as
Empty / 0: Absent
  1: The adverse event was easily tolerated.
  2: The adverse event was sufficiently discomforting to interfere with daily activity.
  3: The adverse event prevented normal everyday activities.

RE : Redness : in mm (greatest diameter)
SW : Swelling : in mm (greatest diameter)

Appendix table IIB

G? : Any solicited general symptom reported? Y / N: Yes / No
Exp : adverse event: Y / N: Yes / No
Out : Outcome :
  1 = recovered
2 = recovered with sequelae
3 = ongoing
4 = died
5 = unknown

RTE : Route (for body temperature recording)
R : rectal
A : axillary
REL : Relationship: R = related
PB = probable relationship
SU = suspected relationship
U = unrelated

Symptoms
DR: Drowsiness
IR: Irritability
LO: Loss of Appetite
TE: Fever

DR, IR, LO scored as
0: Absent
1: The adverse event was easily tolerated.
2: The adverse event was sufficiently discomforting to interfere with daily activity.
3: The adverse event prevented normal everyday activities.

Fever was scored as:
Axillary Rectal
0: < 37.5 °C 0: < 38.0 °C
1: ≥ 37.5 °C and ≤ 38.0 °C 1: ≥ 38.0 °C and ≤ 38.5 °C
2: > 38.0 °C and ≤ 39.0 °C 2: > 38.5 °C and ≤ 39.5 °C
3: > 39 °C 3: > 39.5 °C

Appendix table III A

Pre: Pre-vaccination blood sample at Month 0 (birth dose of Engerix™ B)
PII (M4): Blood sample taken two months after first dose of DTPw-HBV/Hib vaccine
PIII (M6): Blood sample taken two months after second dose of DTPw-HBV/Hib vaccine
PIV (M7): Blood sample taken one month after third dose of DTPw-HBV/Hib vaccine
This section contained data from each individual patient, rather than in aggregate. They have been excluded to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the GSK Clinical Study Register.
CIOMS
This section contained patient narratives which are textual descriptions of medical history, treatment and outcome for individual patients who experienced a clinically important adverse event including serious adverse events during the trial. They have been excluded to protect patient privacy. This data may be made available subject to an approved research proposal and a determination of the ability to provide information from the specific narratives whilst protecting the patient’s privacy. For further information please see the Patient Level Data section of the GSK Clinical Study Register.
Serious Adverse Events Table
Study vaccines

- SmithKline Beecham Biologicals’ recombinant hepatitis B vaccine: Engerix™-B
- SmithKline Beecham Biologicals’ combined diphtheria-tetanus-whole cell *Bordetella pertussis*-hepatitis B vaccine: Tritanrix™-HB
- SmithKline Beecham Biologicals’ *Haemophilus influenzae* type b (Hib) vaccine: Hiberix™

CPMS Protocol No. 213501/019 (DTPw-HBV-Hib-019)
Date of approval Final November 23, 1999
Amended: May 31, 2000

Title Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of SmithKline Beecham Biologicals’ quadrivalent diphtheria, tetanus, whole cell *Bordetella pertussis*, hepatitis B (DTPw-HBV) and *Haemophilus influenzae* type b conjugate (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with SmithKline Beecham Biologicals’ hepatitis B vaccine.

Co-ordinating author

Scientific Writer

Other contributing authors

Clinical Study Management

Statistician

Medical Monitor

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Av. Eldorado 91-50
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Colombia *(Amended: May 31, 2000)*
Tel: Fax: 

Principal Investigator

Dr.
Colombia
Synopsis

Title
Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of SmithKline Beecham Biologicals’ quadrivalent diphtheria, tetanus, whole cell Bordetella pertussis, hepatitis B (DTPw-HBV) and Haemophilus influenzae type b (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with SmithKline Beecham Biologicals’ hepatitis B vaccine.

Indication/Study Population
Three-dose immunisation course against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae in the 1st year of life in healthy infants previously primed with a birth dose of hepatitis B vaccine.

Rationale
The combined trivalent diphtheria, tetanus, whole-cell pertussis (DTPw) vaccine has been available since the 1940’s and has been part of the World Health Organisation’s Program on Immunisation (EPI) since the late 1970’s. It is well established as part of the routine paediatric vaccine practice worldwide. WHO now recommends inclusion of hepatitis B vaccine (HBV) in all national immunisation programs independent of the hepatitis B carrier rate and recently has recommended worldwide inclusion of Haemophilus influenzae type b (Hib) conjugate vaccine in infant immunisation programs. The complicated logistics of administering different multi-dose vaccines that each requires several inoculations can be a significant barrier to successful universal immunisation. Increasing attention is therefore being paid to the development of combined vaccines, such as SmithKline Beecham Biologicals’ (SB Biologicals) DTPw-HBV vaccine, which provide immunisation against several diseases through single injections. In addition, the ability to mix vaccines and/or administer simultaneously without causing interference with the immune response to the vaccines or intensifying the reactogenicity and safety profiles of the vaccines would enhance compliance with vaccination schedules. In areas of high endemicity of hepatitis B infection, it is recommended that infants receive hepatitis B vaccine at or as near birth as possible. This study will assess the immunogenicity, safety and reactogenicity of syringe mixing of SB Biologicals’ DTPw-HBV and Hib conjugate vaccines. The rationale for this study is to assess the kinetics of antibody response to the recombinant hepatitis B antigen administered according to this regimen in a cohort of infants previously primed with a birth dose of hepatitis B vaccine.
Objectives

**Primary**
To assess the antibody response to the recombinant hepatitis B surface antigen

**Secondary**
To assess the antibody response to all other vaccine antigens: diphtheria and tetanus toxoids, whole cell *Bordetella pertussis* and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP)

To assess the safety and reactogenicity of the vaccines

Study design

- Open study with one group conducted at 1 site
- 4 blood samples: one taken at birth, one at the time of the second dose of the mixed vaccines, one at the time of the third dose of the mixed vaccines and one taken one month after the third dose of the mixed vaccines
- 4-day follow-up for solicited local and general symptoms after each dose of the vaccine(s): Day 0 to Day 3
- One month (30 days) follow-up for unsolicited symptoms after each dose of the vaccine(s)
- Recording of serious adverse events throughout the entire study period up to and including a minimum of 30 days after the last dose of the mixed vaccines

Number of subjects

A target enrolment of 120 eligible subjects at birth to ensure a minimum of 100 eligible healthy male and female infants between 6 to 10 weeks of age at the time of the first dose of the three-dose vaccination course
Primary endpoint

Percentage of infants with anti-HBs titres ≥10 mIU/ml at the time of the second dose of the mixed vaccines, i.e., at 4 months of age

Secondary endpoints

At each blood sampling timepoint:
- anti-HBs antibody titres
- anti-PRP antibody titres
- anti-BPT antibody titres
- anti-tetanus antibody titres
- anti-diphtheria antibody titres

Occurrence of any solicited local and/or general symptoms within 4 days after each dose of vaccine(s)

Occurrence of unsolicited symptoms within 30 days after each dose of vaccine(s)

Occurrence of Serious Adverse Events (SAEs) over the course of the study (beginning with first study procedure at birth up to and including 30 days following the 3rd dose of the mixed vaccines)
Table of Contents

1 INTRODUCTION ............................................................................................................. 10

2 OBJECTIVES ................................................................................................................ 12
   2.1 PRIMARY OBJECTIVE .......................................................................................... 12
   2.2 SECONDARY OBJECTIVES ................................................................................. 12

3 STUDY DESIGN OVERVIEW ....................................................................................... 12

4 STUDY COHORT .............................................................................................................. 13
   4.1 NUMBER OF SUBJECTS / CENTRES ................................................................. 13
   4.2 INCLUSION CRITERIA FOR ENROLMENT AT BIRTH ....................................... 14
   4.3 EXCLUSION CRITERIA FOR ENROLMENT AT BIRTH ........................................ 14
   4.4 INCLUSION CRITERIA FOR ADMINISTRATION OF THE MIXED VACCINES ..... 14
   4.5 EXCLUSION CRITERIA FOR ADMINISTRATION OF THE MIXED VACCINES .... 14
   4.6 ELIMINATION CRITERIA DURING THE STUDY ................................................. 15
   4.7 CONTRAINDICATIONS TO VACCINATION ....................................................... 16

5 CONDUCT OF THE STUDY ............................................................................................. 17
   5.1 ETHICS AND REGULATORY CONSIDERATIONS ............................................. 17
      5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) ........ 17
      5.1.2 Informed consent ......................................................................................... 18
   5.2 GENERAL STUDY ASPECTS .............................................................................. 20
   5.3 OUTLINE OF STUDY PROCEDURES ................................................................... 21
   5.4 DETAILED DESCRIPTION OF STUDY STAGES/VISITS .................................... 22
   5.5 SAMPLE HANDLING AND ANALYSIS ................................................................... 27
      5.5.1 Treatment and storage of biological samples .............................................. 27
      5.5.2 Laboratory assays ....................................................................................... 27
      5.5.3 Serology plan .............................................................................................. 28
      5.5.4 Endpoints for suboptimal response ............................................................ 28

6 STUDY VACCINES AND ADMINISTRATION ............................................................... 29
   6.1 STUDY VACCINES ............................................................................................... 29
      6.1.1 SmithKline Beecham Biologicals’ recombinant hepatitis B vaccine: Engerix™B 29
      6.1.2 SmithKline Beecham Biologicals’ combined quadrivalent diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™-HB ........................................ 29
      6.1.3 SmithKline Beecham Biologicals’ Haemophilus influenzae type b conjugate vaccine: Hiberix™ .......................................................... 30
   6.2 DOSAGE AND ADMINISTRATION ......................................................................... 30
      6.2.1 Hepatitis B administration at birth ................................................................. 30
6.2.2 Extemporaneous mixing of the DTPw-HBV and Hib vaccines..................................30
6.2.3 Injection technique ..................................................................................................31
6.3 STORAGE ...................................................................................................................31
6.4 TREATMENT ALLOCATION AND RANDOMISATION .................................................31
6.5 METHOD OF BLINDING AND BREAKING THE STUDY BLIND ..................................31
6.6 REPLACEMENT OF UNUSABLE VACCINE DOSES ..................................................32
6.7 PACKAGING ..............................................................................................................32
6.8 VACCINE ACCOUNTABILITY ....................................................................................32
6.9 CONCOMITANT MEDICATION/TREATMENT ............................................................32
7 HEALTH ECONOMICS ................................................................................................33
7.1 OUTCOMES MEASUREMENT AND ANALYSIS .........................................................33
7.2 ECONOMIC DATA COLLECTION AND ANALYSES ..................................................33
8 ADVERSE EVENTS .......................................................................................................33
8.1 ELICITING AND DOCUMENTING ADVERSE EVENTS ..............................................33
8.1.1 Solicited adverse events..........................................................................................35
8.2 ASSESSMENT OF INTENSITY ...................................................................................36
8.3 ASSESSMENT OF CAUSALITY ..................................................................................37
8.4 FOLLOWING-UP OF ADVERSE EVENTS AND ASSESSMENT OF OUTCOME ..........38
8.5 SERIOUS ADVERSE EVENTS ..................................................................................38
8.5.1 Definition of a serious adverse event.................................................................38
8.5.2 Reporting serious adverse events .....................................................................40
8.6 TREATMENT OF ADVERSE EVENTS .....................................................................41
9 SUBJECT COMPLETION AND DROP-OUT ..................................................................41
9.1 DEFINITION ...............................................................................................................41
9.2 PROCEDURES FOR HANDLING DROP-OUTS ........................................................41
9.3 REASONS FOR DROP-OUT ......................................................................................41
10 DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES ...............42
10.1 PRIMARY ENDPOINT ...............................................................................................42
10.2 SECONDARY ENDPOINTS ......................................................................................42
10.3 STUDY COHORTS/DATA SETS TO BE EVALUATED ..............................................42
10.4 ESTIMATED SAMPLE SIZE ....................................................................................43
10.5 FINAL ANALYSES ....................................................................................................43
10.5.1 Analysis of demographics ..................................................................................43
10.5.2 Analysis of efficacy ............................................................................................43
10.5.3 Analysis of safety ................................................................................................45
10.6 PLANNED INTERIM ANALYSIS ............................................................................45
11 ADMINISTRATIVE MATTERS .....................................................................................45
APPENDIX A: WORLD MEDICAL ASSOCIATION DECLARATION OF HelsINKI
APPENDIX B: ADMINISTRATIVE MATTERS
APPENDIX C: OVERVIEW OF THE RECRUITMENT PLAN
APPENDIX D: HANDLING OF BIOLOGICAL SAMPLES COLLECTED BY THE INVESTIGATOR
APPENDIX E: SHIPMENT OF BIOLOGICAL SAMPLES
APPENDIX F: LABORATORY ASSAYS
APPENDIX G: VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY
APPENDIX H: PROTOCOL AMENDMENTS/MODIFICATIONS
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-BPT</td>
<td>antibody to <em>Bordetella pertussis</em></td>
</tr>
<tr>
<td>anti-HBs</td>
<td>antibody to hepatitis B surface antigen</td>
</tr>
<tr>
<td>anti-PRP</td>
<td>antibody to polyribosylribitol phosphate</td>
</tr>
<tr>
<td>B. pertussis</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CVI</td>
<td>Children’s Vaccine Initiative</td>
</tr>
<tr>
<td>DTPw</td>
<td>Diphtheria, Tetanus, Whole Cell Pertussis vaccine</td>
</tr>
<tr>
<td>DTPw-HBV</td>
<td>Combined Diphtheria, Tetanus, Whole Cell Pertussis and Hepatitis B Vaccine</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>EL.U</td>
<td>ELISA Units</td>
</tr>
<tr>
<td>EL.U/ml</td>
<td>ELISA Units per milliliter</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Program on Immunisation</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B Virus</td>
</tr>
<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td>IU</td>
<td>International Units</td>
</tr>
<tr>
<td>IU/ml</td>
<td>International Units per milliliter</td>
</tr>
<tr>
<td>LF</td>
<td>Limit Flocculation</td>
</tr>
<tr>
<td>mIU</td>
<td>milli-International Units</td>
</tr>
<tr>
<td>mIU/ml</td>
<td>milli-International Units per milliliter</td>
</tr>
<tr>
<td>ml</td>
<td>milliliter</td>
</tr>
<tr>
<td>mM</td>
<td>milli-Moles</td>
</tr>
<tr>
<td>OU</td>
<td>Opacity Units</td>
</tr>
<tr>
<td>PRP</td>
<td>Polyribosyl-Ribitol-Phosphate: polysaccharide component of the Hib bacterium capsule</td>
</tr>
<tr>
<td>r-DNA HBsAg</td>
<td>Recombinant Deoxyribonucleic Acid Hepatitis B Surface Antigen</td>
</tr>
<tr>
<td>RIA</td>
<td>Radioimmunoassay</td>
</tr>
<tr>
<td>SAGE</td>
<td>Scientific Advisory Group of Experts</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Glossary of terms

Subject(s): Term used throughout the protocol to denote the enrolled individual(s).

Medical Monitor: An individual medically qualified to assure the responsibilities of the sponsor especially as regards the ethics, clinical safety of a study and the assessment of adverse events.

Study Monitor: An individual assigned by and centrally located at SmithKline Beecham who is responsible for assuring proper conduct of a clinical study.

Site Monitor: An individual assigned by SmithKline Beecham who is responsible for assuring proper conduct of a clinical study at one or more investigational sites.

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

Evaluable: Meeting all eligibility criteria, complying with the procedures defined in the protocol, and, therefore, included in analysis (see Sections 4.4 and 10.3 for details on criteria for evaluability).

Protocol amendment: Any change in a clinical protocol which affects the safety of subjects, the scope, design, assessments or scientific validity of the clinical investigation, e.g., dose change, treatment, duration.

Protocol modification: Strictly, any change to a clinical protocol, which is not considered to be an amendment, e.g., changes to clarify (but not alter) design features or encourages greater compliance with the intent of the clinical trial protocol.

Conjugated vaccine: Vaccine in which the pathogenic antigen is linked to a more immunogenic ‘protein carrier’.

Whole-cell pertussis vaccine: Vaccine which consists of adsorbed, formalin-inactivated whole *Bordetella pertussis* bacteria
1 Introduction

The prevalence of hepatitis B (HBV) varies around the world from 4% in countries with low endemicity to 95% in countries with high endemicity. Different areas of the world are affected by different major routes of disease transmission: in hyperendemic areas it tends to be perinatal (infection transmitted from mother to infant either in utero, in the perinatal period or during the postnatal period), or horizontal (e.g. sibling to sibling). Up to 65-90% of these infants at risk of infection in infancy or childhood become chronic carriers themselves, serving as a continuous reservoir for hepatitis B transmission and the potential to develop hepatitis B-related diseases later in life including chronic hepatitis, cirrhosis and primary hepatocellular carcinoma. Therefore, it is essential that perinatal HBV infection be prevented. In areas of high endemicity where infants are at high risk of contracting hepatitis B infection in the first year of life, the goal is that the first dose of hepatitis B vaccine should be given at or as near birth as possible. SmithKline Beecham Biologicals’ recombinant hepatitis B vaccine, Engerix™-B, was first registered in 1986 and was approved for commercial use in Colombia in 1989, is universally accepted as a vaccine for administration to neonates at birth. 2 3 4

In 1991, faced with the failure of the “high risk” vaccination stratagem and the availability of a highly economical means of producing the hepatitis B vaccine in potentially unlimited quantities, the Global Advisory Group of the Expanded Program on Immunisation (EPI) recommended that countries with a carrier prevalence for hepatitis B of 8% or more should include hepatitis B vaccination in their notional infant immunisation programs by 1995 and that all countries should do so by 1997. This initiative required the addition of another series of inoculations into the recommended schedule for infants and children. The complicated logistics of administering different multi-dose vaccines that each requires several inoculations seemed a significant barrier to the successful universal immunization with hepatitis B vaccine. In view of this, the Scientific Advisory Group of Experts (SAGE) of the Children’s Vaccine Initiative (CVI) recommended in 1992 the development of hepatitis B combination vaccines based on the well-established and accepted diphtheria-tetanus-whole cell pertussis (DTPw) vaccine. The DTPw vaccine has been available since the 1940’s and has been part of the World Health Organisation’s (WHO) Expanded Program on Immunisation (EPI) since the late 1970’s.

SmithKline Beecham Biologicals (SB Biologicals) developed the first DTPw-Hepatitis B combination (DTPw-HBV) vaccine. Studies have shown it to be safe
and effective following a three dose primary course. Tritanrix™-HB has been commercially available in Europe since 1996 after approval by centralised procedure and was approved for commercial use in Colombia in June 1998.

Another infection which has gained focus of attention is Haemophilus influenzae type b (Hib), a leading cause of invasive bacterial illness such as meningitis and pneumonia among infants and children worldwide. Currently available evidence demonstrates that generalised use of Hib vaccine causes a fast and substantial decline (80% to virtually 100%) in invasive Hib disease and provides encouragement that elimination of invasive Hib disease is possible. Hib vaccination is currently incorporated in the universal childhood immunisation calendar in various countries and recently the WHO recommended the worldwide inclusion of Hib conjugate vaccines in infant immunisation programs, as appropriate to national capacities and priorities. Acceptance would be greatest if Hib vaccines would be available in combination with DTP-HBV combinations. SmithKline Beecham’s Hib conjugate vaccine (Hiberix™) was first registered for commercial use in April 1997 and has been registered in Colombia since May 1998.

Results of clinical studies performed in healthy neonates vaccinated with SmithKline Beecham Biologicals’ combined quadrivalent Tritanrix™-HB and Haemophilus influenzae type b (Hiberix™) vaccine mixed as a pentavalent vaccine in a single injection have proven that the combination of the DTPw-HBV and Hib vaccines had no negative impact on the immune response to vaccination against any of the 5 disease antigens nor on the safety profile. The combined use of the pentavalent DTPw-HBV (Tritanrix™-HB) with Hib (Hiberix™) is licensed by centralised procedure in European countries. With this pentavalent combination, children will be protected with 3 injections against 5 diseases, whereas in the past 9 injections were needed to reach this goal.

This study will assess the immunogenicity, safety and reactogenicity of syringe-mixing of SmithKline Beecham Biologicals’ DTPw-HBV and Hib conjugate vaccines in infants previously primed with a birth dose of SmithKline Beecham Biologicals’ hepatitis B vaccine. The rationale for this study is to assess the kinetics of antibody response to the recombinant hepatitis B surface antigen administered according to this regime.

Please refer to the Investigator Brochure for Hiberix™ for a review of the preclinical and clinical studies with this vaccine as well as the clinical studies with the combined DTPw-HBV and Hib vaccines. Please refer to the Master Data
Sheets for Tritanrix™-HB and Engerix™-B that serve as a reference documents for these vaccines.

2 Objectives

2.1 Primary objective

To assess the antibody response to the recombinant hepatitis B surface antigen

See Section 10.1 for delineation of primary endpoint.

2.2 Secondary objectives

To assess the antibody response to all other vaccine antigens: diphtheria and tetanus toxoids, whole cell *Bordetella pertussis* and the Hib capsular polysaccharide polyribosyl-ribitol phosphate (PRP)

To assess the safety and reactogenicity of the vaccines

See Section 10.2 for delineation of secondary endpoints.

3 Study Design Overview

- Experimental design: open study with a single group

- Indication: three-dose immunisation course against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b in the 1st year of life in infants previously primed with a birth dose of hepatitis B vaccine

- Control: none

- Treatment allocation: All subjects will receive SmithKline Beecham Biologicals’ combined DTPw-HBV and Hib conjugate vaccines extemporaneously mixed and administered as a single injection at 2, 4 and 6 months of age subsequent to a birth dose of SmithKline Beecham Biologicals’ hepatitis B vaccine.

- The study is self-contained, i.e., the study is not designed as an extension of one or more existing protocols nor is it planned to be combined with other protocols for a joint analysis
• Subjects will receive a study number in the order in which they are enrolled into the study at birth. The study number will serve as subject identifier for all data collected under the study.

• For each individual subject, the duration of the study will be approximately 7 months.

• It is expected that all subjects will be enrolled within 13 weeks of study initiation. Details of the recruitment plan are summarised in Appendix C.

• Data collection: hard copy Case Report Form (CRF).

• Replacement of unusable vaccine doses: In addition to the number of vials for the planned number of subjects, 5% additional doses will be provided to replace broken or lost vials.

4 Study Cohort

4.1 Number of subjects / centres

Target enrolment will be 120 eligible subjects at birth to ensure a minimum of 100 eligible healthy male and female infants between 6 to 10 weeks of age at the time of the first dose of the three-dose vaccination course. Enrolment will be terminated when 120 subjects have been enrolled at birth. Drop-outs will not be replaced.

Only subjects for whom the investigator believes the requirements of the protocol will be complied with (e.g. completion of the diary cards, return for follow-up visits) should be enrolled in the study.

An overview of the recruitment plan is provided in Appendix C of this document.

Investigator Dr. [Redacted]
Study centre [Redacted]

Colombia
4.2 Inclusion criteria for enrolment at birth

All subjects must satisfy the following criteria at birth:
- Written informed consent obtained from the parents or guardians of the subject.
- Born after a normal gestation period (between 36 and 42 weeks).
- Free of obvious health problems as established by medical history of pregnancy and clinical examination before entering into the study.

4.3 Exclusion criteria for enrolment at birth

The following criteria should be checked at birth. If any apply at the time of birth, the subject must not be considered for enrolment:
- A family history of congenital or hereditary immunodeficiency.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- Major congenital defect(s).

4.4 Inclusion criteria for administration of the mixed vaccines

All subjects enrolled must satisfy the following criteria at study entry:
- A male or female between, and including, 6 and 10 weeks of age at the time of the first dose of the three-dose course of vaccination.
- Free of obvious health problems as established by medical history and clinical examination before entering into the study.

4.5 Exclusion criteria for administration of the mixed vaccines

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study:
- Use of any investigational or non-registered drug or vaccine other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs since birth. (For corticosteroids, this will mean prednisone, or equivalent, \( \geq 0.5 \text{ mg/kg/day} \). Inhaled and topical steroids are allowed.)
- Any chronic drug therapy to be continued during the study period.
- Planned administration/administration of a vaccine except oral polio vaccine (OPV) or Bacille Calmette-Guérin (BCG) vaccine during the period starting from 30 days before each dose of vaccines and ending 30 days after.
- Previous vaccination against diphtheria, tetanus, pertussis or *Haemophilus influenzae* type b disease.
- History of, or intercurrent, diphtheria, tetanus, pertussis, hepatitis B and/or Hib disease.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
- A family history of congenital or hereditary immunodeficiency.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Serious chronic illness.
- History of any neurologic disorders or seizures.
- Acute disease at the time of enrolment. (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., axillary temperature <37.5°C.)
- Administration of immunoglobulins and/or any blood products during the study period.

### 4.6 Elimination criteria during the study

The following criteria should be checked at each visit subsequent to the first visit of the three-dose immunisation course. If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from analysis. See Section 10.3 for definition of study cohorts/datasets to be evaluated.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune modifying drugs. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of vaccines and ending 30 days after, with the exception of oral polio vaccine (OPV) or Bacille Calmette-Guérin (BCG) vaccine.
- Administration of immunoglobulins and/or any blood products during the study period.
4.7 Contraindications to vaccination

The following adverse events constitute contraindications to administration of the vaccines at that point in time; if any one of these adverse events occurs 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 5.3), or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event as with any adverse event (see Section 8.4).

- 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., axillary temperature of <37.5°C.)
- Axillary temperature of ≥37.5°C at the time of vaccination.

The following adverse events constitute absolute contraindications to further administration of the vaccines; if any of these adverse events occur during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event (see Section 8.4):

- Anaphylactic reaction following the administration of vaccines.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.

The following adverse events associated with DTP vaccination constitute absolute contraindications to further administration of DTP; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event (see Section 8.4)

**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 consisting of major alterations in consciousness, unresponsiveness, generalised or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

**Precautions:**

- Fever ≥ 40°C (axillary 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.

5 Conduct of the Study

5.1 Ethics and regulatory considerations

The study will be conducted according to Good Clinical Practice, the Declaration of Helsinki (Protocol Appendix A and local rules and regulations of the country.

5.1.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The IRB/IEC must be constituted according to the local laws/customs of each participating country. It is recommended that it should include:
(a) At least five members.
(b) At least one member whose primary area of interest is in a non-scientific area.
(c) At least one member who is independent of the institution/ study site.
Only those IRB/IEC members who are independent of the investigator and the sponsor of the study should vote/ provide opinion [delete as appropriate] on a study-related matter.

A list of IRB/IEC members and their qualifications should be obtained by

This protocol and any other documents that the IRB/IEC may need to fulfil its responsibilities, including subject recruitment procedures, and information about payments and compensation available to subjects, will be submitted to an appropriate Committee or Board by the investigator, and their written unconditional approval should be in the possession of the investigator and the sponsor before commencement of the study. Relevant SmithKline Beecham Biologicals data will be supplied by the hospital/ university/ independent IRB/IEC for the protocol's review and approval. Verification of IRB/IEC unconditional approval of the protocol and the written informed consent statement will be transmitted by the investigator to the investigator using the standard notification form, generally prior to shipment of vaccine supplies and CRFs to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and state the date of review.
No deviations from, or changes to, the protocol should be initiated without prior written IRB/IEC approval/ favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). Modifications are submitted to the IRB/IEC for information only. However, written verification that the modification was submitted should be obtained. Approvals/ verifications must be transmitted in writing to [redacted] by the investigator.

The IRB/IEC must be informed by the investigator of
- all subsequent protocol amendments, informed consent changes or revisions of other documents originally submitted for review
- serious and/or unexpected adverse events occurring during the study, where required
- all subsequent protocol modifications (for information)
- new information that may affect adversely the safety of the subjects or the conduct of the study
- an annual update and/or request for re-approval, where required
- when the study has been completed, where required.

5.1.2 Informed consent

The principles of informed consent in the current edition of the Declaration of Helsinki (Protocol Appendix A) should be implemented in each clinical study before any protocol-specified procedures or interventions are carried out.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki as revised in 1996 and will also comply with local regulations. This form may be read to the subject and/or the subject's legally authorised representative, but, in any event, the investigator shall give the subject and/or the representative adequate opportunity to inquire about the form is signed.

Subjects and/or their legally-authorised representative must be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject [or to the embryo or foetus, if the subject is or may become pregnant] which are currently
unforeseeable) and procedures of the research study). They must also be informed of alternative procedures. Subjects and/or their legally-authorised representative must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact (e.g. the investigator) for answers to any questions relating to the research project. The subjects and/or their legally-authorised representative must be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of the confidentiality of subject records must be defined, and subjects must be informed that applicable data protection legislation will be complied with. Subjects must be informed that the monitor(s), auditor(s), IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject and/or the subject's legally authorised representative is authorising such access.

The consent form generated by the investigator with the assistance of SmithKline Beecham Biologicals, must be approved (along with the protocol, and any other necessary documentation) by the IRB/IEC and be acceptable to SmithKline Beecham Biologicals. Consent forms must be in a language fully comprehensible to the prospective subject. Informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject and/or the subject's legally authorised representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or SmithKline Beecham professional and Regulatory Compliance persons. The subject and/or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects. Oral witnessed consent will replace written consent only in countries where the local custom is contrary or if the subject’s incapacity precludes this and provided that the local legal obligations are fulfilled.
5.2 General study aspects

Oral Polio Vaccine (OPV) and/or Bacille Calmette-Guérin (BCG) vaccine administration (according to local schedule) during the study will be documented in the concomitant vaccination section of the individual Case Report Form.
### 5.3 Outline of study procedures

<table>
<thead>
<tr>
<th>AGE VISIT TIMING</th>
<th>BIRTH VISIT 1 DAY 0/MONTH 0 PRE</th>
<th>6-10 WEEKS VISIT 2 MONTH 2</th>
<th>4 MONTHS VISIT 3 MONTH 4 POST VACC II</th>
<th>6 MONTHS VISIT 4 MONTH 6 POST VACC III</th>
<th>7 MONTHS VISIT 5 MONTH 7 POST VACC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD SAMPLING TIMEPOINT</td>
<td>Written informed consent from parents/guardians ● ●</td>
<td>Check of inclusion criteria for eligibility at birth ●</td>
<td>Check of exclusion criteria for eligibility at birth ●</td>
<td>Physical examination ● ● ● ● ●</td>
<td>Check of inclusion criteria for 3-dose mixed vaccine course ●</td>
</tr>
<tr>
<td></td>
<td>Peripheral blood sampling for antibody determination (3 ml) ● ● ● ●</td>
<td>Vaccination ● ● ● ●</td>
<td>Daily post-vaccination recording of solicited symptoms (days 0–3) by parents/guardians ● ● ● ●</td>
<td>Recording of unsolicited adverse events occurring one month (30 days) post-vaccination, by investigator ● ● ● ●</td>
<td>Return of diary cards ● ● ● ●</td>
</tr>
</tbody>
</table>

*SmithKline Beecham Biologicals’ hepatitis B vaccine (Engerix™-B); **SmithKline Beecham Biologicals’ DTPw-HBV (Tritanrix™-HB) and Hib (Hiberix™) vaccines extemporaneously mixed and administered as a single injection; * is used to indicate a study procedure which requires documentation in the individual CRF.

1. Medical history of pregnancy – See Section 4.2 Inclusion criteria for enrolment at birth
2. Medical history since birth – See Section 4.4 Inclusion criteria for administration of the mixed vaccines
It is the investigator’s responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject’s evaulability in the according to protocol analyses (see Sections 4.4 and 10.3 for details of criteria for evaluability and cohorts to be analysed).

Intervals between study visits*

<table>
<thead>
<tr>
<th>Interval</th>
<th>Size of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Visit 1→Visit 2)</td>
<td>6-10 weeks</td>
</tr>
<tr>
<td>2 (Visit 2→Visit 3)</td>
<td>56-70 days</td>
</tr>
<tr>
<td>3 (Visit 3→Visit 4)</td>
<td>56-70 days</td>
</tr>
<tr>
<td>4 (Visit 4→Visit 5)</td>
<td>30-35 days</td>
</tr>
</tbody>
</table>

*The date of the previous visit is the reference date.

5.4 Detailed description of study stages/visits

Visit 1: (Birth)

- Written informed consent from the parents/guardians for infant participation
- Collection of cord blood sample blood sample for serology: a minimum of 3 ml of whole blood according to instructions in Appendix D (Amended: May 31, 2000)

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all serum samples be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

- Check of inclusion criteria for enrolment at birth (See Section 4.2)
- Check of exclusion criteria for enrolment at birth (See Section 4.3)
- Physical examination by the investigator and axillary body temperature recording
- Infants will be assigned a study number in the order of enrolment beginning with the number 1. This number will serve as a subject identifier for all data collected under the study.
- Individual Case Report Forms (CRF) will be filled in by the investigator.
- Check of contraindications to vaccination (See Section 4.7)
- Pre-vaccination assessment of adverse events (See Section 8.1.1.)
- Vaccination: intramuscular administration of one dose of SmithKline Beecham Biologicals’ hepatitis B vaccine in the anterolateral thigh, according to guidelines set out in Section 6.2
The vaccinees will be observed closely for at least 15 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

- Diary cards will be provided for the parents/guardians to record axillary temperature and any local (at the injection site) or general adverse events occurring on the day of vaccination (day 0) and during the 3 subsequent days (days 1-3). The parents/guardians will record this data on the diary cards in the evening (See Section 8.1.1.). The parents/guardians will return their completed diary card to the investigator at the next visit.

The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

Visit 2: At 6—10 weeks of age

- Check of inclusion criteria for administration of the mixed vaccines (See Section 4.4)
- Check of exclusion criteria for administration of the mixed vaccines (See Section 4.5)
- Check of elimination criteria (See Section 4.6.)
- Medical history taking
- Recording of any concomitant medication (See Section 6.9.)
- The parents/guardians will return their completed diary card to the investigator. The investigator will collect and verify them. He will transcribe the information into the appropriate sections of the case report form, in English. Any unreturned cards will be sought from the parents/guardians through any convenient procedure.
- Recording of any unsolicited adverse events which might have occurred within 30 days following the previous vaccination (See Section 8.1.)
- Physical examination by the investigator and axillary body temperature recording
- Check of contraindications for vaccination (See Section 4.7.)
- Pre-vaccination assessment of adverse events (See Section 8.1.1)
- Vaccination: intramuscular administration of one dose of each of the study vaccines, combined in a single injection, in the left anterolateral thigh, according to the guidelines set out in Section 6.2

The vaccinees will be observed closely for at least 15 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.

Important: concomitant administration of any other vaccine with the
exception of OPV and/or BCG is not permitted. Concomitant administration of OPV and/or BCG vaccine will be recorded in the concomitant vaccination section of the CRF.

- Diary cards will be provided for the parents/guardians to record axillary temperature and any local (at the injection site) or general adverse events occurring on the day of vaccination (day 0) and during the 3 subsequent days (days 1-3). The parents/guardians will record this data on the diary cards in the evening (See Section 8.1.1.). The parents/guardians will return their completed diary card to the investigator at the next visit.

The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

### Visit 3: At 4 months of age (56—70 days after Visit 2)

- Check of elimination criteria (See Section 4.6)
- Recording of any concomitant medication (See Section 6.9.)
- The parents/guardians will return their completed diary card to the investigator. The investigator will collect and verify them. He will transcribe the information into the appropriate sections of the case report form, in English. Any unreturned cards will be sought from the parents/guardians through any convenient procedure.
- Recording of any unsolicited adverse events which might have occurred within 30 days following the previous vaccination (See Section 8.1.)
- Physical examination by the investigator and axillary body temperature recording
- Check of contraindications for vaccination (See Section 4.7.)
- Pre-vaccination assessment of adverse events (See Section 8.1.1.)

Collection of blood sample for serology: a **minimum of 3 ml of whole blood** according to instructions in Appendix D

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all serum samples be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

- Vaccination: intramuscular administration of one dose of each of the study vaccines, combined in a single injection, in the left anterolateral thigh, according to the guidelines set out in Section 6.2

The vaccinees will be observed closely for at least 15 minutes, with
appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.**Important:** concomitant administration of any other vaccine with the exception of OPV and/or BCG is not permitted. Concomitant administration of OPV and/or BCG vaccine will be recorded in the concomitant vaccination section of the CRF.

- Diary cards will be provided for the parents/guardians to record axillary temperature and any local (at the injection site) or general adverse events occurring on the day of vaccination (day 0) and during the 3 subsequent days (days 1-3). The parents/guardians will record this data on the diary cards in the evening (See Section 8.1.1.). The parents/guardians will return their completed diary card to the investigator at the next visit. **The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.**

### Visit 4: At 6 months of age (56—70 days after Visit 3)

- Check of elimination criteria (See Section 4.6)
- Recording of any concomitant medication (See Section 6.9.)
- The parents/guardians will return their completed diary card to the investigator. The investigator will collect and verify them. He will transcribe the information into the appropriate sections of the case report form, in English. Any unreturned cards will be sought from the parents/guardians through any convenient procedure.
- Recording of any unsolicited adverse events which might have occurred within 30 days following the previous vaccination (See Section 8.1.)
- Physical examination by the investigator and axillary body temperature recording
- Check of contraindications for vaccination (See Section 4.7.)
- Pre-vaccination assessment of adverse events (See Section 8.1.1.)
- Collection of blood sample for serology: a **minimum of 3 ml of whole blood** according to instructions in Appendix D

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all serum samples be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

- Vaccination: intramuscular administration of one dose of each of the
study vaccines, combined in a single injection, in the left anterolateral
thigh, according to the guidelines set out in Section 6.2

The vaccinees will be observed closely for at least 15 minutes, with
appropriate medical treatment readily available in case of a rare
anaphylactic reaction following the administration of vaccines.

**Important:** concomitant administration of any other vaccine with the
exception of OPV and/or BCG is not permitted.

Concomitant administration of OPV and/or BCG vaccine will be
recorded in the concomitant vaccination section of the CRF.

- Diary cards will be provided for the parents/guardians to record axillary
temperature and any local (at the injection site) or general adverse events
occurring on the day of vaccination (day 0) and during the 3 subsequent
days (days 1-3). The parents/guardians will record this data on the diary
cards in the evening (See Section 8.1.1.). The parents/guardians will
return their completed diary card to the investigator at the next visit.

**The parents/guardians will be instructed to contact the investigator
immediately should the subject manifest any signs or symptoms they
perceive as serious.**

<table>
<thead>
<tr>
<th>Visit 5: At 7 months of age (30—35 days after Visit 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Check of elimination criteria (See Section 4.6)</td>
</tr>
<tr>
<td>- Recording of any concomitant medication (See Section 6.9.)</td>
</tr>
<tr>
<td>- The parents/guardians will return their completed diary card to the investigator. The investigator will collect and verify them. He will transcribe the information into the appropriate sections of the case report form, in English. Any unreturned cards will be sought from the parents/guardians through any convenient procedure.</td>
</tr>
<tr>
<td>- Recording of any unsolicited adverse events which might have occurred within 30 days following the previous vaccination (See Section 8.1.)</td>
</tr>
<tr>
<td>- Physical examination by the investigator and axillary body temperature recording</td>
</tr>
<tr>
<td>- Collection of blood sample for serology: <strong>a minimum of 3 ml of whole blood</strong> according to instructions in Appendix D</td>
</tr>
</tbody>
</table>

When materials are provided by SmithKline Beecham Biologicals, it is
mandatory that all serum samples be collected using exclusively those
materials in the appropriate manner. The use of other materials could
result in the exclusion of the subject from analysis. The investigator must
ensure that his/her personnel and the laboratory(ies) under his/her
supervision comply with this requirement.
Study Conclusion

5.5 Sample handling and analysis

5.5.1 Treatment and storage of biological samples

See Appendix D of the protocol for details of treatment and storage of pre- and post-vaccination serum samples. The separated pre- and post-vaccination serum samples will be stored at temperatures between -20°C and -70°C for later measurements in SmithKline Beecham Biologicals' laboratory.

See Appendix E for instructions for shipment of biological samples.

5.5.2 Laboratory assays

The presence of antibody to the recombinant hepatitis B surface antigen (anti-HBs) titres will be determined using radioimmunoassay (AUSAB, Abbott) and titres will be calculated in milli-international units per ml (mIU/ml) as described by Hollinger, et al.\textsuperscript{15} The assay cut-off used for this study is 10 mIU/ml, the level which is generally accepted to be protective.\textsuperscript{16-17,19-20} Antibodies to the Hib polysaccharide PRP (anti-PRP) will be measured by Enzyme-Linked Immunosorbent Assay (ELISA) technique. The cut-off of the test is 0.15 micrograms per milliliter (mcg/ml).

Antibodies to the whole cell \textit{Bordetella pertussis} antigen (anti-BPT) will be assayed by ELISA using the IgG EIA test kit, Labsystems, and expressed in ELISA Units per ml (EL.U/ml), with an assay cut-off of 15 EL.U/ml.

Anti-diphtheria and anti-tetanus titres will be measured by ELISA and expressed in international units per ml (IU/ml).\textsuperscript{22} It is generally accepted that for both diphtheria and tetanus, titres $\geq 0.01$ IU/ml, as measured by \textit{in vivo} neutralisation tests, are protective. It has been previously demonstrated that a good correlation exists between \textit{in vivo} neutralisation tests and the ELISAs\textsuperscript{23-24} for antibodies to diphtheria and tetanus toxoids but this correlation may be reduced at antibody titres $<0.1$ IU/ml. For this reason, a titre of 0.1 IU/ml by ELISA will be arbitrarily and conservatively set as the cut-off (for both anti-diphtheria and anti-tetanus ELISAs).
5.5.3 Serology plan

Pre- (Month 0) and post-vaccination (Month 4, 6 and 7) serum samples will be tested in all subjects for antibodies against all vaccine antigens [hepatitis B surface antigen, PRP, pertussis antigen, diphtheria and tetanus toxoids].

In case of insufficient blood sample volume to perform assays for all antibodies, they will be analysed according to the following priority ranking:

- anti-HBs
- anti-PRP
- anti-BPT
- anti-tetanus
- anti-diphtheria

Any additional serology on antigens contained in the study vaccines will be performed if deemed necessary by SmithKline Beecham Biologicals if any findings in the present study or in other studies necessitate investigation of the immunogenicity of the vaccine. In this case, the ranking above may also be changed.

5.5.4 Endpoints for suboptimal response

An additional dose of licensed vaccines will be offered to subjects who, after the three dose primary series demonstrate a suboptimal response to any of the antigens contained in the vaccines.

Suboptimal response will be defined as follows:

anti-HBs titre \(<10 \text{ mIU/ml}\)
Anti-PRP titre \(<0.15 \text{ mcg/ml}\)
anti-BPT titre \(<15 \text{ EL.U/ml}\)
anti-tetanus titre \(<0.1 \text{ IU/ml}\)
anti-diphtheria titre \(<0.1 \text{ IU/ml}\)

Since booster immunisations are not generally provided for hepatitis B (until 4 to 6 years of age), subjects who demonstrate a suboptimal response to either of these vaccines will be offered an additional dose of hepatitis B vaccine.

Subjects who demonstrate a suboptimal response to the Hib conjugate vaccine after the primary series and who have not yet received a booster dose of Hib vaccine will be contacted and will be requested to present early for an additional dose of vaccine. For subjects who demonstrate a suboptimal response to the Hib
conjugate vaccine after the primary series and have already received their booster immunization, no additional vaccination will be provided.

Subjects who demonstrate a suboptimal response to one or more antigen(s) in the DTP vaccine after the primary series will receive their booster dose of licensed DTP at 12-18 months as is routine.

6 Study Vaccines and Administration

6.1 Study vaccines

The vaccines to be used in this study have been developed and manufactured by SmithKline Beecham Biologicals. The Quality Control Standards and Requirements for each vaccine are described in separate release protocols and the required approvals have been obtained. Commercial vaccines comply with the specifications given in the manufacturer's Summary of Product Characteristics.

One lot of each of the vaccines will be used.

Appendix G provides details of vaccine supplies.

6.1.1 SmithKline Beecham Biologicals’ recombinant hepatitis B vaccine: Engerix™-B

Engerix™-B has been registered for commercial use in Colombia since 1989. The vaccine will be supplied in monodose vials. One dose (0.5 ml) contains the following components:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>recombinant hepatitis B surface antigen (r-DNA HBsAg)</td>
<td>10 mcg</td>
</tr>
<tr>
<td>aluminium as salts</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>thiomersal</td>
<td>25 mcg</td>
</tr>
</tbody>
</table>

in a sterile saline solution (150 mM NaCl)

6.1.2 SmithKline Beecham Biologicals’ combined quadrivalent diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™-HB

Tritanrix™-HB has been registered for commercial use in Colombia since June 1998.
The vaccine will be supplied as a whitish liquid in monodose vials. One dose (0.5 ml) contains the following components:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>diphtheria toxoid</td>
<td>not less than 30 IU (7.5 Lf)</td>
</tr>
<tr>
<td>tetanus toxoid</td>
<td>not less than 60 IU (3.25 Lf)</td>
</tr>
<tr>
<td><em>Bordetella pertussis</em>, killed</td>
<td>not less than 2 IU (15 OU)</td>
</tr>
<tr>
<td>r-DNA HBsAg</td>
<td>10 mcg</td>
</tr>
<tr>
<td>aluminium (as salts)</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>2-phenoxyethanol</td>
<td>50 mcg</td>
</tr>
<tr>
<td></td>
<td>in a sterile saline solution (150 mM NaCl)</td>
</tr>
</tbody>
</table>

6.1.3 SmithKline Beecham Biologicals’ *Haemophilus influenzae* type b conjugate vaccine: Hiberix™

Hiberix™ has been registered for commercial use in Colombia since May 1998.

This vaccine will be supplied as a white freeze dried pellet in monodose vials to be reconstituted before use with the liquid DTPw-HBV vaccine (Tritanrix™-HB). One dose contains the following components:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugate of <em>Haemophilus influenzae</em> type b capsular polysaccharide (PRP) and Tetanus toxoid (T)</td>
<td>10 mcg PRP (20 to 40 mcg of T)</td>
</tr>
<tr>
<td>Lactose</td>
<td>12.6 mg</td>
</tr>
</tbody>
</table>

6.2 Dosage and administration

6.2.1 Hepatitis B administration at birth

The liquid hepatitis B vaccine (Engerix™-B) should always be shaken before use. One dose (0.5 ml) of the hepatitis B vaccine should be administered by intramuscular injection into the left anterolateral thigh.

6.2.2 Extemporaneous mixing of the DTPw-HBV and Hib vaccines

The liquid DTPw-HBV vaccine should always be shaken before use. The full content of the DTPw-HBV vaccine vial should be extracted and injected into the vial containing the lyophilised Hib conjugate vaccine. The vial should be agitated until the lyophilised Hib vaccine pellet has completely dissolved. The mixed
vaccines will appear white. The reconstituted DTPw-HBV/Hib mixed vaccines should be used promptly after reconstitution (within 30 minutes):

- withdraw the full volume of the mixed vaccines from the vial;
- the needle should be changed before injection;
- one dose (0.5 ml) of the mixed DTPw-HBV/Hib vaccines should be administered by intramuscular injection into the left anterolateral thigh.

### 6.2.3 Injection technique

In order to ensure proper intramuscular injection of the study vaccines, a needle of at least 1 inch (2.54 cm) length and 25 gauge will be used. The following injection technique is recommended:

The needle should be inserted in the upper lateral quadrant of the thigh, directed inferiorly at an angle of 45 degrees with the long axis of the leg, and posteriorly at a 45-degree angle to the tabletop, with the subject supine. During the injection, the tissues of the injection site are compressed with the free hand, increasing the penetrable muscle mass and stabilising the extremity.

**The vaccinees will be observed closely for at least 15 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccines.**

### 6.3 Storage

All vaccines must be stored in a safe and locked place with no access for unauthorised personnel. They must be kept in the refrigerator (+2°C to +8°C/36°F to 46°F) and must not be frozen. Storage temperature should be monitored at least once per week. It is advisable to have a back-up refrigerator in case of power failure/breakdown.

### 6.4 Treatment allocation and randomisation

Not applicable. All subjects will receive the same vaccination regimen.

### 6.5 Method of blinding and breaking the study blind

Not applicable. The study is open label and non-blinded.
6.6 Replacement of unusable vaccine doses

Additional vaccine doses will be provided to replace those that are unusable (see Appendix G for details of supplies).

In addition to the vials numbered from 1 up to the planned number of subjects, 5% additional doses of each vaccine will be supplied. In case a vial of vaccine is broken, the investigator should replace it with replacement vaccine vial. Although the sponsor need not be notified immediately in these cases, documentation of the procedure and reason for using it must be recorded by the investigator on the vaccine accountability form.

6.7 Packaging

See Appendix G.

6.8 Vaccine accountability

See Appendix G.

6.9 Concomitant medication/treatment

At each study visit/contact, the investigator should question the subject or their legal representative about any medication taken.

Concomitant medication—including any vaccine other than the study vaccines, and any other medication relevant to the protocol, including any specifically contraindicated—administered during the period starting from one week before each dose and ending one month (maximum 30 days) after must be recorded in the CRF with tradename and/ or generic name of the medication, medical indication, start and end dates of treatment. It must also be recorded whether the medication was given

- prophylactically in anticipation of reaction to the vaccination (coded as ‘P’ in the CRF)
- as therapy for an existing symptom (coded as ‘T’ in the CRF).
- neither of the above (coded as ‘N’ in the CRF).

Medications, which do not need to be recorded, include any homeopathic remedies, vitamins, minerals and any other dietary supplements.
7 Health Economics

Not applicable.

7.1 Outcomes measurement and analysis

Not applicable.

7.2 Economic data collection and analyses

Not applicable.

8 Adverse Events

The recording of adverse events is an important aspect of study documentation. It is the responsibility of the investigator to document all adverse events according to the detailed guidelines set out below.

The parents/guardians will be instructed to contact the investigator immediately should the subject manifest any signs or symptoms they perceive as serious.

8.1 Eliciting and documenting adverse events

Adverse event definition

An adverse event includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical study whether associated with the study vaccine, active comparator or placebo and whether or not considered vaccination related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, or vaccine or drug interaction. Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation need not be considered adverse events. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse events in order to assess changes in frequency or severity.

Adverse events should be documented in terms of a medical diagnosis(es). When this is not possible, the adverse event should be documented in terms of signs
and/or symptoms observed by the investigator or reported by the subject at each study visit.

Pre-existing conditions or signs and/or symptoms (including any which are not recognised at study entry but are recognised during the study period) present in a subject prior to the administration of the mixed vaccines should be recorded on the Medical History form within the subject's CRF. Any of the signs or symptoms to be solicited present during physical examination of the subject at each vaccination visit should be recorded on the Pre-Vaccination Assessment page of the subject's CRF.

Adverse events that occur after informed consent is obtained, but prior to administration of the mixed vaccines, will be documented the Medical History form within the subject's CRF as instructed by the SmithKline Beecham Study Monitor.

In the case of open studies involving a marketed drug or vaccine in an established indication, an adverse event includes significant failure of expected pharmacological or biological action.

Although not considered as an adverse event, hospitalisation for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study, or for routine clinical procedures (including hospitalisation for “social” reasons) that are not the result of an adverse event, must be recorded in the CRF. If the hospitalisation arises from a pre-existing condition, or was planned prior to the first vaccination, it should be recorded in the Medical History form of the CRF. If it was planned after the first vaccination, it should be recorded in the adverse event page of the CRF. In both cases, it should be recorded as ‘Hospitalisation (Not an adverse event)’, and the relationship will be Not Related to vaccination.

N.B. Adverse events to be recorded as endpoints are described in Section 8.1.1. All other adverse events will be recorded as unsolicited adverse events.

**Surveillance period for occurrence of adverse events**

All adverse events occurring within one month (maximum 30 days) following administration of each dose of mixed vaccines must be recorded on the Adverse Event form in the subject's CRF, irrespective of severity or whether or not they are considered vaccination-related.

Additionally, all serious adverse events (see Section 8.5) occurring during the period starting from the day of administration of the birth dose of hepatitis B
vaccine to each subject and ending within one month (maximum 30 days) of administration of the last dose of study vaccine for that subject must be recorded. See Section 8.5.2 for instructions for reporting and recording of serious adverse events.

Instances of death, cancer or congenital abnormality in offspring if brought to the attention of the investigator AT ANY TIME after cessation of study AND suspected by the investigator to be related to study vaccine, should be reported to the Study Monitor.

Recording adverse events
At each visit/assessment, all adverse events either observed by the investigator or one of his clinical collaborators or reported by the parents/guardians spontaneously or in response to a direct question will be evaluated by the investigator. Adverse events not previously documented in the study will be recorded in the Adverse Event form within the subject's CRF. The nature of each event, date and time (where appropriate) of onset, outcome, intensity and relationship to vaccination should be established. Details of any corrective treatment should be recorded on the appropriate page of the CRF. See Section 8.5.2 for instructions for reporting and recording of Serious Adverse Events.

As a consistent method of soliciting adverse events, the parents/guardians 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?"

N.B. The investigator should record only those adverse events having occurred within the time frames defined above.

Adverse events already documented in the CRF, i.e. at a previous assessment, and designated as ‘ongoing’ should be reviewed at subsequent visits, as necessary. If these have resolved, the documentation in the CRF should be completed. N.B. If an adverse event changes in frequency or intensity during a study period, a new record of the event will be started.

8.1.1 Solicited adverse events
A four-day follow-up (day 0 to 3) of solicited adverse events will be performed by the parents/guardians after vaccination. Data concerning the following adverse events will be solicited using diary cards provided by the sponsor:
Local (injection site) adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at injection site</td>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Minor reaction to touch</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Cries/protests on touch</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Cries when limb is moved/spontaneously painful</td>
</tr>
<tr>
<td>Redness at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
<tr>
<td>Swelling at injection site</td>
<td></td>
<td>Record greatest surface diameter in mm</td>
</tr>
</tbody>
</table>

General adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Intensity grade</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>Behaviour as usual</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Drowsiness easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Drowsiness that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Drowsiness that prevents normal activity</td>
</tr>
<tr>
<td>Fever*</td>
<td></td>
<td>Record temperature in °C</td>
</tr>
<tr>
<td>Irritability/ Fussiness</td>
<td>0</td>
<td>Behaviour as usual</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Crying more than usual/ no effect on normal activity</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Crying more than usual/ interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>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>Drowsiness easily tolerated</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Drowsiness that interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Drowsiness that prevents normal activity</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Eating less than usual/ no effect on normal activity</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Eating less than usual/ interferes with normal activity</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Not eating at all</td>
</tr>
</tbody>
</table>

N.B. Axillary temperature will be recorded in the evening. Should temperature measurement additionally be performed at another time of day, the highest temperature will be recorded.

8.2 Assessment of intensity

Intensity of the following adverse events should be assessed as described:

*Fever is defined as axillary temperature ≥ 37.5°C

For each solicited symptom, parents/guardians of the subjects will be asked if they sought medical advice (i.e. contact with a member of medical personnel) for this symptom.
For all other adverse events, maximum intensity should be assigned to one of the following categories:

0 = No adverse event
1 = An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 = An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3 = An adverse event which prevents normal, everyday activities.
   (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/ a day-care centre and would cause the parents/ guardians to seek medical advice.)

8.3 Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any, to administration of the study vaccines.

In case of concomitant administration of multiple vaccines, it will not be possible to determine causal relationship of general adverse events to the individual vaccines administered. The investigator should, therefore, assess whether the adverse event 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 adverse events should be assessed by the investigator using the following categories: not related, unlikely, suspected (reasonable possibility), probable.

NR = Not related  The adverse event is definitely not causally related to administration of the study vaccine(s).
UL = Unlikely  There are other, more likely causes and administration of the study vaccine(s) is not suspected as a cause.
SU = Suspected (reasonable possibility)

A direct cause and effect relationship between administration of the study vaccine(s) and the adverse event has not been demonstrated but there is a reasonable possibility that the event was caused by administration of the study vaccine(s).
PB = Probable

There probably is a direct cause and effect relationship between the adverse event and administration of the study vaccine(s).

The degree of certainty with which an adverse event can be attributed to administration of the study vaccine(s) (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of vaccine and/or formulation.
- The event having often been reported in literature for similar types of vaccines.
- The event being temporally associated with vaccination or reproduced on re-vaccination.

### 8.4 Following-up of adverse events and assessment of outcome

Investigators should follow-up subjects with serious adverse events until the event has subsided (disappeared) or until the condition has stabilised. Investigators should follow-up subjects with non-serious adverse events until study conclusion for that subject. Reports relative to the subsequent course of an adverse event noted for any subject must be submitted to the Study Monitor.

Outcome should be assessed as

1 = Recovered
2 = Recovered with sequelae
3 = Ongoing at subject study conclusion
4 = Died
5 = Unknown

### 8.5 Serious adverse events

#### 8.5.1 Definition of a serious adverse event

A serious adverse event is any untoward medical occurrence that results in death, is life threatening*, results in persistent or significant disability/incapacity†, requires in-patient hospitalisation‡ or prolongation of existing hospitalisation or is a congenital anomaly/birth defect in the offspring of a study subject. In addition,
important medical events that may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such treatments are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.)

Although not considered as ‘serious adverse events’, pregnancies and cancers should be reported in the same way as serious adverse events.

*Life threatening—definition: An adverse event is life threatening if 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 if it were more severe.

†Disabling/incapacitating—definition: An adverse event is incapacitating or disabling if the event results in a substantial disruption of the subject's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle).

‡Hospitalisation: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for treatment that would not have been appropriate in the physician’s office or out-patient setting.

Hospitalisation for either elective surgery related to a pre-existing condition which did not increase in severity or frequency following initiation of the study or for routine clinical procedures¶ (including hospitalisation for “social” reasons) that are not the result of an adverse event need not be considered as adverse events and are therefore not serious adverse events.

¶Routine Clinical Procedure—definition: One which is defined in the protocol as a procedure which may take place during the study period and should not interfere with the study vaccine administration or any of the ongoing protocol specific procedures.

N.B. If anything untoward is reported during an elective procedure, that occurrence must be reported as an adverse event, either ‘serious’ or ‘non-serious’ according to the usual criteria.

When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the adverse event should be considered serious.
8.5.2 Reporting serious adverse events

Any serious adverse events occurring during the period starting from the day of administration of the birth dose of hepatitis B vaccine to each subject and ending within one month (maximum 30 days) of administration of the last dose of the mixed vaccines for that subject, whether or not considered to be related to the study vaccine, must be reported by the investigator to the SmithKline Beecham monitoring personnel by fax or telephone within 24 hours.

<table>
<thead>
<tr>
<th>Medical Monitor</th>
<th>Site Monitor</th>
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<tbody>
<tr>
<td>Director, Clinical R&amp;D</td>
<td>SmithKline Beecham</td>
</tr>
<tr>
<td>SmithKline Beecham Biologicals</td>
<td>Av. Eldorado 91-50</td>
</tr>
<tr>
<td>Rue de l’Insitut 89</td>
<td>Santafé de Bogota</td>
</tr>
<tr>
<td>B-1330 Rixensart</td>
<td>Colombia</td>
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<tr>
<td>Belgium</td>
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Tel: [Redacted] Tel: [Redacted]
Fax: [Redacted] Fax: [Redacted]

Notification should also include:

Manager Clinical Safety Vaccines

<table>
<thead>
<tr>
<th>Manager Clinical Safety Vaccines</th>
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</thead>
<tbody>
<tr>
<td>SmithKline Beecham Biologicals</td>
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<td>Rue de l’Insitut 89</td>
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<td>B-1330 Rixensart</td>
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<tr>
<td>Belgium</td>
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</tbody>
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Tel: [Redacted] Fax: [Redacted]

Mobile phone for 7/7 day availability: [Redacted]

This initial notification should include, as a minimum, sufficient information to permit identification of:

- the reporter
- the subject
- study vaccine(s)
- adverse event(s)
- date of onset

Investigators should not wait to receive additional information to fully document the event before notifying SmithKline Beecham Biologicals of a serious adverse
event. The telephone report should be followed by a full written summary utilising the SmithKline Beecham Biologicals Serious Adverse Event form detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained.

Instances of death, cancer or congenital abnormality in offspring if brought to the attention of the investigator AT ANY TIME after cessation of study medication AND suspected by the investigator to be related to study medication, should be reported to the Study Monitor.

8.6 Treatment of adverse events

Treatment of any adverse event is at the sole discretion of the investigator and according to current Good Medical Practice. The applied measures should be recorded in the CRF of the vaccinee.

9 Subject Completion and Drop-out

9.1 Definition

From an analysis perspective, a 'drop-out' is any subject who did not come back for the concluding visit foreseen in the protocol. A subject who returns for the concluding visit foreseen in the protocol is considered to have completed the study.

9.2 Procedures for handling drop-outs

Investigators should make an attempt to contact those subjects who do not return for scheduled visits or follow-up. Information gathered should be described on the Study Conclusion page of the CRF and on Medication/Adverse event forms.

9.3 Reasons for drop-out

It should be specified on the Study Conclusion page of the CRF which of the following possible reasons were responsible for drop-out of the subject from the study:

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

10 Data Evaluation: criteria for evaluation of objectives

10.1 Primary endpoint

Percentage of infants with anti-HBs titres ≥10 mIU/ml at the time of the second dose of the mixed vaccines, i.e., at 4 months of age

10.2 Secondary endpoints

At each blood sampling timepoint:
- anti-HBs antibody titres
- anti-PRP antibody titres
- anti-BPT antibody titres
- anti-tetanus antibody titres
- anti-diphtheria antibody titres

Occurrence of any solicited local and/or general symptoms within 4 days after each dose of vaccine(s)

Occurrence of unsolicited symptoms within 30 days after each dose of vaccine(s)

Occurrence of Serious Adverse Events (SAEs) over the course of the study (beginning with first study procedure at birth up to and including 30 days following the 3rd dose of the mixed vaccines)

10.3 Study cohorts/data sets to be evaluated

Total cohort
The Total cohort will include all enrolled (i.e. vaccinated with the mixed vaccines) subjects for whom data are available. For the Total analysis of safety, this will include all vaccinated subjects for whom safety data are available. For the Total analysis of efficacy, this will include vaccinated subjects for whom data concerning efficacy endpoint measures are available.
Protocol defined or According To Protocol (ATP) cohort for analysis of safety

The ATP cohort for analysis of safety will include all subjects
- who have received at least one dose of the mixed vaccines
- with sufficient data to perform an analysis of safety
- for whom administration site of study vaccine is known
- who have not received a vaccine not specified or forbidden in the protocol

ATP cohort for analysis of efficacy

The ATP cohort for analysis of efficacy will serve as the cohort of primary interest in this study and will include all subjects for whom differential treatment effect on efficacy is likely (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol) and for whom data concerning efficacy endpoint measures are available. This will include subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

10.4 Estimated sample size

A sample size of 100 eligible subjects is considered to provide enough confidence on seroprotection rate for anti-HBs (percentage of subjects with anti-HBs antibody titre ≥10 mIU/ml) after each vaccination, e.g., if seroprotection rate is 20%, one can expect a 95% confidence interval (95% CI) of [13;30]

- 50% seroprotection rate one can expect a 95% CI [40;60]
- 95% seroprotection rate one can expect a 95% CI [89;98]

10.5 Final analyses

10.5.1 Analysis of demographics

Demographic characteristics (age, sex) of each study cohort will be tabulated.

The mean age (plus range and standard deviation) by sex of the enrolled subjects will be calculated.

10.5.2 Analysis of efficacy

Immunogenicity of the vaccine, i.e. antibody response, will be the measure of vaccine efficacy. Analysis of efficacy will be as follows:

The seropositivity rate and its 95% confidence interval (95% CI) will be calculated for antibodies to each vaccine antigen component for each blood
The seropositivity rate is the percentage of seropositive subjects, i.e., subjects with antibody titres \( \geq \) the assay cut-off. See Section 5.5.2 for laboratory defined cut-off value of each assay utilised in this study. A seronegative subject is a subject whose titre is below the cut-off value. A seropositive subject is a subject whose titre is greater than or equal to the cut-off value.

The Geometric Mean Titre (GMT) calculations will be performed for all antibodies to all vaccine antigen components by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMT calculation.

**Anti-HBs antibodies**

The percentage of subjects with protective levels of anti-HBs with 95% CI will be determined at each blood sampling time point. In this study the assay cut-off is 10 mIU/ml; therefore, the percentage of seropositive subjects equals the percentage of seroprotected subjects.

**Anti-PRP antibodies**

The percentage of subjects with a serum antibody concentration for anti-PRP \( \geq \) 0.15 mcg/ml (defined as seropositive) and \( \geq \) 1.0 mcg/ml and the corresponding 95% CI will be tabulated.

**Anti-Bordetella pertussis antibodies**

The percentage of subjects with anti-*B. pertussis* titre \( \geq \) the assay cut-off of 15 EL.U/ml with 95% CI will be calculated.

Vaccine response for the whole cell *Bordetella pertussis* antigen with 98% CI will be calculated. A vaccine response with respect to anti-BPT is defined as follows:

- the appearance of antibodies (titre \( \geq \) cut-off) in initially seronegative subjects,
- post-vaccination antibody titres \( \geq \) pre-vaccination titres in initially seropositive subjects.

This takes into consideration the expected decrease in maternal antibody titre. The half-life for decay of maternal pertussis antibodies is approximately 6 weeks.\(^{26}\)

**Anti-diphtheria and anti-tetanus toxoid antibodies**

The percentage of subjects with titres \( \geq \) 0.1 IU/ml with 95% CI will be determined.
10.5.3 Analysis of safety

The percentage of doses followed by a report of any symptom (solicited or unsolicited) and percentage of doses followed by at least one local or general symptom during the four day follow-up period after vaccination will be determined. The incidence of each solicited symptom over the four-day follow-up period will be reported. The relationship of solicited general symptoms to vaccination will be tabulated.

The verbatim reports of unsolicited symptoms will be coded by use of the World Health Organisation’s Dictionary for Adverse Reaction Terminology; every verbatim term, as stated by the reporter, will be matched to the appropriate WHO Preferred Term. The incidence, relationship to vaccination and intensity of unsolicited symptoms will be tabulated.

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

10.6 Planned interim analysis

No interim analysis will be performed.

11 Administrative Matters

To comply with Good Clinical Practice important administrative obligations relating to investigator responsibilities, monitoring, archiving data, audits, confidentiality and publications must be fulfilled. See Appendix B for details.

References


Appendix A: World Medical Association Declaration of Helsinki

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly
Tokyo, Japan, October 1975
35th World Medical Assembly
Venice, Italy, October 1983
41st World Medical Assembly
Hong Kong, September 1989
and the
48th General Assembly
Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic
for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I.  BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE  
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The Physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS  
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the
life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.
Appendix B: Administrative Matters

I. RESPONSIBILITIES OF THE INVESTIGATOR

- To ensure that he/she has sufficient time to conduct and complete the study and has adequate staff and appropriate facilities which are available for the duration of the study and to ensure that other studies do not divert essential subjects or facilities away from the study at hand.

- To submit an up-to-date curriculum vitae and other credentials (e.g. medical license number in the United States) to the sponsor and—where required—to relevant authorities.

- To acquire the normal ranges for laboratory tests performed locally and, if required by local regulations, obtain the Laboratory License or Certification.

- To prepare and maintain adequate case histories designed to record observations and other data pertinent to the study.

- To conduct the study in compliance with the protocol and appendices.

- To cooperate with a representative of SmithKline Beecham Biologicals in the monitoring process of the study and in resolution of queries about the data.

II. PROTOCOL AMENDMENTS AND MODIFICATIONS

No changes to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Biologicals’ Clinical Project Manager and filed as an amendment/modification to this protocol.

Any amendment/modification to the protocol will be adhered to by the participating centre(s) and will apply to all subjects. Written IRB/IEC approval of protocol amendments is required prior to implementation; modifications are submitted to IRBs/IECs for information only.

III. SPONSOR’S TERMINATION OF STUDY

SmithKline Beecham Biologicals reserves the right to discontinue the clinical study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be tendered.
IV. CASE REPORT FORM INSTRUCTIONS

Prior to screening the first potential participant, the investigator will provide a list showing the signature and hand-written initials of all individuals authorised to make or change entries on CRFs. If the authorised individuals should change during the study, the investigator is to inform SmithKline Beecham.

Case report forms (and subject diary cards, if applicable), will be supplied by SmithKline Beecham for recording all data. It is the responsibility of the investigator or co-investigator to ensure that CRFs (and subject diary cards) are legible and completely filled in with a black ink fountain or ballpoint pen.

Errors must be corrected by drawing a single line through the incorrect entry and writing in the new value/data positioned as close to the original as possible. The correction must then be initialled, dated and justified, where necessary, by the authorised individual making the change. The original entry must not be obliterated, overwritten or erased when a correction is made.

When a subject completes a visit, it is anticipated that relevant sections of the CRF will be completed by the investigator (or designated staff) within 24 hours of the last data becoming available, but in no case later than 5 days. Similarly, when a subject completes a study, it is anticipated that all relevant CRF pages will be completed within 24 hours of the last data becoming available, but in no case later than 5 days. This also applies to forms for potential study participants who were screened but not randomised to a study group.

As soon as the subject has completed/withdrawn from the study and the CRF is completed the principal investigator or designated physician(s) under his/her supervision will sign the study conclusion pages of the CRF to confirm that they have reviewed the data and that the data are completed and accurate.

An original (top copy) CRF or log sheets must be submitted for all subjects who have undergone protocol specific procedures, whether or not the subject completed the study.

While completed CRFs will be reviewed by a SmithKline Beecham Biologicals professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors and documentation and approval by the investigator. Wherever possible the investigator should assist in clarification or correction of errors detected after study finalisation within 48 hours of them being brought to the attention of the investigator.
Any questions or comments related to the CRF should be directed to the assigned Site Monitor.

V. **MONITORING BY SMITHKLINE BEECHAM (I.E. THE SPONSOR)**

Monitoring visits by a professional representative of the sponsor will be scheduled to take place before entry of the first subject, during the study at appropriate intervals and after the last subject has completed. It is anticipated that monitoring visits will occur at a minimum frequency of once every eight weeks.

These visits are for the purpose of confirming that SmithKline Beecham Biologicals sponsored studies are being conducted in compliance with the relevant Good Clinical Practice regulations/guidelines, verifying adherence to the protocol and the completeness and exactness of data entered on the CRF and Vaccine Inventory Forms. The monitor will verify CRF entries by comparing them with the source data/documents which will be made available by the investigator for this purpose. The monitor will mark completed and approved screens at each visit. At the end of the monitoring visit, the monitor will transmit. The investigator must ensure provision of reasonable time, space and adequate qualified personnel for monitoring visits.

VI. **ARCHIVING OF DATA**

The investigator/institution should maintain all study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of the clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Similarly, the sponsor-specific study documentation should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or if needed by the sponsor. The sponsor should inform the investigator/institution
in writing of the need for record retention and should notify the investigator/institution in writing when the study-related records are no longer needed.

VII. AUDITS

For the purpose of compliance with Good Clinical Practice and Regulatory Agency Guidelines it may be necessary for SmithKline Beecham Biologicals or a Drug Regulatory Agency to conduct a site audit. This may occur at any time from start to after conclusion of the study.

When an investigator signs the protocol, he agrees to permit Drug Regulatory Agency and SmithKline Beecham Biologicals' audits, providing direct access to source data/documents. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

SmithKline Beecham Biologicals has a substantial investment in clinical studies. Having the highest quality data and studies are essential aspects of vaccine development. SmithKline Beecham Biologicals has a Regulatory Compliance staff who audit investigational sites. Regulatory Compliance assesses the quality of data with regard to accuracy, adequacy and consistency. In addition, Regulatory Compliance assures that SmithKline Beecham Biologicals sponsored studies are in accordance with the Good Clinical Practices and that relevant regulations/guidelines are being followed.

To accomplish these functions, Regulatory Compliance selects investigational sites to audit. These audits usually take 1 to 2 days. The SmithKline Beecham Biologicals audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on vaccine accountability. The SmithKline Beecham Biologicals audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SmithKline Beecham Biologicals of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Log of visits from the sponsor's representatives
- IRB/IEC approval
- Vaccine accountability
- Approved study protocol and amendments
- Informed consent of the subjects (written or witnessed oral consent)
• Medical records supportive of CRF data
• Reports to the IRB/IEC and the sponsor
• Record retention

SmithKline Beecham Biologicals will gladly help investigators prepare for an inspection.

VIII. CONFIDENTIALITY AND PUBLICATION

You agree that all information communicated to you by SmithKline Beecham Biologicals is the exclusive property of SmithKline Beecham Biologicals and you will ensure that the same shall be kept strictly confidential by you or any other person connected with the work and shall not be disclosed, either orally or in written form, by you or such person to any third party without the prior written consent of SmithKline Beecham Biologicals. You shall communicate the results of the work promptly to SmithKline Beecham Biologicals.

We agree that you shall have the right to publish or permit the publication of any information or material relating to or arising out of the work after prior submission to us provided that if we shall so request you will delay publication for a maximum of six months to enable us to protect our rights in such information or material. Any proposed publication or presentation (e.g. manuscript, abstract or poster) for submission to a journal or scientific meeting, should be sent to the Site Monitor prior to submission, together with confirmation that any other author(s) has seen and agreed the proposed publication/presentation. SmithKline Beecham Biologicals will undertake to comment on such documents within four weeks.

All rights and interests worldwide in any inventions, know-how or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this Protocol or which otherwise arise from the information or materials supplied under this Agreement, shall be assigned to, vest in and remain the property of SmithKline Beecham plc.
Appendix C: Overview of the recruitment plan

Mothers can be recruited by the physician during prenatal care or by the paediatrician while in the maternity hospital in order to enrol their infants at birth. Target enrolment will be 120 eligible subjects at birth to ensure a minimum of 100 eligible healthy male and female infants between 6 to 10 weeks of age at the time of the first dose of the three-dose vaccination course. Enrolment will be terminated when 120 subjects have been enrolled. The enrolment period, e.g. the period between the first and the last enrolled subject, is maximum 13 weeks. [SMITHKLINE BEECHAM BIOB] will be responsible for monitoring and direct implementation of the recruitment plan.

The investigator may use one of the following strategies to recruit the volunteers: advertising; physician referral; group meetings (e.g. for students); direct mailings; hospital staff recruiting ‘on the spot’. The budget for this recruitment effort is included in the overall budget for the study.

Subject information sheet (SIS) and informed consent forms (IC) will be provided by SmithKline Beecham Biologicals.
Appendix D: Handling of Biological Samples Collected by the Investigator

Instructions for Handling of Serum Samples

When materials are provided by SmithKline Beecham Biologicals, it is mandatory that all clinical samples (including serum samples) be collected using exclusively those materials in the appropriate manner. The use of other materials could result in the exclusion of the subject from analysis. The investigator must ensure that his/her personnel and the laboratory(ies) under his/her supervision comply with this requirement.

1. Collection
The whole blood (by cord blood sampling at birth, capillary or venous route) should be collected observing appropriate aseptic conditions. It is recommended that Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood Medical) be used so as to minimise the risk of haemolysis and to avoid blood cell contamination of the serum when transferring to standard serum tubes.

2. Serum separation
These guidelines aim to ensure high quality serum by minimising the risk of haemolysis, blood cell contamination of the serum or serum adverse cell toxicity at testing.

- For separation of serum using Vacutainer® tubes, the instructions provided by the manufacturer should be followed. Siliconised tubes should never be used (cell toxicity).

- Following separation, the serum should be aseptically transferred to the appropriate standard tubes using a sterile disposable pipette. The serum should be transferred as gently as possible to avoid blood cell contamination.

- The tube should not be overfilled (max. 3/4 of the total volume) to allow room for expansion upon freezing.

- The tube should be identified by the appropriate, provided label (see point 3).

3. Labeling
- The standard labels provided by SmithKline Beecham Biologicals should be used to label each serum sample.
• If necessary, any hand-written additions to the labels should be made using indelible ink.

• The label should be attached to the tube as follows (see diagram):
  - first attach the paper part of the label to the tube
  - than wrap the label around the tube so that the transparent, plastic part of the label overlaps with the label text and bar code and shields them.

This will ensure optimal label attachment.

Labels should not be attached to caps.

4. Sorting and storage
• Tubes should be placed in the SmithKline Beecham Biologicals racks in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, then with the post vaccination sample series.

• When this is not possible, as is the case with the new sealed bag/box (IATA regulation), samples should be sorted in numerical order into batches of 20 and packed into plastic bags. All plastic bags should then be packed together in a sealed box.

• The tubes of serum should be stored in a vertical position at a temperature between -20°C and -70°C until shipment to SmithKline Beecham Biologicals.
Wherever possible, a backup facility for storage of serum samples should be available.

- A standard serum listing form, specifying the samples being shipped for individual subjects at each timepoint, should be prepared for each shipment. A copy of this list should be retained at the study site, while the original should be sealed in a plastic envelope and shipped with the serum samples.
Appendix E: Shipment of Biological Samples

Instructions for Shipment of Serum Samples

Serum samples should be sent to the sponsor at regular intervals. The frequency of shipment of samples should be decided upon by the site monitor with the investigator prior to the study start.

Serum samples should always be sent by air, preferably on a Monday, Tuesday or Wednesday, unless otherwise requested by the sponsor.

Serum samples must be placed with dry ice (-20°C) in a container complying with IATA requirements. The completed standard serum listing form should always accompany the shipment.

The container must be clearly identified with the labels provided by SmithKline Beecham Biologicals specifying the shipment address and the storage temperature (-20°C).

The airway bill should contain the instruction for storage of samples at -20°C.

A "proforma" invoice, stating a value for customs purposes only, should be prepared and attached to the container. This document should contain the instruction for storage of samples at -20°C.

Details of the shipment, including: * airway bill number
* flight number
* flight departure and arrival times

should be sent by fax, two days before shipment, to:

SMITHKLINE BEECHAM BIOLOGICALS
Attn. Clinical Immunology
R & D Department/Building 44
Rue de l'Institut, 89
B-1330 Rixensart - Belgium

Telephone:  
Fax:  
Appendix F: Laboratory Assays

The presence of anti-HBs will be determined using radioimmunoassay (AUSAB, Abbott). The assay cut-off used for this study is 10 mIU/ml.

Anti-PRP will be measured by ELISA technique. The cut-off of the test is 0.15 mcg/ml.

Anti-BPT antibody titres will be determined by ELISA using the IgG EIA test kit, Labsystems, and expressed in ELISA Units per ml (EL.U/ml), with an assay cut-off of 15 EL.U/ml.

Anti-diphtheria and anti-tetanus titres will be measured by ELISA and expressed in international units per ml (IU/ml). The assay cut-off is 0.1 IU/ml.
Appendix G: Vaccine Supplies, Packaging and Accountability

It is under no circumstances permitted to use supplies for purposes other than those specified in the protocol. Unused supplies will be collected by the sponsor on completion of the study.

1. Vaccine supplies
The investigator will be supplied by the sponsor the following amounts of numbered doses of study vaccines, sufficient to administer a birth dose of hepatitis B vaccine and 3 doses of the mixed vaccines to all subjects as described in the present protocol:

- 120 doses of SmithKline Beecham Biologicals’ recombinant hepatitis B vaccine: Engerix™-B
- 360 doses of SmithKline Beecham Biologicals’ combined diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™-HB
- 360 doses of SmithKline Beecham Biologicals’ Haemophilus influenzae type b conjugate vaccine: Hiberix™

An additional 5% of their respective amounts will be supplied for replacement in case of breakage or bad storage conditions.

All vials need to be accounted for on the form provided.

2. Vaccine packaging
The vaccines will be packed in labelled boxes. The box label will contain the following information: study number, subject number, lot number, instructions for vaccine administration.

3. Vaccine accountability
The investigator or pharmacist must sign a statement that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products will be handled and stored safely and properly; that investigational products will only be dispensed to study subjects/patients in accordance with the protocol; and that any unused products will be returned to SmithKline Beecham Biologicals. At any time the figures on supplied, used and remaining vaccine doses should match. At the end of the study, it must be possible to reconcile delivery records with those of usage and returned stocks. Account must be given of any discrepancies. Certificates of returns must be signed with the assurance from investigator/pharmacist that all unused dosage
forms for the stated study have been returned- including all opened and unopened packages.

4. Labels for sample identification
The investigator will receive labels to identify samples taken from each subject at each timepoint. The label will contain the following information: study number, subject number, sampling timepoint [e.g., post vacc II], timing [e.g., study month 4].

Description of sera labels:
Pre Study Month 0
Post Vacc II Study Month 4
Post Vacc III Study Month 6
Post Vacc IV Study Month 7

5. Other supplies provided by the sponsor
In addition to the vaccines, the study documentation and the sample labels, the investigator will receive the following supplies:
- tubes for blood sampling
- tubes with screw caps for serum samples
- racks for the tubes of serum
Appendix H: Protocol Amendments/Modifications

Protocol Amendment Approval

Study Drug

Protocol Number
213501/019 (DTPw-HBV-Hib-019)

Protocol Title: Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of SmithKline Beecham Biologicals’ quadrivalent diphtheria, tetanus, whole cell Bordetella pertussis, hepatitis B (DTPw-HBV) and Haemophilus influenzae type b conjugate (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with SmithKline Beecham Biologicals’ hepatitis B vaccine.

Amendment Date
31-May-2000

Co-ordinating Author:

Rationale/background for changes: The protocol allows that mothers will be recruited by the physician “during prenatal care or by the paediatrician while in the maternity hospital”. Thus the protocol has been amended to remove the specification that a cord blood sample will be obtained at birth. This will allow for either cord or peripheral blood sampling to be used for pre-vaccination serological analysis.

The following items were Amended: May 31, 2000—

- Section 5.3 Outline of study procedures
- Section 5.4 Visit 1 in Detailed description of study stages/visits
- Parent Information Sheet

[Name] will replace [Name] as Site Monitor. Thus, the name of [Name] has been replaced with that of [Name] throughout the protocol.

Approved by:

Director

[Name]  dd-mm-yyyy

Investigator

[Name]  dd-mm-yyyy
GENERAL INSTRUCTIONS

Print clearly in CAPITAL LETTERS using a black fountain or ball-point pen and press firmly so that all copies are legible. Insert the writing board beneath all copies of the form being completed. Fill in the subject number on every page and answer all questions except where otherwise indicated.

Do not write in shaded areas which are qualified “For SB”. Information written in these areas are not the responsibility of the investigator.

For each subject’s INITIALS, please enter the first two letters of the first name and the first two letters of the family name.

ABBREVIATIONS: Abbreviations for medical conditions, clinical events or drug names should not be used. Units and route of administration of medication may be abbreviated. NA: not applicable.

IMPORTANT: Errors should be crossed out with a single line and the alteration made as near to the original as possible. All alterations must be printed, initialed and dated by the investigator or authorized staff.

DATE

Use the following three-letter abbreviations for each month:

January = JAN
February = FEB
March = MAR
April = APR
May = MAY
June = JUN
July = JUL
August = AUG
September = SEP
October = OCT
November = NOV
December = DEC

Example: 0 1 J A N 1 9 9 8 = 1st January 1998

day month year

TIME

Unless specified otherwise, use the 24 hour clock: 00:00-23:59

Example: 1 5 3 0 = 3.30 p.m.

hours min

The Medication section, the Concomitant Vaccination section, the Non-Serious Adverse Events section and the Serious Adverse Event (SAE) form have to be checked for final assessment at the end of the study.

For all subjects enrolled, please complete the Study Conclusion form.
ADVERSE EVENT DEFINITIONS

INTENSITY FOR SOLICITED SYMPTOMS

<table>
<thead>
<tr>
<th>Pain at injection site</th>
<th>Drowsiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Absent</td>
<td>0: Absent</td>
</tr>
<tr>
<td>1: Minor reaction to touch</td>
<td>1: Drowsiness easily tolerated</td>
</tr>
<tr>
<td>2: Cries/protests on touch</td>
<td>2: Drowsiness that interferes with normal activity</td>
</tr>
<tr>
<td>3: Cries when limb is moved/spontaneously painful</td>
<td>3: Drowsiness that prevents normal activity</td>
</tr>
</tbody>
</table>

Irritability/Fussiness

<table>
<thead>
<tr>
<th>Loss of appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Behavior as usual</td>
</tr>
<tr>
<td>1: Crying more than usual/ no effect on normal activity</td>
</tr>
<tr>
<td>2: Crying more than usual/ interferes with normal activity</td>
</tr>
<tr>
<td>3: Crying that cannot be comforted/ prevents normal activity</td>
</tr>
<tr>
<td>1: Eating less than usual/ no effect on normal activity</td>
</tr>
<tr>
<td>2: Eating less than usual/ interferes with normal activity</td>
</tr>
<tr>
<td>3: Not eating at all</td>
</tr>
</tbody>
</table>

INTENSITY FOR NON-SOLICITED SYMPTOMS

1: An adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse event which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse event which prevents normal, everyday activities
   (In a young child, such an adverse event would, for example, prevent attendance at school/ kindergarten/ a day-care center and would cause the parents/ guardians to seek medical advice).

RELATIONSHIP

<table>
<thead>
<tr>
<th>NR</th>
<th>UL</th>
<th>SU</th>
<th>PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not related</td>
<td>Unlikely</td>
<td>Suspected</td>
<td>Probable</td>
</tr>
</tbody>
</table>

The adverse event is definitely not causally related to administration of the study vaccine(s).
There are other, more likely causes and administration of the study vaccine(s) is not suspected as a cause.
A direct cause and effect relationship between administration of the study vaccine(s) and the adverse event has not been demonstrated but there is a reasonable possibility that the event was caused by administration of the study vaccine(s).
There probably is a direct cause and effect relationship between the adverse event and administration of the study vaccine(s).

OUTCOME

1: Recovered
2: Recovered with sequelae
3: Ongoing at subject study conclusion
4: Died
5: Unknown

SERIOUS ADVERSE EVENTS

A serious adverse event is any untoward medical occurrence that:
1: results in death
2: is life threatening
3: results in persistent or significant disability/incapacity
4: requires in-patient hospitalization
5: prolongation of existing hospitalization
6: is a congenital anomaly/birth defect in the offspring of a study subject
7: In addition, important medical events that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious. (Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not results in hospitalization; or development of drug dependency or drug abuse).

Although not considered as ‘serious adverse events’, pregnancies and cancers should be reported in the same way as serious adverse events.

For each serious adverse event, please fill in the Serious Adverse Event (SAE) form and contact SmithKline Beecham within 24 hours.
### FLOW SHEET

**AGE**

<table>
<thead>
<tr>
<th>VISIT</th>
<th>BIRTH</th>
<th>6-10 WEEKS</th>
<th>4 MONTHS</th>
<th>6 MONTHS</th>
<th>7 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISIT 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 2</strong></td>
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<td></td>
<td></td>
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<tr>
<td><strong>VISIT 3</strong></td>
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<td></td>
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<tr>
<td><strong>VISIT 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VISIT 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TIMING**

<table>
<thead>
<tr>
<th>BLOOD SAMPLING TIMEPOINT</th>
<th>PRE</th>
<th>POST VACC II</th>
<th>POST VACC III</th>
<th>POST VACC IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written informed consent from parents/guardians</td>
<td>✔</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Check of inclusion criteria for eligibility at birth</td>
<td>✏</td>
<td>✔</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Check of exclusion criteria for eligibility at birth</td>
<td>✏</td>
<td>✏</td>
<td>✔</td>
<td>✏</td>
</tr>
<tr>
<td>Physical examination</td>
<td>✔</td>
<td>✏</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Check of inclusion criteria for 3-dose mixed vaccine course</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Check of exclusion criteria for 3-dose mixed vaccine course</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Check of elimination criteria</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Check of contraindications</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Medical history</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Pre-vaccination assessment of adverse events</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Cord blood sampling for antibody determination (3 ml)</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Peripheral blood sampling for antibody determination (3 ml)</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Vaccination</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Daily post-vaccination recording of solicited symptoms (days 0–3) by parents/guardians</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Recording of unsolicited adverse events occurring one month (30 days) post-vaccination, by investigator</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Return of diary cards</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>Recording medication</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
<tr>
<td>Reporting of any SAEs occurring at any time from birth up to and including 30 days after the last dose of mixed vaccines</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
<td>✏</td>
</tr>
</tbody>
</table>

**STUDY CONCLUSION**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Size of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Visit 1 → Visit 2)</td>
<td>6-10 weeks</td>
</tr>
<tr>
<td>2 (Visit 2 → Visit 3)</td>
<td>56-70 days</td>
</tr>
<tr>
<td>3 (Visit 3 → Visit 4)</td>
<td>56-70 days</td>
</tr>
<tr>
<td>4 (Visit 4 → Visit 5)</td>
<td>30-35 days</td>
</tr>
</tbody>
</table>

**Intervals between study visits**

- Directed by the investigator
- Required documentation in the individual CRF

*SmithKline Beecham Biologicals’ hepatitis B vaccine (Engerix™-B)*

**SmithKline Beecham Biologicals’ DTPw-HBV (Tritanrix™-HB) and Hib (Hiberix™) vaccines extemporaneously mixed and administered as a single injection;**

It is the investigator’s responsibility to ensure that the intervals between visits are strictly followed. These intervals determine a subject’s evaluable status in the protocol analyses.

<table>
<thead>
<tr>
<th>Intervals between study visits*</th>
<th>Interval</th>
<th>Size of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Visit 1 → Visit 2)</td>
<td>6-10 weeks</td>
<td></td>
</tr>
<tr>
<td>2 (Visit 2 → Visit 3)</td>
<td>56-70 days</td>
<td></td>
</tr>
<tr>
<td>3 (Visit 3 → Visit 4)</td>
<td>56-70 days</td>
<td></td>
</tr>
<tr>
<td>4 (Visit 4 → Visit 5)</td>
<td>30-35 days</td>
<td></td>
</tr>
</tbody>
</table>

*The date of the previous visit is the reference date.*
## ELIGIBILITY CHECKLIST

### INCLUSION CRITERIA FOR ENROLMENT AT BIRTH

All subjects must satisfy the following criteria at birth:

1. Written informed consent obtained from the parents or guardians of the subject.
2. Born after a normal gestation period (between 36 and 42 weeks).
3. Free of obvious health problems as established by medical history of pregnancy and clinical examination before entering into the study.

### EXCLUSION CRITERIA FOR ENROLMENT AT BIRTH

The following criteria should be checked at birth. If any apply at the time of birth, the subject must not be considered for enrolment:

4. A family history of congenital or hereditary immunodeficiency.
5. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
6. Major congenital defect(s).

### INCLUSION CRITERIA FOR ADMINISTRATION OF THE MIXED VACCINES

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

7. A male or female between, and including, 6 and 10 weeks of age at the time of the first dose of the three-dose course of vaccination.
8. Free of obvious health problems as established by medical history and clinical examination before entering into the study.

### EXCLUSION CRITERIA FOR ADMINISTRATION OF THE MIXED VACCINES

The following criteria should be checked at the time of study entry. If any apply at the time of study entry, the subject must not be included in the study:

9. Use of any investigational or non-registered drug or vaccine other than the study vaccines within 30 days preceding the first dose of study vaccine, or planned use during the study period.
10. Administration of chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs since birth. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)
11. Any chronic drug therapy to be continued during the study period.
12. Planned administration/administration of a vaccine except oral polio vaccine (OPV) or Bacille Calmette-Guérin (BCG) vaccine during the period starting from 30 days before each dose of vaccines and ending 30 days after.
13. Previous vaccination against diphtheria, tetanus, pertussis or *Haemophilus influenzae* type b disease.
14. History of, or intercurrent, diphtheria, tetanus, pertussis, hepatitis B and/or Hib disease.
15. Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.
16. A family history of congenital or hereditary immunodeficiency.
17. History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
18. Serious chronic illness.
19. History of any neurologic disorders or seizures.
20. Acute disease at the time of enrolment. (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., axillary temperature < 37.5°C.)
21. Administration of immunoglobulins and/or any blood products since birth or planned administration during the study period.
ELIGIBILITY CHECKLIST

ELIMINATION CRITERIA DURING THE STUDY

The following criteria should be checked at each visit subsequent to the first visit of the three-dose immunization course. If any become applicable during the study, the subject will not be required to discontinue the study but may be eliminated from analysis.

- Use of any investigational or non-registered drug or vaccine other than the study vaccine(s) during the study period.
- Administration of chronic (defined as more than 14 days) immunosuppressants or other immune modifying drugs. (For corticosteroids, this will mean prednisone, or equivalent, ≥ 0.5 mg/kg/day. Inhaled and topical steroids are allowed.)
- Administration of a vaccine not foreseen by the study protocol during the period starting from 30 days before each dose of vaccines and ending 30 days after, with the exception of oral polio vaccine (OPV) or Bacille Calmette-Guérin (BCG) vaccine.
- Administration of immunoglobulins and/or any blood products during the study period.

Contraindications to vaccination

The following adverse events constitute contraindications to administration of the vaccines at that point in time; if any one of these adverse events occurs at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the time window specified in the protocol, or withdrawn at the discretion of the investigator. The subject must be followed until resolution of the event as with any adverse event.

- 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., axillary temperature of < 37.5°C.)
- Axillary temperature of ≥ 37.5°C at the time of vaccination.

The following adverse events constitute absolute contraindications to further administration of the vaccines; if any of these adverse events occur during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event:

- Anaphylactic reaction following the administration of vaccines.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection.

The following adverse events associated with DTP vaccination constitute absolute contraindications to further administration of DTP; if any of these adverse events occurs during the study, the subject must be withdrawn and must be followed until resolution of the event, as with any adverse event

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 consisting 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 DTP vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

Precautions:

- Fever ≥ 40°C (axillary 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.
Informed Consent has to be obtained prior to any study procedure
I certify that Informed Consent has been obtained prior to any study procedure.

Informed Consent date: [day] [month] [year]

DEMOGRAPHICS

Subject initials: [first name] [family name]

Date of birth: [day] [month] [year]

Gender: Male [ ] Female [ ]

Race: White [ ] Black [ ] Oriental [ ] Other [ ]

Other [ ] please specify: _________________________________

Height: [ ] [ ] [ ] cm

Weight: [ ] [ ] [ ] kg

Is the subject eligible for the study, according to the criteria listed hereby?

YES [ ]

NO [ ] if no, please give the corresponding criterion number(s): _________________________________

Investigator Signature: ____________________________
GENERAL MEDICAL HISTORY/PHYSICAL EXAMINATION

Are you aware of any pre-existing conditions or signs and/or symptoms present in the subject prior to the start of the study?

**NO** □

**YES** □ → Please tick appropriate box(es) and give diagnosis

<table>
<thead>
<tr>
<th>PAST</th>
<th>CURRENT</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Please report medication(s) as specified in the protocol and fill in the Medication section.
LABORATORY TESTS

CORD BLOOD SAMPLE

Has a blood sample been taken? 
YES ☐ NO ☐

PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature: __. __°C ➔ Route: Axillary ☐ Oral ☐ Rectal ☐

GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms on the day of vaccination (before injection)?

NO ☐

YES ☐ ➔ For each symptom, please tick a No/Yes box.
Please give intensity for any event observed just before injection.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability / Fussiness</td>
<td>1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>3</td>
</tr>
</tbody>
</table>

IntENSITY: 1 2 3
VACCINE ADMINISTRATION

Has the study vaccine been administered?

NO  □  → Please specify reason: ________________________________________________________________

YES  □  →

<table>
<thead>
<tr>
<th>VACCINE ADMINISTRATION</th>
<th>Side / Site Route</th>
<th>Has the study vaccine been administered according to the protocol?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engerix™-B Vaccine</td>
<td>Left Antero-lateral Thigh I.M.</td>
<td>Yes □ No  □  If NO, please tick all items.</td>
</tr>
</tbody>
</table>

NB: any other vaccines administered during the study period must be recorded in the Concomitant Vaccination section.

POST-VACCINATION OBSERVATION

If any adverse events occurred during the immediate post-vaccination time specified in the protocol, please fill in the Solicited Adverse Events section, the Non-Serious Adverse Events section or the Serious Adverse Event form.

MEDICATION

If any prophylactic medication has been administered in anticipation of study vaccine reactions, please complete the Medication section.
**SOLICITED ADVERSE EVENTS - LOCAL SYMPTOMS**

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

- **NO**
- **UNKNOWN**
- **YES** → Please tick a No/Yes box for each symptom.

If Yes is ticked, please fill in the complete line.

<table>
<thead>
<tr>
<th>LOCAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
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<tr>
<td>Yes → size:</td>
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<td>mm</td>
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<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
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<tr>
<td>Yes → size:</td>
<td>mm</td>
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<td></td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Pain</td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
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<td></td>
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<tr>
<td>Yes → intensity:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intensity:**

- 0
- 1
- 2
- 3

Did the subject seek medical advice?

- **NO**
- **YES** → please tick appropriate box(es):

Redness

Swelling

Pain

If any of these adverse events is **serious** according to protocol definition,

→ please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form.**
# SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

**NO** □ **UNKNOWN** □ **YES** □

Please tick a No/Yes box for each symptom. If Yes is ticked, please fill in the complete line.

<table>
<thead>
<tr>
<th>GENERAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Relationship</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No □</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes □ → °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Axillary</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Oral</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Rectal</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Irritability/ Fussiness</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No □</td>
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<tr>
<td>Yes □ → intensity:</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drowsiness</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>No □</td>
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<td></td>
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<tr>
<td>Yes □ → intensity:</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Loss of appetite</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No □</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes □ → intensity:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Fever:**
- Axillary: ≥ 37.5°C
- Oral: ≥ 37.5°C
- Rectal: ≥ 38°C

**Intensity:**
- 0
- 1
- 2
- 3

**Relationship:**
- NR: Not related
- UL: Unlikely
- SU: Suspected
- PB: Probable

**→ Did the subject seek medical advice?**
- NO □
- YES □ → please tick appropriate box(es):

**→ If any of these adverse events is serious according to protocol definition,**
- please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the Serious Adverse Event form.
VISIT 2
MONTH 2
6-10 WEEKS AFTER VISIT 1

DOSE 2
REMINDER

ELIGIBILITY CRITERIA

→ Please check the Inclusion and Exclusion Criteria for the administration of the mixed vaccines before continuing the visit.

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the Non-Serious Adverse Events section or the Serious Adverse Event (SAE) form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the Medication section.
→ Please report concomitant vaccination in the Concomitant Vaccination section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the Contraindications as specified in the protocol
PRE-VACCINATION ASSESSMENT

PRE-VACCINATION TEMPERATURE

Temperature: [ ] °C → Route: [ ] Axillary, [ ] Oral, [ ] Rectal

GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms on the day of vaccination (before injection)?

NO [ ]

YES [ ] → For each symptom, please tick a No/Yes box.
Please give intensity for any event observed just before injection.

Irritability / Fussiness
No [ ]
Yes [ ] → intensity: [ ]

Drowsiness
No [ ]
Yes [ ] → intensity: [ ]

Loss of appetite
No [ ]
Yes [ ] → intensity: [ ]
VACCINE ADMINISTRATION

Has the study vaccine been administered?

NO  →  Please specify reason: ________________________________________________________________

YES  →  VACCINE ADMINISTRATION  Side / Site Route  Has the study vaccine been administered according to the protocol?

<table>
<thead>
<tr>
<th>DTPw-HBV vaccine mixed with Hib conjugate vaccine</th>
<th>Left Antero-lateral Thigh I.M.</th>
<th>Yes  No  →  If NO, please tick all items.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side:</td>
<td>Site:</td>
<td>Route:</td>
</tr>
<tr>
<td>Left  Δ</td>
<td>Deltoid  Δ</td>
<td>IM  Δ</td>
</tr>
<tr>
<td>Right Δ</td>
<td>Thigh  Δ</td>
<td>SC  Δ</td>
</tr>
<tr>
<td>Buttock Δ</td>
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</tr>
</tbody>
</table>

**Important:** concomitant administration of any other vaccine with the exception of OPV and/or BCG is not permitted. Concomitant administration of OPV and/or BCG vaccine as well as any other vaccines administered during the study period must be recorded in the Concomitant Vaccination section.

POST-VACCINATION OBSERVATION

If any adverse events occurred during the immediate post-vaccination time specified in the protocol, please fill in the Solicited Adverse Events section, the Non-Serious Adverse Events section or the Serious Adverse Event form.

MEDICATION

If any prophylactic medication has been administered in anticipation of study vaccine reactions, please complete the Medication section.
### SOLICITED ADVERSE EVENTS - LOCAL SYMPTOMS

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

- **NO** [ ] **UNKNOWN** [ ]

- **YES** [ ] → Please tick a No/Yes box for each symptom.
  
  If Yes is ticked, please fill in the complete line.

<table>
<thead>
<tr>
<th>LOCAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Redness</strong></td>
<td></td>
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<tr>
<td>Yes [ ] size:</td>
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<tr>
<td><strong>Swelling</strong></td>
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<tr>
<td>Yes [ ] size:</td>
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<tr>
<td><strong>Pain</strong></td>
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<tr>
<td>Yes [ ] intensity:</td>
<td>[ ]</td>
<td>[ ]</td>
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<td></td>
</tr>
</tbody>
</table>

- **Intensity**: 0 1 2 3

→ Did the subject seek medical advice?

- **NO** [ ]
- **YES** [ ] → please tick appropriate box(es):
  
  - Redness [ ]
  - Swelling [ ]
  - Pain [ ]

→ If any of these adverse events is **serious** according to protocol definition,
  
  → please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form**.
### SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

**NO**  **UNKNOWN**  **YES**

If Yes is ticked, please fill in the **complete line**.

<table>
<thead>
<tr>
<th>GENERAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Relationship</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
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<td>☐</td>
<td></td>
</tr>
<tr>
<td>Yes → °C</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oral</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Irritability/Fussiness</strong></td>
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<td>☐</td>
<td></td>
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<tr>
<td>Yes → intensity:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>Drowsiness</strong></td>
<td></td>
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<td></td>
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<td></td>
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<td>No</td>
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<tr>
<td>Yes → intensity:</td>
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<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
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<tr>
<td><strong>Loss of appetite</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Yes → intensity:</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td>☐</td>
<td></td>
</tr>
</tbody>
</table>

**Fever:**  
- Axillary: ≥ 37.5°C  
- Oral: ≥ 37.5°C  
- Rectal: ≥ 38°C  

**Intensity:**  
- 0  
- 1  
- 2  
- 3  

**Relationship:**  
- NR: Not related  
- UL: Unlikely  
- SU: Suspected  
- PB: Probable

Did the subject seek medical advice?  
**NO**  **YES**

If any of these adverse events is **serious** according to protocol definition, please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form**.
VISIT 3
MONTH 4
56-70 DAYS AFTER VISIT 2

DOSE 3
Before any vaccine administration, please review the Contraindications as specified in the protocol.

→ Please check all appropriate criteria before continuing the visit.

Please report adverse events as specified in the protocol and fill in the Non-Serious Adverse Events section or the Serious Adverse Event (SAE) form, as appropriate.

Please report medication as specified in the protocol and fill in the Medication section.

Please report concomitant vaccination in the Concomitant Vaccination section.
## LABORATORY TESTS

### BLOOD SAMPLE

Has a blood sample been taken?  
- **YES**  
- **NO**

## PRE-VACCINATION ASSESSMENT

### PRE-VACCINATION TEMPERATURE

Temperature:  
- **°C**  
- Route:  
  - Axillary  
  - Oral  
  - Rectal

## GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms on the day of vaccination (before injection)?  
- **NO**
- **YES**  

For each symptom, please tick a No/Yes box.  
Please give intensity for any event observed just before injection.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritability / Fussiness</td>
<td>1-3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
</tr>
</tbody>
</table>
VACCINE ADMINISTRATION

Has the study vaccine been administered?

NO  Please specify reason: ____________________________________________________________

YES  VACCINE ADMINISTRATION

<table>
<thead>
<tr>
<th>Side / Site Route</th>
<th>Has the study vaccine been administered according to the protocol?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Antero-lateral Thigh I.M.</td>
<td>Yes ☐ No ☐ If NO, please tick all items.</td>
</tr>
</tbody>
</table>

Important: Concomitant administration of any other vaccine with the exception of OPV and/or BCG is not permitted. Concomitant administration of OPV and/or BCG vaccine as well as any other vaccines administered during the study period must be recorded in the Concomitant Vaccination section.

POST-VACCINATION OBSERVATION

If any adverse events occurred during the immediate post-vaccination time specified in the protocol, please fill in the Solicited Adverse Events section, the Non-Serious Adverse Events section or the Serious Adverse Event form.

MEDICATION

If any prophylactic medication has been administered in anticipation of study vaccine reactions, please complete the Medication section.
## SOLICITED ADVERSE EVENTS - LOCAL SYMPTOMS

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

**NO** [ ]  **UNKNOWN** [ ]  **YES** [ ]

Please tick a No/Yes box for each symptom. If Yes is ticked, please fill in the complete line.

### LOCAL SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Redness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No [ ]</td>
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<td>No [ ]</td>
<td></td>
</tr>
<tr>
<td>Yes [ ]</td>
<td>size:</td>
<td></td>
<td></td>
<td></td>
<td>Yes [ ]</td>
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<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Swelling** |       |       |       |       |                       |                              |
| No [ ]       |       |       |       |       | No [ ]               |                              |
| Yes [ ]     | size: |       |       |       | Yes [ ]              |                              |
|             | mm    | mm    | mm    | mm    |                       |                              |

| **Pain**    |       |       |       |       |                       |                              |
| No [ ]      |       |       |       |       | No [ ]               |                              |
| Yes [ ]     | intensity: | | | | | Yes [ ]              |                              |
|             | ___ | ___ | ___ | ___ |                       |                              |

**Intensity:**

<p>| | | | |</p>
<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Did the subject seek medical advice?

**NO** [ ]  **YES** [ ]

Please tick appropriate box(es): **Redness** [ ]  **Swelling** [ ]  **Pain** [ ]

If any of these adverse events is **serious** according to protocol definition,

please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Event form**.
**SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS**

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

- **NO** [ ]
- **UNKNOWN** [ ]
- **YES** [ ] → Please tick a No/Yes box for each symptom. If Yes is ticked, please fill in the complete line.

### SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

<table>
<thead>
<tr>
<th>GENERAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Relationship</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (°C)</td>
<td>No</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>NR</td>
<td>No ☑</td>
<td>day month year</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
<td>SU</td>
<td>Yes ☑</td>
<td></td>
</tr>
</tbody>
</table>

- **Axillary** [ ]
- **Oral** [ ]
- **Rectal** [ ]

<table>
<thead>
<tr>
<th>Irritability/fussiness</th>
<th>intensity</th>
<th>No</th>
<th>Yes</th>
<th>day month year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>☑</td>
<td>No</td>
<td>☑</td>
<td>day month year</td>
</tr>
<tr>
<td>Yes</td>
<td>☑</td>
<td>Yes</td>
<td>☑</td>
<td>day month year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drowsiness</th>
<th>intensity</th>
<th>No</th>
<th>Yes</th>
<th>day month year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>☑</td>
<td>No</td>
<td>☑</td>
<td>day month year</td>
</tr>
<tr>
<td>Yes</td>
<td>☑</td>
<td>Yes</td>
<td>☑</td>
<td>day month year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Loss of appetite</th>
<th>intensity</th>
<th>No</th>
<th>Yes</th>
<th>day month year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>☑</td>
<td>No</td>
<td>☑</td>
<td>day month year</td>
</tr>
<tr>
<td>Yes</td>
<td>☑</td>
<td>Yes</td>
<td>☑</td>
<td>day month year</td>
</tr>
</tbody>
</table>

### Fever

- **Axillary**: ≥ 37.5°C
- **Oral**: ≥ 37.5°C
- **Rectal**: ≥ 38°C

### Intensity

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>NR: Not related</td>
</tr>
<tr>
<td>1</td>
<td>UL: Unlikely</td>
</tr>
<tr>
<td>2</td>
<td>SU: Suspected</td>
</tr>
<tr>
<td>3</td>
<td>PB: Probable</td>
</tr>
</tbody>
</table>

- Did the subject seek medical advice?
  - **NO** [ ]
  - **YES** [ ] → please tick appropriate box(es): →

- If any of these adverse events is **serious** according to protocol definition:
  - please report event to SB monitor by telephone or fax within 24 hours (see protocol)
  - and complete the **Serious Adverse Event form**.

---

SmithKline Beecham Biologicals s.a.
VISIT 4
MONTH 6
56-70 DAYS AFTER VISIT 3

DOSE 4
REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the Non-Serious Adverse Events section or the Serious Adverse Event (SAE) form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the Medication section.
→ Please report concomitant vaccination in the Concomitant Vaccination section.

CONTRAINDICATIONS

→ Before any vaccine administration, please review the Contraindications as specified in the protocol
### LABORATORY TESTS

#### BLOOD SAMPLE

Has a blood sample been taken?  

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

### PRE-VACCINATION ASSESSMENT

#### PRE-VACCINATION TEMPERATURE

Temperature: [___] °C  
Route:  
- Axillary
- Oral
- Rectal

### GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms on the day of vaccination (before injection)?

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
</table>

→ **For each symptom**, please tick a No/Yes box.  
Please give intensity for any event observed just before injection.

#### Irritability / Fussiness

| No | Yes → intensity: [___] |

#### Drowsiness

| No | Yes → intensity: [___] |

#### Loss of appetite

| No | Yes → intensity: [___] |
## VACCINE ADMINISTRATION

Has the study vaccine been administered?

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td>Please specify reason:</td>
<td></td>
</tr>
</tbody>
</table>

### YES

<table>
<thead>
<tr>
<th>VACCINE ADMINISTRATION</th>
<th>Side / Site Route</th>
<th>Has the study vaccine been administered according to the protocol?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTPw-HBV vaccine mixed with Hib conjugate vaccine</td>
<td>Left Antero-lateral Thigh I.M.</td>
<td>Yes [ ] No [ ] If NO, please tick all items.</td>
</tr>
</tbody>
</table>

**Important:** concomitant administration of any other vaccine with the exception of OPV and /or BCG is not permitted. Concomitant administration of OPV and / or BCG vaccine as well as any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section**.

### POST-VACCINATION OBSERVATION

If any **adverse events** occurred during the immediate post-vaccination time specified in the protocol, please fill in the **Solicited Adverse Events section**, the **Non-Serious Adverse Events section** or the **Serious Adverse Event form**.

### MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions, please complete the **Medication section**.
SOLICITED ADVERSE EVENTS - LOCAL SYMPTOMS

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

**NO**  [ ]  **UNKNOWN**  [ ]

**YES**  [ ]  Please tick a No/Yes box for each symptom.

If Yes is ticked, please fill in the complete line.

<table>
<thead>
<tr>
<th>LOCAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>size:</td>
<td></td>
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<tr>
<td></td>
<td>No</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>Yes [ ]</td>
<td></td>
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<tr>
<td></td>
<td>Yes</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>size:</td>
<td></td>
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<td></td>
<td>No</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>Yes [ ]</td>
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<tr>
<td></td>
<td>Yes</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>day</td>
<td>month</td>
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<tr>
<td>Pain</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>intensity:</td>
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<tr>
<td></td>
<td>No</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>Yes [ ]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>day</td>
<td>month</td>
</tr>
</tbody>
</table>

**Intensity**: 0


Did the subject seek medical advice?

**NO**  [ ]  **YES**  [ ]  Please tick appropriate box(es):

- Redness  [ ]
- Swelling [ ]
- Pain  [ ]

If any of these adverse events is **serious** according to protocol definition,

**please report event to SB monitor by telephone or fax within 24 hours (see protocol) and complete the Serious Adverse Event form.**
### SOLICITED ADVERSE EVENTS - GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Relationship</th>
<th>Ongoing after Day 3?</th>
<th>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes → °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td>not taken</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Irritability/ Fussiness</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes → intensity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drowsiness</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes → intensity:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Loss of appetite</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes → intensity:</td>
<td></td>
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</tr>
</tbody>
</table>

Did the subject seek medical advice?

- NO ☐
- YES ☐ → please tick appropriate box(es): ☐

If any of these adverse events is serious according to protocol definition,

- please report event to SB monitor by telephone or fax within 24 hours (see protocol)
- and complete the Serious Adverse Event form.
VISIT 5
MONTH 7
30-35 DAYS AFTER VISIT 4
REMINDER

ELIMINATION CRITERIA

→ Please check all appropriate criteria before continuing the visit.

ADVERSE EVENTS

→ Please report adverse events as specified in the protocol and fill in the Non-Serious Adverse Events section or the Serious Adverse Event (SAE) form, as appropriate.

MEDICATION

→ Please report medication as specified in the protocol and fill in the Medication section.
→ Please report concomitant vaccination in the Concomitant Vaccination section.
### Laboratory Tests

#### Blood Sample

Has a blood sample been taken?  

- YES  
- NO  

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visit</th>
<th>Visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>213501/019 (DTPw-HBV-Hib-019)</td>
<td>VISIT 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Day</strong></td>
<td><strong>Month</strong></td>
</tr>
</tbody>
</table>

**Visit VISIT 5**

**Subject number**
CONCOMITANT VACCINATION
CONCOMITANT VACCINATION

Please report below any other vaccine(s) administered during the study period which are not recorded on the Vaccine Administration page.

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
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<td></td>
</tr>
</tbody>
</table>
MEDICATION

Concomitant medication and any other medication relevant to the protocol, including any specifically contraindicated - administered during the period starting from one week before each dose and ending one month (maximum 30 days) after must be recorded in this page.

<table>
<thead>
<tr>
<th>Trade / Generic Name</th>
<th>Medical Indication</th>
<th>Code</th>
<th>Date</th>
<th>if continuing at end of study, please tick box</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Start: [<strong>] [</strong>] [__]</td>
<td>[<strong>] [</strong>] [__]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>End: [<strong>] [</strong>] [__]</td>
<td>[<strong>] [</strong>] [__]</td>
</tr>
</tbody>
</table>

For SB

Enter appropriate code:
P: Prophylactic medication in anticipation of study vaccine reactions
T: Therapeutic
N: Neither of the above
NON-SERIOUS ADVERSE EVENTS
NON-SERIOUS ADVERSE EVENTS

→ Please report below all non-serious adverse events that occurred within one month (maximum 30 days) post-vaccination, excluding those recorded on the Solicited Adverse Events pages.

→ Please report all serious adverse events only on the Serious Adverse Event (SAE) form.

<table>
<thead>
<tr>
<th>AE No.</th>
<th>AE.1</th>
<th>AE.2</th>
<th>AE.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Serious Adverse Events Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local (injection site)</td>
<td>General (non injection site)</td>
<td>Local (injection site)</td>
<td>General (non injection site)</td>
</tr>
</tbody>
</table>

For SB

<table>
<thead>
<tr>
<th>Date Started</th>
<th>Date Stopped</th>
<th>Intensity</th>
<th>Medical advice</th>
<th>Relationship</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>NO</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>NO</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>NO</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

Medical advice
Did the subject seek medical advice?

<table>
<thead>
<tr>
<th>Medical advice</th>
<th>AE.1</th>
<th>AE.2</th>
<th>AE.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YES</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relationship

<table>
<thead>
<tr>
<th>Relationship</th>
<th>AE.1</th>
<th>AE.2</th>
<th>AE.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR: Not related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL: Unlikely</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU: Suspected (reasonable possibility)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB: Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AE.1</th>
<th>AE.2</th>
<th>AE.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Recovered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: Recovered with sequelae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: Ongoing at subject study conclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4: Died</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Non-Serious Adverse Events (Continued)

<table>
<thead>
<tr>
<th>AE No.</th>
<th>AE.4</th>
<th>AE.5</th>
<th>AE.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Serious Adverse Events Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Local</td>
<td>□ General (injection site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Local</td>
<td>□ General (injection site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Local</td>
<td>□ General (injection site)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### For SB

**Date Started**
- [ ] day month year during immediate post-vaccination period specified in protocol

**Date Stopped**
- [ ] day month year during immediate post-vaccination period specified in protocol

**Intensity**
- 1
- 2
- 3

**Medical advice**
- Did the subject seek medical advice? NO YES

**Relationship**
- NR: Not related NR
- UL: Unlikely UL
- SU: Suspected (reasonable possibility) SU
- PB: Probable PB

**Outcome**
- 1 : Recovered 1
- 2 : Recovered with sequelae 2
- 3 : Ongoing at subject study conclusion 3
- 4 : Died 4
- 5 : Unknown 5
SERIOUS ADVERSE EVENTS
INSTRUCTIONS FOR REPORTING SERIOUS ADVERSE EVENTS (SAE)

SAE's MUST BE REPORTED TO SMITHKLINE BEECHAM WITHIN 24 HOURS.

1. COMPLETE THE SAE PAGES OPPOSITE

   Please complete these pages as fully and accurately as possible in order to minimize the
time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Event Course" blank and
update it later.

2. SIGN AND DATE THE SAE PAGE.

3. PLEASE ENSURE THAT ALL INFORMATION ON THE FOLLOWING CRF
   PAGES IS COMPLETE.

   - Demographics
   - General Medical History / Physical Examination
   - Vaccine Administration page(s) (for doses administered)
   - Medication
   - Concomitant Vaccination

4. PHOTOCOPY THE SAE PAGES AND THE CRF PAGES SPECIFIED ABOVE.
   (Do not separate the NCR pages)

5. FAX A COPY OF THE SAE PAGES AND ALL THE CRF PAGES SPECIFIED
   ABOVE TO :

   → The SB Bio Safety Department, Rixensart, Belgium
     Fax number : [Redacted]

   → The local SB CRA / Medical Monitor
     (see Investigator Site File for appropriate fax number).

   → If no photocopier OR fax is available, please telephone
     to the local SB CRA / Medical Monitor within 24 hours.
### SERIOUS ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Person Reporting SAE:</th>
<th>(Please print clearly)</th>
<th>Serious Adverse Event</th>
<th>(Please print clearly)</th>
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</table>

<table>
<thead>
<tr>
<th>For SB</th>
<th>AEGIS Number:</th>
<th></th>
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</thead>
</table>

- **Date and Time Started**
  - [ ] day
  - [ ] month
  - [ ] year
  - [ ] hours
  - [ ] min

- **Date and Time Stopped**
  - [ ] day
  - [ ] month
  - [ ] year
  - [ ] hours
  - [ ] min

- **Intensity**
  - [ ] 1
  - [ ] 2
  - [ ] 3

- **Relationship to Study Vaccine**
  - [ ] NR Not related
  - [ ] UL Unlikely
  - [ ] SU Suspected (reasonable possibility)
  - [ ] PB Probable

- **Outcome**
  - [ ] 1 Recovered
  - [ ] 2 Recovered with sequelae
  - [ ] 3 Ongoing at subject study conclusion
  - [ ] 4 Died
  - [ ] 5 Unknown

- **Action taken with respect to Study Vaccine**
  - [ ] None
  - [ ] Vaccination course interrupted / restarted
  - [ ] Vaccination course stopped

- **Corrective Therapy**
  - [ ] Yes
  - [ ] No

- **Assessment**
  - The SAE is probably associated with:
    - [ ] Protocol design or procedures (but not to study vaccine)
      - *Please specify: ____________________________*
    - [ ] Another condition (eg, condition under study, intercurrent illness)
      - *Please specify: ____________________________*
    - [ ] Another drug
      - *Please specify: ____________________________*

- **Event Course**
  - [ ] Intermittent → No. of [ ] episodes
  - [ ] Constant

- **Was subject withdrawn due to this specific SAE?**
  - [ ] Yes
  - [ ] No
SERIOUS ADVERSE EVENTS (SAE) (CONTINUED)

Relevant Laboratory Data

Please provide relevant abnormal laboratory data below:

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Value</th>
<th>Units</th>
<th>Normal Range</th>
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<tbody>
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</table>

Remarks (please provide a brief narrative description of the serious adverse event, attaching extra pages eg, hospital discharge summary if necessary).

_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________
_________________________________________________________________________________________________________________________________________________

If applicable, was randomisation code broken at study site? □ No □ Yes

Randomisation / Study Vaccine Number: __________

Investigator Signature: ______________________________ Date: ______/_____/______
(confirming that the above data are accurate and complete)

Please PRINT name: ______________________________

For SB

SB Medical Monitor Signature: ______________________________ Date: ______/_____/______

Please PRINT name: ______________________________
STUDY
CONCLUSION
STUDY CONCLUSION

Has the subject dropped out of the study?
(a drop out is a subject who did not come back for the concluding visit foreseen in the protocol.)

NO □ YES □ → Mark the ONE most appropriate category for drop out

- [ ] Serious adverse event
  (complete the Serious Adverse Event form)
  → please specify AEGIS No.: __________________________

- [ ] Non-serious adverse event
  (complete the Non-Serious Adverse Events section)
  → please specify AE No.: __________________________

- [ ] Protocol violation
  → please specify: __________________________

- [ ] Consent withdrawal, not due to adverse events

- [ ] Migration from study area

- [ ] Lost to follow-up

- [ ] Others
  → please specify: __________________________

Date of last contact: [________] [________] [________]

Was the subject in good condition at date of last contact?

YES □

NO □ → Please give details within the Adverse Events section

INVESTIGATOR SIGNATURE

I certify that I have reviewed the data in this case report form and that all information is complete and accurate.

Date: [______] [______] [______] Investigator Signature: __________________________
This section contained Principal Investigator’s Curriculum Vitae and has been excluded to protect Principal Investigator privacy.
**Parent Information Sheet and Informed Consent**

**Study title:** Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of SmithKline Beecham Biologicals’ quadrivalent diphtheria, tetanus) whole cell Bordetella pertussis, hepatitis B (DTPw-HBV) and Haemophilus influenzae type b conjugate (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with SmithKline Beecham Biologicals’ hepatitis B vaccine.

**Investigator:** Dr. [Redacted]

**Sponsor:** SmithKline Beecham Biologicals

**CPMS Protocol number:** 213501/019 (DTPw-HBV-Hib-019)

**Date of approval:** Final: November 23, 1999
Amended: May 26, 2000

**Prepared by:** [Redacted] Scientific Writer

**Clinical Research and Development**

SmithKline Beecham Biologicals

This document should be presented to the parents/guardians in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the parents/guardians of the participant.
1. Introduction

The main objective of this document is to provide the parents/guardians of the potential study participant with the information necessary to help in deciding for your child to participate in the study with SmithKline Beecham Biologicals’ hepatitis B vaccine (Engerix™-B) combined diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine (Tritanrix™-HB), combined diphtheria-tetanus-whole cell Bordetella pertussis vaccine and Haemophilus influenzae type b conjugate vaccine (Hiberix™). The document aims to provide a full but simple understanding of the scientific reasons for investigation of the vaccines, the characteristics, effectiveness and safety of the vaccines, the likely effects and benefits of the study vaccines in the subjects. This document also informs parents/guardians of subjects about the rights and responsibilities of participating in the trial.

1.1. Background

1.1.1. Hepatitis B

Hepatitis B is a viral disease with more than 300 million carriers of the virus worldwide. The recognised routes of transmission of hepatitis B are parenteral or percutaneous (e.g. reuse of non-sterile needles and other medical and dental equipment, contaminated blood products, tattooing), perinatal (transmission from an infected mother to her infant), and horizontal (e.g. child-to-child), and sexual. As many as 90% of children who become infected with the disease under the age of 3 years become chronic carriers at high risk of serious consequences later in life, such as liver cancer or chronic hepatitis, which can lead to death due to cirrhosis. This probability is reduced to about 50% at 3 years of age, and 6% to 10% at 6 years of age. This last percentage is maintained from then on and throughout life. The World Health Organisation has recommended that hepatitis B vaccination be included in all national childhood immunisation programs. In your country, all infants receive their first dose of hepatitis B vaccine at birth.

1.1.2. Diphtheria-Tetanus-Pertussis

Diphtheria is a highly infectious disease spread through droplet transmission of the bacteria by infected people, characterised primarily by local inflammation of the throat and upper respiratory tract due to production of a toxin at these sites by
the causative bacteria. After acute disease, complications often occur due to damage of other sites such as the heart, kidneys and nervous system.

**Tetanus** (lockjaw) is an infectious disease caused by bacteria which are found in soil in most parts of the world. The bacteria infect humans by entering through a wound such as a splinter or nail puncture or almost any other injury into which contaminated soil may be introduced. Following infection, the bacteria produce a toxin which acts upon the central nervous system resulting in convulsive muscular spasms and eventually a generalised contraction usually leading to asphyxia and death.

**Pertussis** (whooping cough) is a highly infectious respiratory disease that predominantly affects infants and young children. The bacteria which cause this disease are spread by airborne respiratory secretions from infected individuals. It causes severe bouts of coughing, often with a characteristic “whoop”, each day, and may last for several months. Complications of the disease include middle ear inflammation, pneumonia, convulsions, brain damage and coma.

The combined diphtheria, tetanus, whole-cell pertussis vaccine has been available since the 1940’s and has been part of the World Health Organisation’s Program on Immunisation since the late 1970’s. It is well established as part of the routine paediatric vaccine practice worldwide.

1.1.3. **Haemophilus influenzae type b** (Hib)

*Haemophilus influenzae* type b or Hib is usually transmitted through airborne respiratory droplets or by contact with respiratory secretions. Hib can cause infections such as otitis media (infection of the middle ear) or sinusitis but it also can cause serious invasive disease such as pneumonia or meningitis. About one quarter of the children who survive Hib meningitis suffer permanent damage to the brain and/or nerves ranging from mild hearing loss to mental retardation. Hib disease is most common between the ages of 3 months to 3 years and is seldom seen after the age of 5 years. The World Health Organisation has recently recommended worldwide inclusion of vaccination against Hib in infant immunisation programs as appropriate to national capacities and priorities.
1.2. SmithKline Beecham Biologicals’ hepatitis B vaccine: Engerix™-B

SmithKline Beecham Biologicals’ hepatitis B vaccine (Engerix™-B) has been commercially available since 1986 and is universally accepted for administration to newborns.

1.3. SmithKline Beecham Biologicals’ combined diphtheria-tetanus-whole cell Bordetella pertussis-hepatitis B vaccine: Tritanrix™-HB

The recommendation for inclusion of immunisation against each individual disease requires the administration of a series of inoculations into the recommended schedule for infants and children. Multiple injections can be a significant barrier to compliance with immunisation.

SmithKline Beecham developed the first vaccine containing the universally recommended vaccines against diphtheria, tetanus, pertussis and hepatitis B (Tritanrix™ HB). This vaccine was approved for commercial use in your country in May 1998.

1.4. SmithKline Beecham Biologicals’ Haemophilus influenzae type b (Hib) conjugate vaccine: Hib vaccine

The first vaccine against Haemophilus influenzae type b (Hib) disease became available about 10 years ago and was rapidly included in routine vaccination schedules in many countries. SmithKline Beecham Biologicals has developed a Hib conjugate vaccine (Hiberix™) which was approved for commercial use in your country in May 1998. This vaccine is provided as a freeze-dried tablet, which will be reconstituted before use with the liquid DTPw-HBV vaccine.

Acceptance would be greatest if Hib vaccines would be available in combination with the diphtheria-tetanus-pertussis-hepatitis B combinations. Results of clinical studies performed in healthy infants vaccinated with SmithKline Beecham Biologicals’ Hiberix™ and Tritanrix™-HB have proven the mixing of the vaccines had no negative impact on the immune response to any of the 5 disease antigens nor on the safety profile of the individual vaccines.
1.5. Purpose of the study

This present study will assess the immunogenicity, safety and reactogenicity of a three dose immunisation course with Tritanrix™-HB and Hiberix™ vaccines mixed and administered as a single injection. The purpose of this study is to evaluate the antibody response to the hepatitis B antigen administered according to this regimen in infants who have previously received a dose of hepatitis B vaccine at birth.

2. Approval

This study protocol has been reviewed and accepted by an independent ethics review committee.

3. Study Participation

120 infants will be recruited for participation in this study. The study will last approximately 7 months and will consist of:

- Visits to the physician: 4 + the visit at birth
- Vaccinations: 4 Your child will receive one intramuscular injection into the left thigh at birth, 2, 4 and 6 months of age.
- Blood samples: 4 A blood sample will be obtained at birth, at the time of the second vaccination, a blood sample will be obtained at the time of the third vaccination and a blood sample will be obtained one month after the third vaccination to evaluate antibody response to the vaccine. The amount of blood that will be drawn at each time point will be approximately 3 millilitres (approximately ½ teaspoon). If any blood remains after the laboratory assay is performed to test for the presence of antibodies to the vaccine antigen components, this blood may be used in the future as part of anonymous sample for epidemiological investigations.
4. Risks Associated With The Study

Most vaccines cause some side effects in vaccinees. Local reactions such as soreness, redness or swelling might occur at the site of injection. Injection site soreness is the local symptom reported most commonly following vaccination with these vaccines. Short-lived general reactions such as fever, drowsiness, loss of appetite, restlessness and fussiness may sometimes occur.

You should contact the investigator immediately should your child manifest any signs or symptoms you perceive as serious.

The vaccines used in this study may cause some side effects that are not known at the present time. You will be informed of any new findings developed during the course of this research study. You will be notified in a timely manner of any information which becomes available that may be relevant to your willingness for your child to continue participation in this study.

There may be some discomfort, local soreness, or a bruise with the blood drawing. The amount of blood to be taken will not cause anaemia.

The vaccine will not cause diphtheria, tetanus, pertussis, hepatitis B or Hib infection.

5. Voluntary Participation

Participation in this study is voluntary. Although your continuos support will be appreciated, you have the right to withdraw your child from the study at any time with no obligation for further blood sampling or vaccination. Refusal to participate will involve no penalty or loss of benefits to which your child is
otherwise entitled. The investigator may withdraw your child from the study at any time he feels it to be in your child’s best interest. You are entitled to receive a signed copy of this form.

6. Alternative Measures of Prevention

In your country, there are other currently available vaccines, which may be used to protect your child against diphtheria, tetanus, pertussis, hepatitis B and/or Hib infection, which you may choose as an alternative to participation in this study. This vaccine, as previously described regarding the vaccine to be used in this study, can cause some side effects in vaccinees. Local reactions such as pain, redness or swelling might occur at the site of injection.

7. Confidentiality and Data Access

The identity of each participant will remain confidential. Your child will benefit from the protection and the rights granted by the European Union Data Protection Directive and your national laws on the protection of your child’s personal data.

You understand and consent to the following:

I. Your child’s personal data, including data relating to your child’s health, will be recorded and processed for the purpose assessing the outcome of the study. Processing will be done by SmithKline Beecham Biologicals (“SB Bio”) or may be contracted to a third party under strict confidentiality rules. Your child’s data may also be processed for product registration, notify organisations monitoring the safety and effectiveness of medicines. Your child’s data may also be processed in order to add to scientific knowledge;

II. Your child’s participation in the study will be treated as confidential: Your child will not be referred to by name in any report on the study and your child’s identity will not be disclosed to any person other than in circumstances where there is a need to check the correctness or completeness of data or to provide such information to regulatory agencies responsible for registration and safety of medicines;

III. Your child’s medical data or blood may be sent to and processed by any affiliate of SB Bio in any country inside or outside the European Union, always respecting the requirements of the EU Data Protection Directive (95/46/EC) and/or the equivalent applicable law;
IV. You may have access your child’s personal data and to have any justifiable corrections made. If you wish to do so, you should request this from the doctor conducting the study. You agree to the postponement of your access to your child’s medical data up to the completion of the study, including analysis and reporting of data, if deemed appropriate by the doctor conducting the study in order to safeguard the aim and conduct of the study;

V. Your child’s medical records may be accessed by representatives of SB Bio or regulatory bodies for medicines.

8. Right To Ask Questions And/Or Withdraw From The Study

You have the right to ask questions pertaining to the study or the potential risks related to it at any time. You will be informed of any significant new information pertaining to your child’s safety. If you have questions concerning this study, please contact:

________________________________________________________________________

Telephone number: __________________________________________________________

Fax number: ________________________________________________________________

Although your continuous support is appreciated, you have the right to withdraw your child from the study at any time and you/he/she will be under no further obligation for blood samplings or vaccinations.

9. Benefits Of The Study

Your child and other children in the future may benefit from this and other medical research studies. In this study, such benefits include:

- An assessment of your child’s response to the vaccination through analysis of blood samples - a procedure not usually performed outside the study situation.

- The principle benefit of your child’s participation in this study is the opportunity to be protected against 5 major diseases (diphtheria, tetanus,
pertussis, hepatitis B and Hib) with 4 injections, whereas in the past 9 injections were needed to reach this goal.

10. Compensation

If your child becomes ill or injured as a result of taking part in this clinical study, medical treatment will be provided according to good clinical practice and costs of such treatment will be paid for by SmithKline Beecham Biologicals. All participants in the study are covered by global insurance policy contracted by SmithKline Beecham Biologicals. If you have any questions concerning the availability of medical care or if you think your child has experienced a research-related illness or injury, please contact:

__________________________________________

__________________________________________

Telephone number: ________________________________

Fax number: ________________________________
Informed Consent

The diphtheria-tetanus-whole cell pertussis-hepatitis B and Hib vaccine study has been clearly explained to me and I have read and understood the information provided. I agree that my [son/daughter/ward] be enrolled in the study. I understand that my [son/daughter/ward] has the right to decline to enter the study and to withdraw from it at any time for any reasons, without consequence to his/her present or future health care and attention which my child/ward receives from his/her healthcare provider. I have been made aware of my right to access and request correction of my child’s/ward’s personal data. I acknowledge that I have received a copy of this form for future reference.

I, ________________________ ,
(subject’s parent or legal guardian’s first name and family name)

hereby freely give my consent for my child/ward to take part in this vaccine study.

Participant’s Name: ________________________  
(First Name, Family Name)

Parent/Guardian’s name: ________________________  
(First Name, Family Name)

Parent/Guardian’s signature: ________________________  
Relationship to participant: ________________________  
Participant’s main address: ________________________  
Participant’s phone number: ________________________  
Date: ________________________  Time: ________________________  
(DD-MM-YY)

Witness: ________________________  

Final  Page 10 of 11
Statement by Doctor, Nurse or Project Assistant who conducted the informed consent discussion:

I have carefully explained the nature, demands and foreseeable risks and benefits of the vaccination study to the person named above and witnessed the completion of the written informed consent.

Name: 
Signature: 
Designation: 
Date:  
Time:  
(DD-MM-YY)
GlaxoSmithKline Biologicals
Clinical Research and Development
Clinical Study Report Approval form

Report number: 213501/019 (DTPw-HBV-Hib-019)

Study title: Phase III, primary vaccination study to assess the immunogenicity and reactogenicity of GlaxoSmithKline Biologicals' (GSK) quadrivalent diphtheria, tetanus, whole cell Bordetella pertussis, hepatitis B (DTPw-HBV) and Haemophilus influenzae type b (Hib) vaccines when mixed extemporaneously and given in a single injection at 2, 4 and 6 months of age to healthy infants previously primed at birth with GSK Biologicals' hepatitis B vaccine.

Report date: 23 April, 2002

Report prepared by: [Redacted]

Report reviewed by: [Redacted]

Scientific Writer
Statistician
Statistician
Central Study Co-ordinator
Manager Clinical Safety
Scientific Writer (Peer review)
Regulatory

Signature/Date: 23/04/02
### GlaxoSmithKline Biologicals

#### Clinical Research and Development

**Clinical Study Report Approval form**

<table>
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<table>
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<tr>
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<tbody>
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<td>Scientific Writer</td>
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**Signature/Date:**

April 23, 2002
**GlaxoSmithKline Biologicals**  
**Clinical Research and Development**  
**Clinical Study Report Approval form**

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<td><strong>Vice President, Clinical Development International</strong></td>
<td>23/4/2002</td>
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Signature/ Date