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 208127/075 (HAB-075)

An integrated clinical/statistical report

A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigators: Dr. Dr. Australia

Study Start date: August 12, 1997
Study Completion date: March 14, 1998
Report date: March 26, 1999
Corrigendum date: March 31, 1999

See erratum sheet dated March 31, 1999 for details of the changes.

Verification and approval

[Signature] 18/5/01
Date (day/month/year)
Final Study Report 208127/075 (HAB-075)

An integrated clinical/statistical report

A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigators: Dr. [Name], Dr. [Name]

Australia

Study Start date: August 12, 1997
Study Completion date: March 14, 1998
Report date: March 26, 1999
Corrigendum date: March 31, 1999

See erratum sheet dated March 31, 1999 for details of the changes.

Dr. [Name] Principal Investigator

Date (day/month/year)

Dr. [Name] Principal Investigator

Date (day/month/year)
Final Study Report 208127/075 (HAB-075)

Erratum Sheet
for report dated March 26, 1999

The changes involve pages: 6 and 31

Changes:

- All these events were determined by the investigator to be ‘not related’ to the study vaccine.

- [Redacted text]
Final Study Report 208127/075 (HAB-075)

An integrated clinical/statistical report

A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigators: Dr. [Redacted], Dr. [Redacted], Australia

Study Start date: August 12, 1997

Study Completion date: March 14, 1998

Report date: March 26, 1999

Corrigendum date: March 31, 1999

See erratum sheet dated March 31, 1999 for details of the changes.
Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium
Name of Finished Product: Hepatitis A / Hepatitis B
Name of active substance: Hepatitis A (Strain HM 175 - RIT 4380) 
Hepatitis B (Recombinant HBsAg)

TABULAR FORMAT
REFERRING TO PART OF THE DOSSIER

<table>
<thead>
<tr>
<th>Volume</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Title of the study: Clinical Trial: 208127/075 (HAB-075)
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigators: Dr. [Redacted]
Dr. [Redacted]

Study centre: Australia

Publication (reference): None as of March 26, 1999

Studied period: Started: August 12, 1997
Completed: March 14, 1998

Clinical phase: III

Objectives:

Primary Objective:
• To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine one month after the last dose (month 7).

Secondary Objectives:
• To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
• To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
• To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

Methodology:

Study design: Double-blinded, randomized study with two groups.
Population group: Healthy male and female volunteers 11 to 18 years of age, all of whom qualified based on the inclusion / and exclusion criteria after screening results were available.

Number of subjects (total and for each treatment):
Enrolled: 150 (group 1 = 75, group 2 = 75); Completed: 149 (group 1 = 75, group 2 = 74)
Analysed for Reactogenicity: 149 (ATP); Analysed for Immunogenicity: 122 (ATP)

Diagnosis and criteria for inclusion:
Healthy volunteers aged 11 to 18 years, in good physical condition, seronegative for anti-HBc, anti-HBs and anti-HAV antibodies and HBsAg, at the time of screening.

Test product, dose, mode of administration, Lot No.:
Vaccination Schedule: 0, 6 month schedule
Site: Intramuscular (IM) in the deltoid muscle
Vaccine: SmithKline Beecham Biologicals’ combined high-dose hepatitis A - hepatitis B vaccine and SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine (Twinrix™)
### Name of Company
SmithKline Beecham Biologicals, Rixensart, Belgium

### Name of Finished Product
Hepatitis A / Hepatitis B

### Name of active substance
Hepatitis A (Strain HM 175 - RIT 4380)
Hepatitis B (Recombinant HBsAg)

<table>
<thead>
<tr>
<th>GROUP 1</th>
<th>GROUP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Hep A-Hep B (Twinrix™) vaccine</td>
<td>Combined high-dose Hep A - Hep B vaccine</td>
</tr>
<tr>
<td>Hepatitis A (Strain HM 175 - RIT 4380)</td>
<td>at least 720 EL U</td>
</tr>
<tr>
<td>Hepatitis B (recombinant HBsAg)</td>
<td>20 mcg</td>
</tr>
<tr>
<td>Aluminium salt</td>
<td>0.45 mg</td>
</tr>
<tr>
<td>Volume/dose</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>Lot number</td>
<td>HAB116C4/M</td>
</tr>
</tbody>
</table>

### Duration of treatment (study): 7 months

### Criteria for evaluation:

**Immunogenicity:** Seropositivity rates (S+) and GMTs for anti-HBs and anti-HAV antibodies and seroprotection rates (SP) for anti-HBs antibodies, in seroconverters, for all time points for which blood samples were taken. Seropositivity was defined as the appearance of antibodies (≥ 1 mIU/ml for anti-HBs antibodies and ≥ 33 mIU/ml for anti-HAV antibodies). Seroprotection rate for anti-HBs antibodies was defined as the percentage of subjects with titres ≥ 10 mIU/ml.

**Reactogenicity and Safety:** Recording of local and general solicited signs and symptoms by the vaccinees on diary cards on the day of vaccination and for 3 subsequent days, and unsolicited symptoms for 30 days post-vaccination. Recording of any serious adverse event during the study period.

### Statistical methods:

**Demographics:** Age and gender of the study cohort was tabulated and mean age, range and standard deviation, by gender of the enrolled subjects were calculated. Similar analyses were performed for subjects who were included in the different analysis of reactogenicity and immunogenicity. Mean ages between groups and gender was compared using Two-way ANOVA. Ratio of males to females was compared using Fisher’s exact test.

**Immunogenicity:** Seropositivity rates and GMTs, with 95% confidence interval, of anti-HAV antibodies and seroprotection rates for anti-HBs antibodies, in seroconverters was calculated for all time points for which blood sampling were taken. At month 7, GMTs were compared using One-way ANOVA / Kruskal-Wallis test and seropositivity rates were compared between groups using Fisher’s exact test.

**Reactogenicity and Safety:** The incidence of symptoms was calculated on the number of symptom sheets returned.

### SUMMARY-Results:

**Demography:** There was no statistically significant difference in the ratio of male and female subjects between groups and there was no statistically significant difference in age between groups and genders. Hence the two groups were comparable in terms of demography.

**Immunogenicity:** Seropositivity (S+) rates and GMTs of anti-HAV antibodies, seropositivity (S+) rates, seroprotection rates and GMTs of anti-HBs antibodies in seroconverters, for subjects included in the ATP analysis of immunogenicity were as follows:
**Name of Company:** SmithKline Beecham Biologicals, Rixensart, Belgium  
**Name of Finished Product:** Hepatitis A / Hepatitis B  
**Name of active substance:** Hepatitis A (Strain HM 175 - RIT 4380)  
Hepatitis B (Recombinant HBsAg)  

<table>
<thead>
<tr>
<th>Group</th>
<th>PI (m1)</th>
<th>PI (m2)</th>
<th>PI (m6)</th>
<th>PII (m7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N = 67</td>
<td>N = 67</td>
<td>N = 67</td>
<td>N = 67</td>
</tr>
<tr>
<td>Anti-HAV S+ %</td>
<td>97.0</td>
<td>95.5</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>89.6 - 99.6</td>
<td>87.5 - 99.1</td>
<td>94.6 - 100.0</td>
<td>94.6 - 100.0</td>
</tr>
<tr>
<td>GMT</td>
<td>349.3</td>
<td>193.1</td>
<td>135.0</td>
<td>5646.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>280.1 - 435.6</td>
<td>155.0 - 240.6</td>
<td>114.1 - 159.6</td>
<td>4510.0 - 7070.1</td>
</tr>
<tr>
<td>Anti-HBs S+ %</td>
<td>62.7</td>
<td>74.6</td>
<td>95.5</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>50.0 - 74.2</td>
<td>62.5 - 84.5</td>
<td>87.5 - 99.1</td>
<td>94.5 - 100.0</td>
</tr>
<tr>
<td>SP rate %</td>
<td>22.4</td>
<td>32.8</td>
<td>81.2</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.1 - 34.2</td>
<td>21.8 - 45.4</td>
<td>48.5 - 72.9</td>
<td>94.6 - 100.0</td>
</tr>
<tr>
<td>GMT</td>
<td>6.7</td>
<td>6.7</td>
<td>13.9</td>
<td>3046.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.2 - 10.7</td>
<td>4.8 - 9.3</td>
<td>10.1 - 19.2</td>
<td>2081.1 - 4459.8</td>
</tr>
<tr>
<td>2</td>
<td>N = 55</td>
<td>N = 55</td>
<td>N = 55</td>
<td>N = 55</td>
</tr>
<tr>
<td>Anti-HAV S+ %</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>93.5 - 100.0</td>
<td>93.5 - 100.0</td>
<td>93.5 - 100.0</td>
<td>93.5 - 100.0</td>
</tr>
<tr>
<td>GMT</td>
<td>533.3</td>
<td>318.5</td>
<td>249.1</td>
<td>9565.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>426.1 - 667.3</td>
<td>258.6 - 392.4</td>
<td>201.7 - 307.6</td>
<td>7932.5 - 11534.9</td>
</tr>
<tr>
<td>Anti-HBs S+ %</td>
<td>67.3</td>
<td>85.5</td>
<td>94.5</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>53.3 - 79.3</td>
<td>73.3 - 93.5</td>
<td>84.9 - 98.9</td>
<td>93.5 - 100.0</td>
</tr>
<tr>
<td>SP rate %</td>
<td>32.7</td>
<td>41.8</td>
<td>72.7</td>
<td>100.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>20.7 - 46.7</td>
<td>28.7 - 55.9</td>
<td>59.0 - 83.9</td>
<td>93.5 - 100.0</td>
</tr>
<tr>
<td>GMT</td>
<td>9.5</td>
<td>9.7</td>
<td>26.6</td>
<td>3497.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.8 - 15.7</td>
<td>6.6 - 14.3</td>
<td>17.4 - 40.6</td>
<td>2143.5 - 5706.8</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix lot HAB116C4/M  
Group 2 received combined high dose hepatitis A / B lot DHAB404A4  
S+ % = percentage of subjects who were seropositive (for anti-HAV: % of subjects with antibody titres ≥ the assay cut-off of 33 mIU/ml; for anti-HBs: % of subjects with antibody titre ≥ the assay cut-off of 1 mIU/ml)  
SP rate % = percentage of subjects who had seroprotective anti-HBs antibody titres (≥ 10 mIU/ml)  
PI (m1) = post-vaccination blood sampling at month 1, following dose 1  
PII (m7), etc. = post-vaccination blood sampling month 7, following dose 2  
N = number of subjects tested  
GMT = Geometric mean of the antibody titres  
95% CI = 95% confidence intervals  
Anti-HBV GMTs: PII(m7): p = 0.65 (one-way ANOVA)  
Anti-HAV GMTs: PII(m7): p = 0.003 (Kruskal-Wallis test)  

At months 6 and 7, all subjects in both groups were seropositive for anti-HAV antibodies. However, at all time points, the anti-HAV GMTs were higher in group 2 than group 1. By month 7, all subjects in both groups were seroprotected for anti-HBs antibodies.
**Name of Company:** SmithKline Beecham Biologicals, Rixensart, Belgium  
**Name of Finished Product:** Hepatitis A / Hepatitis B  
**Name of active substance:** Hepatitis A (Strain HM 175 - RIT 4380)  
Hepatitis B (Recombinant HBsAg)

### SUMMARY-Results: (continued)

**Reactogenicity:** Soreness at injection site was the most prevalent solicited local symptom. Only two solicited local symptoms were graded “3” in intensity and both events resolved by day 5 following vaccination.

Fatigue and headache were the most prevalent solicited general symptoms in groups 1 and 2, respectively. A total of 9 grade “3” solicited general symptoms were reported (5 in group 1 and 4 in group 2), of which 3 were determined by the investigator to have a ‘suspected’ relationship to the study vaccine. No grade “3” fever was reported.

The total incidence of solicited symptoms, grade “3” solicited symptoms, solicited symptoms with SU/PB relationship to the study vaccine and grade “3” solicited symptoms with SU/PB relationship to the study vaccine, according to per dose analysis, were as follows.

<table>
<thead>
<tr>
<th>Solicited local symptoms:</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Redness Total</td>
<td>37</td>
<td>25.0</td>
<td>35</td>
<td>23.3</td>
</tr>
<tr>
<td>&gt; 30mm, &gt; 24 hrs</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Soreness Total</td>
<td>81</td>
<td>54.7</td>
<td>105</td>
<td>70.0</td>
</tr>
<tr>
<td>grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>1.3</td>
</tr>
<tr>
<td>Swelling Total</td>
<td>22</td>
<td>14.9</td>
<td>18</td>
<td>12.0</td>
</tr>
<tr>
<td>&gt; 30mm, &gt; 24 hrs</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solicited general symptoms:</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue Total</td>
<td>39</td>
<td>26.4</td>
<td>48</td>
<td>32.0</td>
</tr>
<tr>
<td>PB/SU</td>
<td>21</td>
<td>14.2</td>
<td>27</td>
<td>18.0</td>
</tr>
<tr>
<td>Grade “3”</td>
<td>2</td>
<td>1.4</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Fever * Total</td>
<td>7</td>
<td>4.7</td>
<td>18</td>
<td>12.0</td>
</tr>
<tr>
<td>PB/SU</td>
<td>5</td>
<td>3.4</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Gastrointestinal Total</td>
<td>11</td>
<td>7.4</td>
<td>9</td>
<td>6.0</td>
</tr>
<tr>
<td>PB/SU</td>
<td>6</td>
<td>4.1</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Grade “3”</td>
<td>1</td>
<td>0.7</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache Total</td>
<td>26</td>
<td>17.6</td>
<td>50</td>
<td>33.3</td>
</tr>
<tr>
<td>PB/SU</td>
<td>15</td>
<td>10.1</td>
<td>27</td>
<td>18.0</td>
</tr>
<tr>
<td>Grade “3”</td>
<td>2</td>
<td>1.4</td>
<td>3</td>
<td>2.0</td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table II B.
Group 1 received Twinrix lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B lot DHAB404A4

*Fever defined as (axillary) temperature ≥ 37.5°C

N = total number of symptoms sheets completed
n = number of symptom sheets with a specific symptom (during the 4-day follow-up period which included the day of vaccination and the three subsequent days)

Total = total incidence of a symptom

PB/SU = symptoms determined by the investigator to have a ‘probable’/’suspected’ relationship to the study vaccine

Grade “3” = Adverse event which prevented normal everyday activities or fever >39.0°C
Name of Company: SmithKline Beecham Biologicals, Rixensart, Belgium

Name of Finished Product: Hepatitis A / Hepatitis B

Name of active substance:
- Hepatitis A (Strain HM 175 - RIT 4380)
- Hepatitis B (Recombinant HBsAg)

REPORT TO PART OF THE DOSSIER

Volume:

Page

Forty subjects (20 in group 1 and 20 in group 2) reported a total of 54 unsolicited symptoms (26 in group 1 and 28 in group 2) during the 30-day follow-up period after vaccination. Of the 53 doses (26 in group 1 and 27 in group 2) followed by at least one report of unsolicited symptoms classified by WHO Preferred Terms, 20 (37.7%) were followed by symptoms having a ‘probable’ or ‘suspected’ relationship to the study vaccine.

All these events were determined by the investigator to be ‘not related’ to the study vaccine.

SUMMARY-Conclusions:

- There was no statistically significant difference between the two groups in the anti-HBs GMTs at month 7, one month after the last dose.
- At months 1, 2 and 6, the seropositivity rates of anti-HAV and anti-HBs antibodies and seroprotection rate of anti-HBs antibodies were similar for the two groups.
- For the hepatitis A component of the vaccine, a licensed 2-dose schedule of the monovalent vaccine is already available and the data here, with the 2-dose Twinrix™ vaccine confirms the results of the monovalent vaccine. However with the high dose vaccine (1440/40), higher GMTs were elicited. For the hepatitis B component, there is no licensed 2-dose schedule available. Within the limitations of this study, it can be said that with 2 doses of Twinrix™, a good immune response was elicited.
- Within the limitations of this study, it can be concluded that the reactogenicity profile was similar in both groups, with the high dose (1440/40) profile being slightly more reactogenic overall, than the Twinrix™ vaccine (720/20).

Report date: March 26, 1999
## CONTENTS: TEXT

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. OBJECTIVES</td>
<td>11</td>
</tr>
<tr>
<td>2. MATERIALS AND METHODS</td>
<td>11</td>
</tr>
<tr>
<td>2.1 VACCINE</td>
<td>11</td>
</tr>
<tr>
<td>2.2 STUDY PARTICIPANTS AND INCLUSION/EXCLUSION CRITERIA</td>
<td>12</td>
</tr>
<tr>
<td>2.3 STUDY DESIGN</td>
<td>13</td>
</tr>
<tr>
<td>2.4 LABORATORY ANALYSIS</td>
<td>17</td>
</tr>
<tr>
<td>2.5 SAMPLE SIZE ESTIMATION</td>
<td>17</td>
</tr>
<tr>
<td>2.6 ANALYSIS OF RESULTS</td>
<td>18</td>
</tr>
<tr>
<td>3. RESULTS</td>
<td>21</td>
</tr>
<tr>
<td>3.1 ELIGIBILITY AND STUDY ATTRITION</td>
<td>21</td>
</tr>
<tr>
<td>3.2 DEMOGRAPHICS</td>
<td>22</td>
</tr>
<tr>
<td>3.3 IMMUNOGENICITY OF THE VACCINE</td>
<td>23</td>
</tr>
<tr>
<td>3.3.1 Analysis according to protocol</td>
<td>23</td>
</tr>
<tr>
<td>3.3.2 Intention-to-treat analysis</td>
<td>25</td>
</tr>
<tr>
<td>3.4 SAFETY AND REACTOGENICITY OF THE VACCINE</td>
<td>26</td>
</tr>
<tr>
<td>3.4.1 Study compliance</td>
<td>26</td>
</tr>
<tr>
<td>3.4.2 Overall incidence of symptoms</td>
<td>27</td>
</tr>
<tr>
<td>3.4.3 Solicited signs and symptoms</td>
<td>27</td>
</tr>
<tr>
<td>3.4.4 Unsolicited signs and symptoms</td>
<td>30</td>
</tr>
<tr>
<td>3.4.5 Serious adverse events</td>
<td>31</td>
</tr>
<tr>
<td>3.4.6 Concomitant medication</td>
<td>31</td>
</tr>
<tr>
<td>4. CONCLUSIONS</td>
<td>32</td>
</tr>
</tbody>
</table>

TOTAL NUMBER OF PAGES: 155
CONTENTS: REPORT TABLES AND FIGURES

FIGURE 1: NUMBER OF SUBJECTS ................................................................. 21
FIGURE 2 : REASONS FOR DROP OUT .......................................................... 22
TABLE 1 : REFERENCE RATE OF A SYMPTOM ............................................. 18
TABLE 2 : INTERVALS BETWEEN STUDY VISITS .......................................... 19
TABLE 3 : DEMOGRAPHICS - SUBJECTS INCLUDED IN THE ATP ANALYSIS OF IMMUNOGENICITY ..... 23
TABLE 4 : SEROPOSITIVITY RATES (S+), SEROPROTECTION RATES (SP) AND GMTS OF ANTI-HBS ANTIBODIES OF SEROCONVERTERS (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF IMMUNOGENICITY) ................................................................. 24
TABLE 5 : SEROPOSITIVITY RATE (S+) AND GMTS OF ANTI-HAV ANTIBODIES OF SEROCONVERTERS (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF IMMUNOGENICITY) ................................................................. 25
TABLE 6 : SEROPOSITIVITY RATES (S+), SEROPROTECTION RATES (SP) AND GEOMETRIC MEAN TITRES (GMT) OF ANTI-HBS ANTIBODIES (TOTAL POPULATION) ................................................................. 26
TABLE 7 : SEROPOSITIVITY RATE (S+) AND GMTS OF ANTI-HAV ANTIBODIES (TOTAL POPULATION) ................................................................. 26
TABLE 8 : INCIDENCE AND NATURE OF SYMPTOMS AFTER EACH VACCINE DOSE AND OVERALL FOR SUBJECTS INCLUDED IN THE OVERALL ANALYSIS OF REACTOGENICITY ................................................................. 27
TABLE 9 : INCIDENCE OF SOLICITED LOCAL SYMPTOMS AFTER EACH VACCINE DOSE AND OVERALL, ACCORDING TO PER DOSE ANALYSIS (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF REACTOGENICITY) ................................................................. 28
TABLE 10 : INCIDENCE OF SOLICITED GENERAL SYMPTOMS AND THOSE WITH PB/SU RELATIONSHIP TO VACCINATION, INCIDENCE OF SOLICITED GENERAL SYMPTOMS WITH INTENSITY GRADE “3” AND THOSE WITH PB/SU RELATIONSHIP TO VACCINATION, AFTER EACH VACCINE DOSE AND OVERALL (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF REACTOGENICITY) ................................................................. 29
CONTENTS: SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1: DEMOGRAPHY - TOTAL POPULATION .......................................................... 33
SUPPLEMENTARY TABLE 2: DEMOGRAPHICS - SUBJECTS INCLUDED IN THE ATP ANALYSIS OF
  REACTOGENICITY ............................................................................................................................ 34
SUPPLEMENTARY TABLE 3: INCIDENCE AND DURATION OF SOLICITED LOCAL SYMPTOMS AFTER
  EACH VACCINE DOSE AND OVERALL ............................................................................................ 35
SUPPLEMENTARY TABLE 4: INCIDENCE AND DURATION OF SOLICITED GENERAL SYMPTOMS AFTER
  EACH VACCINE DOSE AND OVERALL ............................................................................................ 36
SUPPLEMENTARY TABLE 5: NUMBER OF UNSOLICITED SIGNS AND SYMPTOMS CLASSIFIED BY WHO
  PREFERRED TERM REPORTED DURING THE 30-DAY FOLLOW-UP PERIOD (DAYS 0-30) AFTER
  VACCINATION (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF REACTOGENICITY) .............. 37
SUPPLEMENTARY TABLE 6: NUMBER OF UNSOLICITED SIGNS AND SYMPTOMS CLASSIFIED BY WHO
  PREFERRED TERM REPORTED DURING THE 30-DAY FOLLOW-UP PERIOD (DAYS 0-30) AFTER
  VACCINATION, DETERMINED BY THE INVESTIGATOR TO HAVE A 'PROBABLE' OR 'SUSPECTED'
  RELATIONSHIP TO THE STUDY VACCINE (SUBJECTS INCLUDED IN THE ATP ANALYSIS OF
  REACTOGENICITY) ......................................................................................................................... 38
SUPPLEMENTARY TABLE 7: NUMBER OF DOSES FOLLOWED BY AT LEAST ONE REPORT OF
  UNSOLICITED SYMPTOMS AND NUMBER OF DOSES FOLLOWED BY AT LEAST ONE REPORT OF
  GRADE “3” UNSOLICITED SYMPTOMS, CLASSIFIED BY WHO PREFERRED TERMS, ACCORDING
  TO RELATIONSHIP, SYMPTOMS REPORTED DURING THE 30-DAY FOLLOW-UP PERIOD (SUBJECTS
  INCLUDED IN THE ATP ANALYSIS OF REACTOGENICITY) .......................................................... 39
## CONTENTS: APPENDIX TABLES

<table>
<thead>
<tr>
<th>Section</th>
<th>Subsection</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reasons for Elimination</td>
<td>Codes used</td>
<td>40</td>
</tr>
<tr>
<td>Notes for appendix tables</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>I Individual subject data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Elimination codes</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>B Demography</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>C Dates of birth, vaccination and blood sampling</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>D General medical history - physical examination</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>E Study Conclusion</td>
<td>70</td>
</tr>
<tr>
<td>II Reactogenicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Solicited local adverse events</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>B Solicited general adverse events</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>C Unsolicited adverse events</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>D Concomitant medication</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>E Serious Adverse Events</td>
<td>146</td>
</tr>
<tr>
<td>III Serology Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Immunogenicity</td>
<td>154</td>
</tr>
</tbody>
</table>
1. Objectives

A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

The specific objectives of this study were:

**Primary objective:**
- To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine one month after the last dose (month 7).

**Secondary objectives:**
- To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti HBs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
- To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies, seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
- To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

2. Materials and Methods

2.1 Vaccine

The combined high-dose hepatitis A/hepatitis B vaccine and Twinrix™ used in this study was prepared by SmithKline Beecham Biologicals, Rixensart, Belgium. The vaccine lots used in this study conformed to SmithKline Beecham Biologicals’ Quality Control Standards and Requirements and the required approvals were obtained.
Group 1 received combined hepatitis A / hepatitis B vaccine (Twinrix™) and group 2 received combined high-dose hepatitis A / hepatitis B vaccine. Antigen content in the vaccine lots used in this study were as follows:

<table>
<thead>
<tr>
<th>Group: Group 1</th>
<th>Group 2 Combined high-dose hep A/hep B vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine received: Combined hep A/hep B vaccine (Twinrix™) at least 720 EL.U</td>
<td>Combined high-dose hep A/hep B vaccine at least 1440 EL.U</td>
</tr>
<tr>
<td>Inactivated Hepatitis A antigen (Strain HM 175 - RIT 4380)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B antigen (recombinant HBsAg)</td>
<td>20 mcg</td>
</tr>
<tr>
<td>Aluminium salt</td>
<td>0.45 mg</td>
</tr>
<tr>
<td>Volume/dose</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>Lot number</td>
<td>HAB116C4/M</td>
</tr>
</tbody>
</table>

### 2.2 Study participants and inclusion/exclusion criteria

Subjects who volunteered to participate in this study were healthy adolescents of either sex. A medical evaluation including physical examination and medical history established acceptability for enrollment into the study. The investigator made the decision to include subjects in the study based on the inclusion / exclusion criteria.

**Inclusion criteria:**

- Age: from 11 to 18 years of age.
- Good physical condition as established by clinical examination and history taking at the time of entry
- Sexually active female participants would avoid becoming pregnant during the study period and would have been on a contraceptive program for at least two months before study entry
- Written informed consent would have been obtained from the parents/guardians of the subjects and/or from subjects themselves depending upon local regulations.

**Exclusion criteria:**

- History of hepatitis
- History of previous vaccination against hepatitis A or B.
- History of significant and persisting hematologic, hepatic, renal, cardiac or respiratory disease
- Any acute disease at the moment of entry
- Chronic alcohol consumption
- Hepatomegaly, right upper quadrant abdominal pain or tenderness
- Any chronic drug treatment, including any treatment with immunosuppressive drugs, which in the investigator’s opinion, precluded inclusion into the study
• History of allergic disease likely to be stimulated by any component of the vaccine
• Administration of immunoglobulins within six months of the first vaccination or during the study period
• Receipt of any other vaccine within 1 week of a dose of the study vaccine (period extending from 1 week before to 1 week after a dose of vaccine)
• Simultaneous participation in another clinical trial, the only exception being involvement in long-term follow-up in another vaccine trial

2.3 Study design

The study was approved by the ethics committee of [redacted] on July 11, 1997. The study was conducted in accordance with the provisions of the Declaration of Helsinki as amended in Hong Kong (1989). The study took into consideration the guidelines of Good Clinical Practice (GCP) in place at the study outset.

One hundred and fifty subjects were planned for recruitment and 150 were enrolled into the study to receive the combined high-dose hepatitis A / hepatitis B vaccine according to a 0, 6-month vaccination schedule or combined hepatitis A / hepatitis B vaccine (Twinrix™) according to a 0, 6 month schedule.

Monodose vials were coded according to a randomisation list prepared by the sponsor. The randomisation was made using an algorithm of pseudo random numbers (given by RS/1 from BBN). The subjects were allocated at random to one of the two groups in the order in which they were enrolled into the study starting with the number 1.

The vaccines, which were packed and supplied by the sponsor, were labeled with the subject number, the study number and the name of the sponsor. Each subject was given only the vaccines carrying his/her study number. The vaccines were administered intramuscularly in the deltoid region.

Written informed consent was obtained prior to the first blood sampling (visit 1). All subjects were free to withdraw from the study at any time. It was determined that in all cases, the reason for withdrawal would be recorded by the investigator.

Blood samples were obtained on the day of first vaccination (day 0/month 0) and at months 1, 2, 6, and 7 and tested for the presence of anti-HAV and anti-HBs antibodies. Pre-vaccination samples were also assayed for anti-HBc antibodies and HBsAg.

History taking and evaluation of suitability for participation in the study according to the established inclusion/exclusion criteria and physical examination (including
axillary body temperature) and documentation of baseline symptomatology occurred on the first visit (Month 0/Day 0) prior to administration of the first vaccine dose. Documentation of baseline symptomatology was also done at the fourth visit (before dose 2). The pre-vaccination temperature values were erroneously transcribed as the 15 minutes post vaccination temperature (for both doses) and have therefore been considered as the baseline temperature for analysis for both doses. However, each vaccinee was closely observed for 15 minutes following vaccination for any sign of acute reaction to the vaccine. The 15 minutes post-vaccination temperature values are therefore not available for any of the subjects, after both vaccine doses.

Recording of reactions:

Five to nine hours post vaccination, and in the morning for three subsequent days, systemic / general and local injection site signs and symptoms, including axillary body temperature, and any other findings were recorded by the vaccinee on the diary card provided by the sponsor. The vaccinees were instructed to return the completed diary card with signs/symptoms on the next visit. On that occasion, the forms completed by the vaccinee was transcribed into the individual case report forms (CRF) by the clinical investigator after checking for completion and accuracy.

Diary cards were designed to record information on the following signs and symptoms:

- **General symptoms:**
  - Temperature***
  - Headache*
  - Fatigue*
  - Gastrointestinal symptoms*
  - Any other general symptoms reported by the volunteer*
    (to be specified)

- **Local symptoms:**
  - Soreness*
  - Redness size**
  - Swelling size**
  - Any other local reactions reported by the volunteer*
    (to be specified)

*Systemic and local reactions were scored on a scale of 0 to 3 in severity, which was defined as follows:

0 : No adverse event
1: Adverse event which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: Adverse event sufficiently discomforting to interfere with daily activities.
3: Adverse event which prevents normal everyday activities and necessitates medical advice. (In an adult, such an adverse event would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

**The size of redness and swelling was obtained by measuring their longest diameter and was scored at SmithKline Beecham Biologicals as follows:
1: $\geq 30$ mm
2: $>30$ mm
3: $>30$ mm and persisting more than 24 hours

***The temperature was recorded only when it was $37.5^\circ$C or above and was scored at SmithKline Beecham Biologicals as follows:
1: $37.5^\circ$C - $38.0^\circ$C
2: $>38.0^\circ$C - $39.0^\circ$C
3: $>39.0^\circ$C

Unsolicited symptoms:

Any adverse event that occurred within one month (maximum of 30 days) following administration of each vaccine dose were recorded. These unsolicited symptoms were reported with date of onset and end date, intensity and outcome. The relationship to the vaccination were assessed by the investigator.

The relationship of all reported adverse events following vaccination was assessed by the investigator and recorded in the Case Report Form (CRF). Relationships were assessed as either:

NR: Not Related The adverse event is definitely not related to the study vaccine.
UL: Unlikely There are other more likely causes and the study vaccine is not suspected as a cause.
SU: Suspected (reasonable possibility) The direct cause and effect relationship between the drug and the adverse event has not been demonstrated but there is a reasonable possibility that the event was caused by the study vaccine.
PB: Probable There is probably a direct cause and effect relationship between the adverse event and the study vaccine.

It was the responsibility of the investigator to document all adverse events which occurred within 30 days after each dose administration of the study vaccine. The nature of each event, time of onset after vaccine administration, duration, severity
and relationship to vaccination were established. Treatment of any adverse event was at the sole discretion of the investigator and according to current GCP. Treatment measures were reported in the CRF of the vaccinee. The investigator followed patients with adverse event until the event subsided or until the condition had stabilised.

Any concomitant medication administered during the period extending from 1 month prior until 1 month after each vaccination was recorded in the medication section of the Case Report Form including: name, medical condition, code, start and end dates of treatment. Medications which do not need to be recorded include any homeopathic remedies vitamins and contraceptives.

For antipyretics/analgesics, it was specified whether they were given *prophylactically* in anticipation of a reaction to the vaccine or to treat an existing symptom (therapeutic use). If used prophylactically in anticipation of vaccines reactions, it was coded as “P” within the “medical indication” field of the CRF.

The outcome of adverse events was indicated as follows:

1: Recovered
2: Recovered with sequelae
3: Ongoing
4: Died
5: Unknown

Should any serious adverse event or any severe signs or symptoms occur, the subject was to immediately contact the investigator. Notification by the investigator to SmithKline Beecham was required *within 24 hours of his becoming aware of any serious adverse event occurring during the clinical trial or within 30 days of receiving the last dose of the study vaccine.*

A serious adverse event was defined as any event that, in the investigator’s opinion, posed a significant hazard to the vaccinee and always included:

1. Fatal
2. Life-threatening
3. Disabling or incapacitating
4. Results in hospitalisation or prolongation of hospitalisation

or was

5. A congenital abnormality (in offspring)
6. A cancer
7. An overdose of the vaccine or an adverse event associated with an overdose (either accidental or intentional)
In addition, any adverse event which suggested a significant hazard, contraindication, side effect, or precaution that may be associated with the use of the vaccine was considered a serious adverse event. Following the telephone report, a full written report would follow which included all relevant supporting documentation such as hospital case records, eventual post-mortem reports and/or other documents where applicable.

2.4 Laboratory analysis

Screening serology

Blood samples obtained at the first visit (Day 0) were tested at SmithKline Beecham Biologicals’ laboratory for:

- Anti-HAV, anti-HBs and anti-HBc antibodies
- HBsAg

Antibody titration

At each following visit serum were collected for measurement of anti-HBs and anti-HAV antibodies in SmithKline Beecham Biologicals’ laboratory.

Radioimmunoassay technique (RIA technique) was used to test the presence of HBsAg (AUSAB - Abbott) and anti-HBc (Corab-Abbott).

Antibody titres (anti-HAV and anti-HBs) were expressed in mIU/ml, with reference to World Health Organisation (WHO) standard sera. Anti-HAV antibodies will be measured at day 0, months 1, 2, 6 and 7, using Enzymun (Boehringer Mannheim) kit. The cut-off level of this test is 33 mIU/ml. Measurements of anti-HBs antibodies at day 0, months 1, 2, 6 and 7 were performed using a commercial radioimmunoassay kit (AUSAB-Abbott). The cut-off level of this test is 1 mIU/ml.

2.5 Sample size estimation

Taking into consideration a 10% dropout potential and the seroprevalence of hepatitis A (no screening was planned and it was decided that subjects who were seropositive for anti-HAV at day 0, would be eliminated from the immunogenicity analysis), 150 subjects (75 per group) were enrolled to have at least 90 (45/group) evaluable subjects.

Primary objective: It was planned that a sample size of 45 evaluable subjects per group would enable us to reject the null hypothesis of equivalence of anti-HBs GMTs between groups, if the difference exceeded 50%. The calculation was made
with a type I error of 5% and a type II error of 20%. For these calculation, a variability of log titres of 0.7441 for anti-HBs was used. The variability used came from data generated from a previous study with the combined hepatitis A and B vaccine.

Secondary objectives: It was planned that a sample size of 45 subjects per group would enable us to reject the null hypothesis of equivalence of anti-HAV GMTs between groups, if the difference exceeded 50%. With a type I error of 5% and variability of log titres of 0.1299 for anti-HAV, it was planned that we would reach a power of 97.6%. The variability used came from data generated on a previous study with the combined hepatitis A and vaccine.

For reactogenicity analysis, with the sample size of 45 subjects per group, we would be allowed to detect differences mentioned in the table hereafter with a type I error of 5%, a power of 80% and a reference rate of a symptom or combination of symptoms reported by 1, 2, 5, 10, 20 and 50% of subjects (See Table 1).

<table>
<thead>
<tr>
<th>Reference rate (in %)</th>
<th>Detectable difference (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>21.7</td>
</tr>
<tr>
<td>5</td>
<td>24.1</td>
</tr>
<tr>
<td>10</td>
<td>26.8</td>
</tr>
<tr>
<td>20</td>
<td>29.9</td>
</tr>
<tr>
<td>50</td>
<td>29.9</td>
</tr>
</tbody>
</table>

2.6 Analysis of results

In order to adequately assess the immune responses elicited by the vaccine, time intervals to have been respected between vaccination and blood sampling were detailed in the protocol and were as follows.

These intervals served only as a target and the adapted intervals served as an absolute criterion for inclusion or exclusion from the study. The absolute (Adapted) intervals for inclusion or exclusion in the according-to-protocol analyses are given in Table 2.
Table 2: Intervals between study visits

<table>
<thead>
<tr>
<th>Visit</th>
<th>Protocol-defined intervals</th>
<th>Adapted intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Screening)</td>
<td>-14 days to -7 days</td>
<td>-30 days to -2 days</td>
</tr>
<tr>
<td>2 (Month 1)</td>
<td>30 ± 7 days vs day 0</td>
<td>30 ± 10 days vs day 0</td>
</tr>
<tr>
<td>3 (Month 2)</td>
<td>60 ± 7 days vs day 0</td>
<td>60 ± 14 days vs day 0</td>
</tr>
<tr>
<td>4 (Month 6)</td>
<td>180 ± 14 days vs day 0</td>
<td>180 ± 21 days vs day 0</td>
</tr>
<tr>
<td>5 (Month 7)</td>
<td>30 ± 7 days vs M6</td>
<td>30 ± 10 days vs M6</td>
</tr>
</tbody>
</table>

**Demographics**

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

Similar analysis was performed for subjects who were included in the different analyses of reactogenicity and immunogenicity.

Mean ages between groups and gender were compared using Two-way ANOVA. Ratio of males to females between groups were compared using Fisher’s exact test.

**Immunogenicity**

Two analyses were performed: a first one, which included only subjects corresponding to criteria defined in the protocol (according-to-protocol analysis - ATP) and a second one which included all data available from all subjects (intention-to-treat analysis - ITT).

Seropositivity rates and geometric mean titres (GMTs) with 95% confidence intervals for anti-HBs and anti-HAV antibodies and seroprotection rates for anti-HBs antibodies, were calculated for all time points for which blood samples are taken.

Seropositivity was defined, at each time point, as appearance of antibody titres (≥ 1 mIU/ml anti-HBs antibodies and ≥ 33 mIU/ml for anti-HAV antibodies).
Seroconversion was defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample. Seroprotection for anti-HBs antibodies was defined as the percentage of subjects with titres ≥10 mIU/ml.

The GMTs were calculated using the log-transformation of seropositive titres (≥ 33 mIU/ml for anti-HAV, ≥ 1 mIU/ml for anti-HBs) and taking the anti-log of the mean of these transformed values.
At month 7, GMTs were compared between groups using one-way ANOVA / Kruskal-Wallis test and seropositivity rates were compared between groups using Fisher’s exact test.

**Reactogenicity**

Incidence, frequency, intensity and duration (≤ or > 24 hours) of individual solicited local symptoms; incidence, frequency, intensity, duration (≤ or > 24 hours) and relationship of individual solicited general symptoms, unsolicited symptoms and serious adverse events were evaluated. The incidence was calculated on the number of symptom sheets returned.

Unsolicited adverse events were recorded throughout the clinical trial. The verbatim reports of unsolicited symptoms were 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.
3. Results

3.1 Eligibility and study attrition

A flow chart of subject enrollment and eligibility for analysis is presented in Figure 1. Figure 2 lists the number of drop-outs and the reasons for drop out. Elimination codes are defined in the Appendix Table I A. The details of code numbers are listed on the first page of the Appendix Tables.

Figure 1: Number of subjects

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1 Twinrix™</th>
<th>Group 2 (High-dose vaccine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects enrolled</td>
<td>150 (100 %)</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Elimination due to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administration of vaccine(s) forbidden, in the protocol (code 1040)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of subjects included in the ATP analysis of reactogenicity</td>
<td>149 (99.3%)</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Elimination due to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol violation (code 2010)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Initially seropositive or initially unknown antibody status (code 2020)</td>
<td>24</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule (code 2080)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Essential serological data missing. (code 2100)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of subjects included in the ATP analysis of immunogenicity</td>
<td>122 (81.3%)</td>
<td>67</td>
<td>55</td>
</tr>
</tbody>
</table>

Subjects may have one or more elimination code(s) assigned in which case the lowest code number is listed in the figure. The elimination code numbers are given in parentheses next to the code description (see the first page of Appendix Tables for details of code numbers).

Eligibility for analysis

A total of 150 volunteers were enrolled in the study, of which 149 subjects were included in the ATP analysis of reactogenicity.

A total of 27 subjects were eliminated from the ATP immunogenicity analysis and hence there were 122 subjects included in the ATP analysis of immunogenicity.
were eliminated because they were initially seropositive for anti-HBs or anti-HAV antibodies.

**Study attrition**

Of the 150 subjects enrolled, 149 completed the study up to month 7.

**Figure 2: Reasons for drop out**

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Reason For Drop Out*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Planned (protocol)</td>
</tr>
<tr>
<td>Overall</td>
<td>150</td>
</tr>
<tr>
<td>Group 1</td>
<td>75</td>
</tr>
<tr>
<td>Group 2</td>
<td>75</td>
</tr>
</tbody>
</table>

* Reasons For Drop Out:  
  A - Serious Adverse Event  
  B - Non-Serious Adverse Event  
  C - Protocol Violation  
  D - Consent Withdrawal  
  E - Migration from study area  
  F - Lost To Follow up for full vaccination course  
  G - Lost To Follow up for final blood sample  
  H - Others Reasons  
  C-H : Not related to any adverse event.

### 3.2 Demographics

Individual details of demographic data are listed in Appendix Table IB. Individual details of the subjects’ birth dates, vaccination and blood sampling are listed in Appendix Table IC. The demographics of the subjects included in the ATP analysis of immunogenicity are given in Table 3. Supplementary Tables 1 and 2 present the demographics of the total study population and the study cohort included in the analysis of reactogenicity, respectively.

All subjects (except two) enrolled in the study were of the race “white”.
Table 3: Demographics - Subjects included in the ATP analysis of immunogenicity

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Min age (years)</th>
<th>Max age (years)</th>
<th>S.D (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>36</td>
<td>15.0</td>
<td>12</td>
<td>17</td>
<td>1.44</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>31</td>
<td>14.6</td>
<td>12</td>
<td>17</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>67</td>
<td>14.8</td>
<td>12</td>
<td>17</td>
<td>1.57</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>26</td>
<td>14.7</td>
<td>12</td>
<td>17</td>
<td>1.44</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>29</td>
<td>14.7</td>
<td>12</td>
<td>17</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>55</td>
<td>14.7</td>
<td>12</td>
<td>17</td>
<td>1.45</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>62</td>
<td>14.9</td>
<td>12</td>
<td>17</td>
<td>1.44</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>60</td>
<td>14.6</td>
<td>12</td>
<td>17</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>122</td>
<td>14.8</td>
<td>12</td>
<td>17</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table IB

Group 1 received Twinrix® (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
N = total number of subjects
S.D. = Standard Deviation

Male-to-female ratio between groups: p = 0.59 (Fisher’s exact test); group factor: p = 0.68 (two-way ANOVA); gender factor: p = 0.42 (two-way ANOVA); interaction group-gender: p = 0.42 (two-way ANOVA)

For subjects included in the total population, subjects included in the ATP analyses of immunogenicity or reactogenicity, there was no statistically significant difference in the ratio of male and female subjects between groups and there was no statistically significant difference in age between groups and genders. Hence the two groups were comparable in terms of demography.

### 3.3 Immunogenicity of the vaccine

Individual immunogenicity data can be found in Appendix III A. Two immunogenicity analyses were performed : an analysis according to protocol which included all evaluable subjects, i.e., those who fulfilled the criteria defined in the protocol and for whom assay results were available for antibodies against at least one study vaccine antigen component for at least one blood sampling time point. The second analysis performed was the intention-to-treat analysis which included all subjects for whom assay results were available for antibodies against at least one study vaccine antigen component for at least one blood sampling time point.

#### 3.3.1 Analysis according to protocol

**Hepatitis B response**

Seropositivity rates (antibody titres ≥ 1 mIU/ml), seroprotection rates (antibody titres ≥ 10 mIU/ml) and GMT with 95% confidence interval, of anti-HBs
antibodies, for subjects included in the ATP analysis of immunogenicity are given in Table 4.

**Table 4 : Seropositivity rates (S+), seroprotection rates (SP) and GMTs of anti-HBs antibodies of seroconverters (Subjects included in the ATP analysis of immunogenicity)**

<table>
<thead>
<tr>
<th>G</th>
<th>Timing</th>
<th>N</th>
<th>S+ n</th>
<th>CI 95%</th>
<th>SP n</th>
<th>CI 95%</th>
<th>GMT</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI(m1)</td>
<td>67</td>
<td>42 62.7</td>
<td>50.0 74.2</td>
<td>15 22.4</td>
<td>13.1 34.2</td>
<td>6.7 10.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>67</td>
<td>50 74.6</td>
<td>62.5 84.5</td>
<td>22 32.8</td>
<td>21.8 45.4</td>
<td>6.7 9.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>67</td>
<td>64 95.5</td>
<td>87.5 99.1</td>
<td>41 61.2</td>
<td>48.5 72.9</td>
<td>13.9 19.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>67</td>
<td>67 100.0</td>
<td>94.6 100.0</td>
<td>67 100.0</td>
<td>94.6 100.0</td>
<td>3046.5 4459.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PI(m1)</td>
<td>55</td>
<td>37 67.3</td>
<td>53.3 79.3</td>
<td>18 32.7</td>
<td>20.7 46.7</td>
<td>9.5 15.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>55</td>
<td>47 85.5</td>
<td>73.3 93.5</td>
<td>23 41.8</td>
<td>28.7 55.9</td>
<td>9.7 14.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>55</td>
<td>52 94.5</td>
<td>84.9 98.9</td>
<td>40 72.7</td>
<td>59.0 83.9</td>
<td>26.6 40.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>55</td>
<td>55 100.0</td>
<td>93.5 100.0</td>
<td>55 100.0</td>
<td>93.5 100.0</td>
<td>3497.5 5706.8</td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table III A

G = Group

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4

Anti-HBs antibody titres by RIA (mlU/ml)

S+ = seropositivity: anti-HBs titre ≥ assay cut-off of 1 mlU/ml

SP = seroprotection: anti-HBs titre ≥10 mlU/ml

N = number of subjects tested

n = number of subjects who were anti-HBs seropositive/ seroprotected

PI (m1) = post-vaccination blood sampling at month 1, following dose 1

PII (m7), etc. = post-vaccination blood sampling at month 7, following dose 2.

CI 95% L.L, U.L = 95% confidence interval, lower and upper limits

GMTs: PII(m7): p = 0.65 (one-way ANOVA)

At months 1, 2 and 6, the seropositivity rates and seroprotection rates of anti-HBs antibodies were in the same range for the two groups. At month 7, all subjects in both groups were seroprotected for anti-HBs antibodies.

At month 7, there was no statistically significant difference between groups 1 and 2, in anti-HBs GMTs.

**Hepatitis A response**

Seropositivity (S+) rates and GMTs with 95% confidence interval of anti-HAV antibody titres for subjects included in the ATP analysis of immunogenicity are given in Table 5.
Table 5: Seropositivity rate (S+) and GMTs of anti-HAV antibodies of seroconverters (Subjects included in the ATP analysis of immunogenicity)

<table>
<thead>
<tr>
<th>G</th>
<th>Timing</th>
<th>N</th>
<th>S+ n</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>GMT</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>Min. titre</th>
<th>Max. titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI(m1)</td>
<td>67</td>
<td>65</td>
<td>97.0</td>
<td>89.6</td>
<td>99.6</td>
<td>349.3</td>
<td>280.1</td>
<td>435.6</td>
<td>41 - 4094</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>67</td>
<td>64</td>
<td>95.5</td>
<td>87.5</td>
<td>99.1</td>
<td>193.1</td>
<td>155.0</td>
<td>240.6</td>
<td>44 - 3308</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>135.0</td>
<td>114.1</td>
<td>159.6</td>
<td>34 - 614</td>
</tr>
<tr>
<td></td>
<td>PII(m7)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>5646.8</td>
<td>4510.0</td>
<td>7070.1</td>
<td>135 - 34081</td>
</tr>
<tr>
<td>2</td>
<td>PI(m1)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>533.3</td>
<td>426.1</td>
<td>667.3</td>
<td>36 - 3569</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>318.5</td>
<td>258.6</td>
<td>392.4</td>
<td>52 - 2861</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>249.1</td>
<td>201.7</td>
<td>307.6</td>
<td>51 - 1675</td>
</tr>
<tr>
<td></td>
<td>PII(m7)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>9565.6</td>
<td>7932.5</td>
<td>11534.9</td>
<td>707 - 38579</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table III A

G = Group

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
Anti-HAV antibody titres by Enzymun (Boehringer Mannheim) kit (mIU/ml)
S+ = seropositivity : anti-HAV titre ≥ 33 mIU/ml (the lowest sensitivity limit of the Enzymun Boehringer assay)
N = number of subjects tested; n = number of subjects who were anti-HAV seropositive
PI (m1) = post-vaccination blood sampling at month 1, following dose 1
PII(m7), etc. = post-vaccination blood sampling at month 7, following dose 2.
CI 95% L.L., U.L. = 95% confidence interval, lower and upper limits
Min, Max. titre = minimum and maximum titre of seropositive subjects

GMTs: PII(m7): p = 0.0003 (Kruskal-Wallis test)

At months 1 and 2, the seropositivity rates of anti-HAV antibodies were in the same range for the two groups. At months 6 and 7, all subjects in both groups were seropositive for anti-HAV antibodies.

At month 7, there was a statistically significant difference between groups 1 and 2 in anti-HAV GMTs, with group 2 (which received combined high-dose hepatitis A / hepatitis B vaccine) showing higher anti-HAV GMTs than group 1 (which received Twinrix™).

3.3.2 Intention-to-treat analysis

Table 6 presents the seropositivity and seroprotection rates and GMTs, with 95% confidence interval, of anti-HBs antibodies, for the total population in this study. Table 7 presents the seropositivity rates and GMTs, with 95% confidence interval, of anti-HAV antibodies, for the total population in this study. The results from the intention-to-treat (ITT) analysis were consistent with those obtained from the analysis performed according-to-protocol (ATP).
Table 6: Seropositivity rates (S+), seroprotection rates (SP) and geometric mean titres (GMT) of anti-HBs antibodies (Total population)

<table>
<thead>
<tr>
<th>G</th>
<th>Timing</th>
<th>N</th>
<th>S+ %</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>SP %</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>GMT CI 95% L.L.</th>
<th>U.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI(m1)</td>
<td>75</td>
<td>48</td>
<td>64.0</td>
<td>52.1</td>
<td>74.8</td>
<td>17</td>
<td>22.7</td>
<td>13.8</td>
<td>33.8</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>75</td>
<td>56</td>
<td>74.7</td>
<td>63.3</td>
<td>84.0</td>
<td>23</td>
<td>30.7</td>
<td>20.5</td>
<td>42.4</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>75</td>
<td>72</td>
<td>96.0</td>
<td>88.8</td>
<td>99.2</td>
<td>43</td>
<td>57.3</td>
<td>45.4</td>
<td>68.7</td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
</tr>
<tr>
<td>2</td>
<td>PI(m1)</td>
<td>75</td>
<td>51</td>
<td>68.0</td>
<td>56.2</td>
<td>78.3</td>
<td>24</td>
<td>32.0</td>
<td>21.7</td>
<td>43.8</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>74</td>
<td>63</td>
<td>85.1</td>
<td>75.0</td>
<td>92.3</td>
<td>32</td>
<td>43.2</td>
<td>31.8</td>
<td>55.3</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>75</td>
<td>70</td>
<td>93.3</td>
<td>85.1</td>
<td>97.8</td>
<td>56</td>
<td>74.7</td>
<td>63.3</td>
<td>84.0</td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table III A

G = Group; Group 1 received Twinrix™ (720/20) - lot HAB116C4/M

Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4

S+ = seropositivity: anti-HBs titre ≥ assay cut-off of 1 mIU/ml

SP = seroprotection: anti-HBs titre ≥ 10 mIU/ml

N = number of subjects tested

n = number of subjects who were anti-HBs seropositive/ seroprotected

PI (m1), (m7), etc. = post-vaccination blood sampling at months 1 and 7, following doses 1 and 2 respectively

CI 95% L.L., U.L. = 95% confidence interval, lower and upper limits

Table 7: Seropositivity rate (S+) and GMTs of anti-HAV antibodies (Total population)

<table>
<thead>
<tr>
<th>G</th>
<th>Timing</th>
<th>N</th>
<th>S+ %</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>GMT</th>
<th>CI 95% L.L.</th>
<th>U.L.</th>
<th>Min. titre</th>
<th>Max. titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI(m1)</td>
<td>75</td>
<td>73</td>
<td>97.3</td>
<td>90.7</td>
<td>99.7</td>
<td>372.0</td>
<td>210.7</td>
<td>118.7</td>
<td>137.5</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>75</td>
<td>72</td>
<td>96.0</td>
<td>88.8</td>
<td>99.2</td>
<td>210.7</td>
<td>118.7</td>
<td>118.7</td>
<td>137.5</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>134.5</td>
<td>118.7</td>
<td>4511.3</td>
<td>5687.4</td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>134.5</td>
<td>118.7</td>
<td>7446.0</td>
<td>10960.4</td>
</tr>
<tr>
<td>2</td>
<td>PI(m1)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>510.7</td>
<td>4511.3</td>
<td>135</td>
<td>34081</td>
</tr>
<tr>
<td></td>
<td>PI(m2)</td>
<td>74</td>
<td>73</td>
<td>98.6</td>
<td>92.7</td>
<td>100.0</td>
<td>315.9</td>
<td>7446.0</td>
<td>36</td>
<td>3569</td>
</tr>
<tr>
<td></td>
<td>PI(m6)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>245.9</td>
<td>7446.0</td>
<td>48</td>
<td>1675</td>
</tr>
<tr>
<td></td>
<td>PI(m7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
<td>9033.9</td>
<td>7446.0</td>
<td>316</td>
<td>52755</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table III A

G = Group; Group 1 received Twinrix™ (720/20) - lot HAB116C4/M

Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4

S+ = seropositivity: anti-HAV titre ≥ 33 mIU/ml (lowest sensitivity limit of the Enzymun Boehringer assay)

N = number of subjects tested; n = number of subjects who were anti-HAV seropositive

PI (m1), (m7), etc. = post-vaccination blood sampling at months 1 and 7, following doses 1 and 2 respectively

CI 95% L.L., U.L. = 95% confidence interval, lower and upper limits

Min, Max. titre = minimum and maximum titre of seropositive subjects

3.4 Safety and reactogenicity of the vaccine

3.4.1 Study compliance

A total of 149 subjects included in the analysis of reactogenicity received a total of 298 doses of vaccine and for these subjects, a total of 298 symptom sheets were completed for a compliance of 100.0%.
### 3.4.2 Overall incidence of symptoms

The occurrence and intensity of solicited and unsolicited local and general signs and symptoms recorded by the subjects on the day of each vaccination and for the three following days are tabulated in Appendix Tables II A - C.

Table 8 details the incidence of both solicited and unsolicited symptoms reported over the 4-day follow-up period, for the subjects included in the ATP analysis of reactogenicity. This time period includes the day of vaccination and the three subsequent days.

#### Table 8: Incidence and nature of symptoms after each vaccine dose and overall for subjects included in the overall analysis of reactogenicity

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
<th>N</th>
<th>With symptoms</th>
<th>General</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>74</td>
<td>61</td>
<td>82.4</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>74</td>
<td>49</td>
<td>66.2</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Overall*</td>
<td>148</td>
<td>110</td>
<td>74.3</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>75</td>
<td>61</td>
<td>81.3</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>75</td>
<td>64</td>
<td>85.3</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Overall*</td>
<td>150</td>
<td>125</td>
<td>83.3</td>
<td>81</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table II A and IIB
Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
This table includes both solicited and unsolicited symptoms reported on symptom sheets
Overall = as reported from the total number of symptom sheets completed for all doses administered
N = total number of symptom sheets completed following a given vaccine dose and overall
n = number of symptom sheets with symptoms following a given vaccine dose and overall

Overall, group 2 reported more solicited or unsolicited signs and symptoms, occurring over the 4-day follow-up period after vaccination, when compared to group 1 (reported following 74.3 % of documented doses in group 1 and 83.3 % in group 2). General symptoms and local symptoms were reported more frequently in group 2 than in group 1.

### 3.4.3 Solicited signs and symptoms

#### Solicited local signs and symptoms

Table 9 presents the incidence of solicited local symptoms after each vaccine dose and overall, for subjects included in the ATP analysis of reactogenicity.

Supplementary Table 3 details the incidence and duration (≤ or > 1 day) of solicited local injection site symptoms after each vaccine dose and overall. Details about individual subject data on solicited local adverse events are given in Appendix Table II A.
**Table 9:** Incidence of solicited local symptoms after each vaccine dose and overall, according to per dose analysis (Subjects included in the ATP analysis of reactogenicity)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
</tr>
<tr>
<td></td>
<td>N = 74</td>
<td>N = 75</td>
<td>N = 74</td>
</tr>
<tr>
<td>Redness</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>33.8</td>
<td>24</td>
</tr>
<tr>
<td>&gt;30mm, &gt; 24 hrs</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Soreness</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>64.9</td>
<td>48</td>
</tr>
<tr>
<td>grade “3”**</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>Swelling</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>21.6</td>
<td>11</td>
</tr>
<tr>
<td>&gt;30mm, 24 hrs</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table II A
Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
N = total number of symptoms sheets completed following a given vaccine dose and overall
n = number of symptom sheets with specific symptom following a given vaccine dose (during the 4-day follow-up period which included the day of vaccination and the three subsequent days)

All solicited local signs and symptoms were assumed to have a causal relationship to the study vaccine. Soreness at the injection site was the most prevalent solicited local symptom in both groups.

Two solicited local symptoms were graded “3” in intensity (prevented normal everyday activities).

**Solicited general signs and symptoms**

Table 10 presents the total incidence of solicited general symptoms, incidence of solicited general symptoms with ‘probable’/’suspected’ relationship to the study vaccine, incidence of grade “3” solicited general symptoms and incidence of grade “3” solicited general symptoms with ‘probable’/’suspected’ relationship to the study vaccine, after each vaccine dose and overall, for subjects included in the ATP reactogenicity analysis. Supplementary Table 4 details the incidence and duration (≤ or > 1 day) of solicited general symptoms after each vaccine dose and overall. Details about individual subject data on solicited general adverse events are given in Appendix Table II B.
Table 10: Incidence of solicited general symptoms and those with PB/SU relationship to vaccination, incidence of solicited general symptoms with intensity grade “3” and those with PB/SU relationship to vaccination, after each vaccine dose and overall (Subjects included in the ATP analysis of reactogenicity)

<table>
<thead>
<tr>
<th></th>
<th>Dose 1 Group 1</th>
<th>Dose 1 Group 2</th>
<th>Dose 2 Group 1</th>
<th>Dose 2 Group 2</th>
<th>Overall Group 1</th>
<th>Overall Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 74</td>
<td>n</td>
<td>%</td>
<td>N = 75</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>33.8</td>
<td></td>
<td>25</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>PB/SU</td>
<td>9</td>
<td>12.2</td>
<td></td>
<td>11</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>1</td>
<td>1.4</td>
<td></td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>5.4</td>
<td></td>
<td>12</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>PB/SU</td>
<td>2</td>
<td>2.7</td>
<td></td>
<td>3</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>8</td>
<td>10.8</td>
<td></td>
<td>6</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>PB/SU</td>
<td>4</td>
<td>5.4</td>
<td></td>
<td>3</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>21.6</td>
<td></td>
<td>23</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>PB/SU</td>
<td>7</td>
<td>9.5</td>
<td></td>
<td>11</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>PB/SU Grade “3”</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table II B.
Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
*Fever defined as (axillary) temperature ≥ 37.5°C
N = total number of symptoms sheets completed following a given vaccine dose and overall
n = number of symptom sheets with a specific symptom following a given vaccine dose (during the 4-day follow-up period which included the day of vaccination and the three subsequent days)
Total = total incidence of symptom following a given vaccine dose
PB/SU = symptoms determined by the investigator to have a ‘probable’/’suspected’ relationship to the study vaccine
Grade “3” = Adverse event which prevented normal everyday activities or fever >39.0°C

Fatigue and headache were the most prevalent solicited general symptom in groups 1 and 2, respectively. Fatigue was considered to have a ‘probable’ or ‘suspected’ relationship to the study vaccine, followed by 14.2% doses in group 1 and followed by 18.0% doses in group 2. Headache was considered to have a ‘probable’ or ‘suspected’ relationship to the study vaccine, followed by 10.1% doses in group 1 and followed by 18.0% doses in group 2.

A total of 9 grade “3” solicited general symptoms were reported (5 in group 1 and 4 in group 2), of which 3 cases were grade “3” fatigue, 1 case was grade “3” gastro-intestinal disorder and 5 cases were grade “3” headache. Of these 9 grade “3” solicited general symptoms, 3 cases were determined by the investigator to have a ‘suspected’ relationship to the study vaccine. No grade “3” fever was reported.

All grade “3” solicited general symptoms resolved within the 4-day follow-up, except for 4 symptoms.
All these events resolved 5 days after vaccination.

There was no statistically significant difference between the groups, in the incidence of the solicited general symptom, fever, following dose 1 or dose 2. However there was a statistically significant difference between the groups, in the overall incidence of fever, with group 2 reporting more symptoms than group 1.

3.4.4 Unsolicited signs and 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 symptom sheets were also included under unsolicited symptoms if they occurred outside the 4-day follow-up period for solicited symptoms. Unsolicited signs and symptoms were coded by use of the World Health Organisation’s Dictionary for Adverse Reaction Terminology; every verbatim term was matched to the appropriate WHO preferred term.

Unsolicited signs and symptoms classified by WHO preferred term reported, during the 30-day follow-up period after vaccination, for subjects included in the ATP analysis of reactogenicity are listed in Supplementary Table 5. Unsolicited signs and symptoms classified by WHO preferred term, reported during the 30-day follow-up period after vaccination and determined by the investigator to have a ‘probable’/‘suspected’ relationship to the study vaccine, for subjects included in the ATP analysis of reactogenicity are listed in Supplementary Table 6. Number of doses followed by at least one report of unsolicited symptoms and number of doses followed by at least one report of grade “3” unsolicited symptoms, classified by WHO Preferred Terms, according to relationship, for symptoms reported during the 30-day follow-up period is presented in Supplementary Table 7. Individual subject data about unsolicited symptoms can be found in Appendix Table IIC.

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.

Forty subjects (20 in group 1 and 20 in group 2) reported a total of 54 unsolicited symptoms (26 in group 1 and 28 in group 2) during the 30-day follow-up period after vaccination.

Fifty-three doses (26 in group 1 and 27 in group 2) were followed by at least one report of unsolicited symptoms classified by WHO Preferred Terms during the 30-
day follow-up period after vaccination. Of these, 8 (15.1 %) doses were followed by local symptoms and 45 (84.9 %) doses were followed by general symptoms.

Twenty (37.7 %) doses were followed by symptoms with ‘probable’ or ‘suspected’ relationship to the study vaccine. Of the 53 doses followed by at least one report of unsolicited symptom, 3 (5.7%) doses were followed by symptoms with intensity grade “3” (prevented normal everyday activities), but all three symptoms were determined by the investigator to be ‘not related’ to the study vaccine.

The majority of the unsolicited symptoms reported resolved within the 30-day follow-up period. The subjects who had unsolicited symptoms ongoing at time of freezing database, have recovered and are in good condition.

### 3.4.5 Serious adverse events

Both subjects recovered completely and the investigator considered the event to be ‘not related’ to the study vaccine.

The investigator stated that the event was ‘not related’ to the study vaccine.

The investigator stated that the event was ‘not related’ to the study vaccine.

Details are provided in the CIOMS I in Appendix Table IIE.

### 3.4.6 Concomitant medication

Individual subject data on subjects who received concomitant medication can be found in Appendix Table II D.

A total of 30 subjects (14 in group 1 and 16 in group 2) received concomitant medication during the study period, all of which were either therapeutic or corrective.
4. Conclusions

- There was no statistically significant difference between the two groups in the anti-HBs GMTs at month 7, one month after the last dose.

- At months 1, 2 and 6, the seropositivity rates of anti-HAV and anti-HBs antibodies and seroprotection rate of anti-HBs antibodies were similar for the two groups.

- For the hepatitis A component of the vaccine, a licensed 2-dose schedule of the monovalent vaccine is already available and the data here, with the 2-dose Twinrix™ vaccine confirms the results of the monovalent vaccine. However with the high dose vaccine (1440/40), higher GMTs were elicited. For the hepatitis B component, there is no licensed 2-dose schedule available. Within the limitations of this study, it can be said that with 2 doses of Twinrix™, a good immune response was elicited.

- Within the limitations of this study, it can be concluded that the reactogenicity profile was similar in both groups, with the high dose (1440/40) profile being slightly more reactogenic overall, than the Twinrix™ vaccine (720/20).
### Supplementary Table 1: Demography - Total population

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Min age (years)</th>
<th>Max age (years)</th>
<th>S.D  (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>38</td>
<td>15.1</td>
<td>12</td>
<td>17</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>37</td>
<td>14.5</td>
<td>10</td>
<td>17</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>75</td>
<td>14.8</td>
<td>10</td>
<td>17</td>
<td>1.61</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>40</td>
<td>14.9</td>
<td>11</td>
<td>17</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>35</td>
<td>14.7</td>
<td>12</td>
<td>17</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>75</td>
<td>14.8</td>
<td>11</td>
<td>17</td>
<td>1.46</td>
</tr>
<tr>
<td>Total</td>
<td>Female</td>
<td>78</td>
<td>15.0</td>
<td>11</td>
<td>17</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>72</td>
<td>14.6</td>
<td>10</td>
<td>17</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>150</td>
<td>14.8</td>
<td>10</td>
<td>17</td>
<td>1.53</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table IB.
Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4N
N = total number of subjects
S.D. = Standard Deviation
Male-to-female ratio between groups: p = 0.87 (Fisher’s exact test); group factor: p = 0.88 (two-way ANOVA); gender factor: p = 0.13 (two-way ANOVA); interaction group-gender: p = 0.39 (two-way ANOVA)
### Supplementary Table 2: Demographics - Subjects included in the ATP analysis of reactogenicity

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex</th>
<th>N</th>
<th>Mean age (years)</th>
<th>Min age (years)</th>
<th>Max age (years)</th>
<th>S.D. (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>38</td>
<td>15.1</td>
<td>12</td>
<td>17</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>36</td>
<td>14.4</td>
<td>10</td>
<td>17</td>
<td>1.78</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>74</td>
<td>14.8</td>
<td>10</td>
<td>17</td>
<td>1.62</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>40</td>
<td>14.9</td>
<td>11</td>
<td>17</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>35</td>
<td>14.7</td>
<td>12</td>
<td>17</td>
<td>1.41</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>75</td>
<td>14.8</td>
<td>11</td>
<td>17</td>
<td>1.46</td>
</tr>
<tr>
<td>Total</td>
<td>Female</td>
<td>78</td>
<td>15.0</td>
<td>11</td>
<td>17</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>71</td>
<td>14.6</td>
<td>10</td>
<td>17</td>
<td>1.60</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>149</td>
<td>14.8</td>
<td>10</td>
<td>17</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table IB

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M

Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4

N = total number of subjects

S.D. = Standard Deviation

Male-to-female ratio between groups: p = 0.87 (Fisher’s exact test); group factor: p = 0.86 (two-way ANOVA); gender factor: p = 0.13 (two-way ANOVA); interaction group-gender: p = 0.38 (two-way ANOVA)
Supplementary Table 3: Incidence and duration of solicited local symptoms after each vaccine dose and overall

| Symptom | Duration | Group 1 | | | Group 2 | | | Group 1 | | | Group 2 | | | N = 148 | | | N = 150 |
|---------|----------|--------|---|---|--------|---|---|--------|---|---|--------|---|---|--------|---|---|
|         |          | N = 74 | n  | % | N = 75 | n  | % | N = 74 | n  | % | N = 75 | n  | % |        |   |   |
| Redness | =<1 day  | 18     | 24.3| 17 | 22.7   | 7  | 9.5| 9      | 12.0| 25 | 16.9 | 26 | 17.3|        |   |   |
|         | >1 day   | 7      | 9.5 | 7  | 9.3    | 5  | 6.8| 2      | 2.7 | 12 | 8.1  | 9  | 6.0 |        |   |   |
|         | Total    | 25     | 33.8| 24 | 32.0   | 12 | 16.2| 11     | 14.7| 37 | 25.0 | 35 | 23.3|        |   |   |
| Soreness | =<1 day | 34     | 45.9| 22 | 29.3   | 25 | 33.8| 26     | 34.7| 59 | 39.9 | 48 | 32.0|        |   |   |
|         | >1 day   | 14     | 18.9| 26 | 34.7   | 8  | 10.8| 31     | 41.3| 22 | 14.9 | 57 | 38.0|        |   |   |
|         | Total    | 48     | 64.9| 48 | 64.0   | 33 | 44.6| 57     | 76.0| 81 | 54.7 | 105| 70.0|        |   |   |
| Swelling | =<1 day | 11     | 14.9| 10 | 13.3   | 2  | 2.7| 6      | 8.0 | 13 | 8.8  | 16 | 10.7|        |   |   |
|          | >1 day   | 5      | 6.8 | 1   | 1.3    | 4  | 5.4| 1      | 1.3 | 9  | 6.1  | 2  | 1.3 |        |   |   |
|          | Total    | 16     | 21.6| 11 | 14.7   | 6  | 8.1| 7      | 9.3 | 22 | 14.9 | 18 | 12.0|        |   |   |

Individual subject data in Appendix Table II A.

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
N= total number of symptom sheets returned... given symptom following a given dose
≤1 day = incidence of symptom reported on one day or more but on non consecutive days
>1 day = incidence of symptom reported on more than one consecutive day
Total = total incidence of symptom following a given vaccine dose
**Supplementary Table 4: Incidence and duration of solicited general symptoms after each vaccine dose and overall**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Duration</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>All doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 74</td>
<td>N = 75</td>
<td>N = 148</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Fatigue</td>
<td>=&lt;1 day</td>
<td>18</td>
<td>24.3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt;1 day</td>
<td>7</td>
<td>9.5</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>25</td>
<td>33.8</td>
<td>14</td>
</tr>
<tr>
<td>Fever</td>
<td>=&lt;1 day</td>
<td>4</td>
<td>5.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;1 day</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4</td>
<td>5.4</td>
<td>3</td>
</tr>
<tr>
<td>Gastro-</td>
<td>=&lt;1 day</td>
<td>7</td>
<td>9.5</td>
<td>2</td>
</tr>
<tr>
<td>intestinal</td>
<td>&gt;1 day</td>
<td>1</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>8</td>
<td>10.8</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>=&lt;1 day</td>
<td>12</td>
<td>16.2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>&gt;1 day</td>
<td>4</td>
<td>5.4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>16</td>
<td>21.6</td>
<td>10</td>
</tr>
</tbody>
</table>

Individual subject data in Appendix Table II B.

- Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
- Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A

N= total number of symptom sheets returned for a given vaccine dose
n = total number of symptom sheets reporting a given symptom following a given dose
=1 day = incidence of symptom reported on one day or more but on non consecutive days
>1 day = incidence of symptom reported on more than one consecutive day
Total = total incidence of symptom following a given vaccine dose
Fever = (axillary) temperature ≥37.5°C
Supplementary Table 5: Number of unsolicited signs and symptoms classified by WHO Preferred Term reported during the 30-day follow-up period (days 0-30) after vaccination (Subjects included in the ATP analysis of reactogenicity)

<table>
<thead>
<tr>
<th>WHO BODY SYSTEM (CODE)</th>
<th>WHO PREFERRED TERM (CODE)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site (1820)</td>
<td>Injection site pain (0057)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Injection site reaction (0058)</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Body as a whole general (1810)</td>
<td>Fatigue (0724)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>HotFlushes (0726)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Injury (9001)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Malaise (0728)</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pain (0730)</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular general (1010)</td>
<td>Syncope (0223)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Central and peripheral nervous system (410)</td>
<td>Dizziness (0101)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Headache (0109)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Migraine (0121)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Paresis (0141)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal system (200)</td>
<td>Arthralgia (0063)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Arthrosis (0066)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Platelet bleeding and clotting (1230)</td>
<td>Purpura (0459)</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Resistance mechanism (1830)</td>
<td>Infection viral (0740)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Upper respiratory tract infection (0543)</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory system (1100)</td>
<td>Coughing (0513)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Epistaxis (0515)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis (0523)</td>
<td>4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Sinusitis (0540)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin and appendages (100)</td>
<td>Rash (0027)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rash erythematous (0028)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>White cell and reticuloendothelial system (1220)</td>
<td>Lymphadenopathy (0577)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>26</td>
<td>28</td>
<td>54</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
Supplementary Table 6: Number of unsolicited signs and symptoms classified by WHO preferred term reported during the 30-day follow-up period (days 0-30) after vaccination, determined by the investigator to have a ‘probable’ or ‘suspected’ relationship to the study vaccine (Subjects included in the ATP analysis of reactogenicity)

<table>
<thead>
<tr>
<th>WHO BODY SYSTEM (CODE)</th>
<th>WHO PREFERRED TERM (CODE)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>All Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site (1820)</td>
<td>Injection site pain (0057)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Injection site reaction (0058)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Body as a whole general (1810)</td>
<td>Fatigue (0724)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hot flushes (0726)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Malaise (0728)</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pain (0730)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular general (1010)</td>
<td>Syncope (0223)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Central and peripheral nervous system (410)</td>
<td>Paresis (0141)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal system (200)</td>
<td>Arthralgia (0063)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Arthrosis (0066)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Platelet bleeding and clotting (1230)</td>
<td>Purpura (0459)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>9</td>
<td>12</td>
<td>21</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix™ (720/20) - lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B (1440/40) - lot DHAB404A4
Supplementary Table 7: Number of doses followed by at least one report of unsolicited symptoms and number of doses followed by at least one report of grade “3” unsolicited symptoms, classified by WHO Preferred Terms, according to relationship, symptoms reported during the 30-day follow-up period (Subjects included in the ATP analysis of reactogenicity)

<table>
<thead>
<tr>
<th>RELATION</th>
<th>Group 1</th>
<th></th>
<th>Group 2</th>
<th></th>
<th>All Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 20.0</td>
<td>7 25.9</td>
<td>12 23.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4 16.0</td>
<td>4 14.8</td>
<td>8 15.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5 20.0</td>
<td>5 18.5</td>
<td>10 19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11 44.0</td>
<td>11 40.7</td>
<td>22 42.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>1 9.1</td>
<td>1 9.1</td>
<td>2 9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25 100.0</td>
<td>27 100.0</td>
<td>52 100.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade “3”</td>
<td>1 4.0</td>
<td>1 3.7</td>
<td>2 3.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group 1 received Twinrix lot HAB116C4/M
Group 2 received combined high dose hepatitis A / B lot DHAB404A4
PB = symptoms determined by the investigator to have a ‘probable’ relationship to the study vaccine
SU = symptoms determined by the investigator to have a ‘suspected’ relationship to the study vaccine
UL = symptoms determined by the investigator to have an ‘unlikely’ relationship to the study vaccine
NR = symptoms determined by the investigator to be ‘not related’ to the study vaccine
Total = total number of doses followed by at least one report of unsolicited symptom, determined by the investigator to have a particular relationship to the study vaccine
Grade “3” = number of doses followed by at least one report of grade “3” unsolicited symptom, determined by the investigator to have a particular relationship to the study vaccine
SMITHKLINE BEECHAM BIOLOGICALS VACCINES

CLINTRIAL ELIGIBILITY CODES

Elimination from reactogenicity and serology analysis

1010 Subject or vaccine number not allocated
   Vaccine not administered at all
   No subject attributed for the randomised number

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

1040 Administration of vaccine(s) forbidden, in the protocol

1500 Randomisation failure
   Wrong vaccine vial given

1060 Randomisation code broken at investigator site

1070 Study vaccine dose not administered according to protocol
   Side, site or route of study vaccine administered 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 (inclusion/exclusion criteria)
   Demographics: Too young
   Too old
   Unknown age, sex
   Gender not according to the protocol
   Others

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

2030 Biochemistry, hematology 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 component.
   (e.g. lyme infection in a lyme study)

2070 Concomitant infection not related to the vaccine which may influence immune response.
   (e.g. Hepatitis infection in a lyme study)
SMITHKLINE BEECHAM BIOLOGICALS VACCINES
CLINTRIAL ELIGIBILITY CODES

(continued)

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, )
   Absence of parallelism
2110  Blood sample available but not yet tested (interim analysis)
2120  Obvious incoherence or abnormality or error in data
   Wrong labeling in BS
   Abnormal serology evolution
2130  Subject not planned to be bled for all their blood sampling visits
2500  Others
SMITHKLINE BEECHAM BIOLOGICALS VACCINES
NOTES TO APPENDIX TABLES

Sub. No. : subject number
Ctr : centre
Elig : eligibility
Elim : eliminated from analysis (es)
I : indicative of elimination for serological reason
F : female
M : male

Appendix table IC
Pre : pre vaccination blood sampling
PI(m1), PI(m2) : post-vaccination blood sampling 1, 2 months following dose 1, etc.
VAC ND : vaccination administration not documented
VIS ND : visit not documented
BS : blood sampling not documented

Appendix table 1E
E : Eliminated
I : Eliminated for immunogenicity analysis only

Appendix table II A
P? : According to protocol? Y / N: Yes / No
Any Loc? : Any solicited local symptom reported? Y / N: Yes / No
Site : site of vaccination
Side : Left / Right
Exp : adverse event: Y / N : Yes / No
Last day : last date symptom recorded
SO : Soreness : 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

RE : Redness : in mm (greatest diameter)
SW : Swelling : in mm (greatest diameter)
## Appendix table IIB

<table>
<thead>
<tr>
<th>Column</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G?</td>
<td>Any solicited general symptom reported? Y / N: Yes / No</td>
</tr>
<tr>
<td>Exp</td>
<td>Adverse event: Y / N: Yes / No</td>
</tr>
<tr>
<td>Out</td>
<td>Outcome: 1 = recovered 2 = recovered with sequel 3 = ongoing 4 = died 5 = unknown</td>
</tr>
<tr>
<td>Cor</td>
<td>Corrective therapy</td>
</tr>
<tr>
<td>REL</td>
<td>Relationship: NR = Not related UL = Unlikely SU = Suspected (reasonable possibility) PB = Probable</td>
</tr>
<tr>
<td>RTE</td>
<td>Route (for body temperature recording): O = oral A = axillary R = rectal T = tympanic</td>
</tr>
</tbody>
</table>

### General symptoms:

<table>
<thead>
<tr>
<th>Column</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Fatigue</td>
</tr>
<tr>
<td>TE</td>
<td>Temperature</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro-intestinal symptoms</td>
</tr>
<tr>
<td>HE</td>
<td>Headache</td>
</tr>
</tbody>
</table>

FA, HE, GI ... scored as

0: Absent 1: Mild 2: Moderate 3: Severe

TE scored as

1: 37.5° C-38.0° C 2: >38.0° C-39.0° C 3: >39.0° C

(MC: missing confirmed)
Appendix table IIC

| Verbatim  | description of the event as recorded in the case report form by the investigator |
| Keyword   | description of event as listed in the clinical database |
| WHO code  | code for WHO preferred term, a WHO adverse reaction classification system |
| Preferred term | specific identification terminology linked to the WHO classification code |
| Body syst | numerical code in relation with the location on the event in the body |
| ERR       | for events not recognized by the AE dictionary |
| REL       | Relationship: NR = not related, UL = unlikely, SU = suspected, PB = probable |
| Start date | date of onset of adverse event |
| Day onset  | number of days since last vaccine dose |
| End date   | date of end of adverse event |
| Dur (d)    | duration (days) |
| Int.       | intensity |
| L / G      | local or general symptom |
| 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, L/G: local or general |
| Out        | outcome: 1 = recovered, 2 = recovered with sequelae, 3 = ongoing, 4 = died, 5 = unknown |
| Sit        | site of vaccination: L/T = limb or thigh, D = deltoid |
| Sid        | side i.e. L = left; R = right |
| Ther       | corrective therapy required |
| Ser        | serious adverse event: N/Y = No/yes |
| AEGIS No.  | SmithKline Beecham Biologicals’ code for case identification of serious adverse events |
### Appendix table IID
Rel. day of onset : Day of onset of medication, relative to day of vaccination (0)
Start Date : date therapy started
End Date : last date of therapy
DUR (day) : duration (days)
Code : treatment or chronic

A direct link was recorded between the adverse event and the medication
AE1, AE2, AE3 : adverse event 1, 2 or 3 as detailed on CRF
P : preventative
NA : not applicable
TE = temperature, HE= headache etc.

### Appendix table III
PRE : prevaccination blood sample
PI(m1), PI(m2) : post-vaccination blood sampling 1, 2 months following dose 1, etc.
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.
Protocol Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

FIRST AMENDMENT
CPMS No. 208127/099 (EXT HAB-075) – MONTH 36 FOLLOW-UP
CPMS No. 208127/100 (EXT HAB-075) – MONTH 48 FOLLOW-UP
CPMS No. 208127/101 (EXT HAB-075) – MONTH 60 FOLLOW-UP
DATE: JUNE 23, 2000

Protocol HAB-075 dated July 3, 1997

Coordinating Author: [REDACTED]

BACKGROUND FOR CHANGES:
The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile.
To follow-up the long term antibody persistence, it was decided to bleed the volunteers at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, and to determine their anti-HAV and anti-HBs antibody titres.

THE FOLLOWING SECTIONS WERE AMENDED ON JUNE 23, 2000:
Section 4.2: Enrollment strategy/plan
Section 7: Study Procedures
Section 10: Laboratory Assays
Section 11.3: Immunogenicity
Approved by:

Associate Director, Clinical Development

26/06/00
dd-mm-yy

Dr.

Principal Investigator

20.7.00
dd-mm-yy

Dr.
Study Vaccine: SmithKline Beecham Biologicals’ combined Hepatitis A/Hepatitis B vaccine.

CPMS Protocol No: 208127/075 (HAB-075)

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Protocol HAB-075 dated July 3, 1997

1) RATIONALE

The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile.

Present Rationale:
Open follow-up study to evaluate the long term anti-HAV and anti-HBs antibody persistence in both groups (720/20 and 1440/40), at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, by drawing blood samples from all available subjects who received the primary vaccination schedule.

2) SECTIONS AMENDED

4.2 Enrolment strategy/plan

Signed informed consent (for this amendment) will be obtained from each subject before the blood sampling.
7 Study Procedures

The intervals to be respected for the long-term time points are as summarised below.

<table>
<thead>
<tr>
<th>Interval between visits</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0 – Month 36</td>
<td>36 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 48</td>
<td>48 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 60</td>
<td>60 months ± 6 weeks</td>
</tr>
</tbody>
</table>

The intervals between visits are indicative and should be followed as closely as possible. These intervals may determine evaluation of the subjects.

**Detailed description of study stages/visits are as follows:** At month 36 (Visit 6), month 48 (Visit 7) and month 60 (Visit 8):

- **Before each bleeding:**
  The investigator will ask each volunteer if he/she has received, since the last visit
  - a dose of hepatitis A or hepatitis B vaccine and/or
  - a dose of hepatitis A or hepatitis B immunoglobulin.
  If so, subjects will be excluded from this extended long-term follow-up study.

- **Bleeding:**
  From each subject, 7 ml of whole venous blood will be collected for testing anti-HAV and anti-HBs antibodies. Serum will be stored at −20 °C until transported to SB Bio for testing.

- **Recording of serious adverse events (SAEs):**
  Documentation of any SAE, which the subject may have experienced since the last study visit.

10 Laboratory Assays

- The presence of anti-HAV antibodies will be determined using an ELISA (Boehringer Manheim Enzymun Kit® or equivalent assay) calibrated by the use of WHO international standard reference serum and expressed in milli-International Units per milliliter (mIU/ml). The assay cut-off is 33 mIU/ml.

- Anti-HBs antibodies will be tested by radio immunoassay (RIA) using the Test-Kit from AUSAB, Abbott Laboratories, North Chicago IL, USA, or equivalent assay. The anti-HBs titres will be expressed in milli-international units per milliliter (mIU/ml). The assay cut-off is 1 mIU/ml.
Subjects with anti-HAV antibody titres ≥ 33 mIU/ml, will be considered to be seropositive for anti-HAV antibodies. Subjects with anti-HBs antibody titres ≥ 1 mIU/ml, will be considered to be seropositive for anti-HBs antibodies. Seroprotection rate for anti-HBs is defined as the percentage of subjects with anti-HBs antibody titres ≥ 10 mIU/ml.

All serology assays will be performed in SmithKline Beecham Biologicals’ central laboratory or in a validated laboratory designated by SmithKline Beecham Biologicals.

11.3 Immunogenicity

The elimination code for an abnormal increase in antibody titres will be assigned for the long-term follow-up. The definition of abnormal increase will depend on the magnitude of the titre reached at the first time point considered (reference value). Abnormal increase in antibody titres is defined as a two-fold increase or more in antibody titres (when the antibody titre at the reference time point is ≥ 100 mIU/ml) or a four-fold increase or more in antibody titres (when the antibody titre at the reference time point is < 100 mIU/ml). This code will be assigned to give a more realistic evaluation of the long-term persistence of antibodies.

The immunogenicity analysis will be performed on two study cohorts: the according-to-protocol study cohort (study cohort eligible for the long-term ATP analysis of immunogenicity) and the total cohort (ITT).

The long-term ATP immunogenicity analysis will include all subjects who are in the ATP immunogenicity analysis in the main study report (except for the subjects who receive the elimination code for abnormal increase in anti-HAV and/or HBs antibody titres during the long-term follow-up). The ITT analysis will be on the total cohort, which will include all subjects for whom assay results are available for anti-HAV and/or anti-HBs antibodies at long term blood sampling time point (months 36, 48 or 60).

Seropositivity rates and GMTs with 95% confidence interval (CI) for anti-HAV and anti-HBs antibodies, seroprotection rates with 95% CI for anti-HBs antibodies will be calculated. Kinetics of anti-HAV and anti-HBs GMTs will be graphically represented.
Study vaccines: SmithKline Beecham Biologicals’ high-dose combined hepatitis A / hepatitis B candidate vaccine

Protocol n°: 208127/075 (HAB-075)

Date of approval: July 3, 1997

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author: Science Writer
Clinical Research & Development

SB Responsible Physician
Dr. Project Manager

Principal Investigators: Dr. Dr. Australia
Study vaccine: SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°: 208127 / 075 (HAB-075)

Date: July 3, 1997

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator's Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date: __________________________

Signature: __________________________

(Day-month-year) Dr. [Signature]
AGREEMENT

SmithKline Beecham Biologicals
89, rue de l'Institut
1330 Rixensart, Belgium

Study vaccine
SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°
208127 / 075 [HAB-075]

Date
July 3, 1997

Title:
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 ELU of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™(containing 720 ELU of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author
Science Writer

Investigator:

Study site address:
Australia

SB responsible physician
Dr.
Project Manager

Approvals
SmithKline Beecham Biologicals
Dr.
Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator's Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date
25.6.97
(Day-month-year)

Dr.
SYNOPSIS OF PROTOCOL 208127/075 (HAB-075)

Vaccine under study: SmithKline Beecham Biologicals' combined high-dose hepatitis A / hepatitis B vaccine

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Rationale for the study: To determine which is the optimal dose of the high-dose HAB 2-dose vaccine, with respect to immunogenicity and reactogenicity & safety in this age category.

Indication/Study population: To protect healthy adolescents between the ages of 11 and 18 years against hepatitis A and B.

Objectives of the study: Primary objective
To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine one month after the last dose (month 7).

Secondary objectives:
To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies; seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.
SYNOPSIS OF PROTOCOL 208127/075 (HAB-075) cont’d

**Study design**: Double blind, randomised study with two groups. Schedule: 0, 6 months.

**Number of subjects**: 150 enrolled (75 subjects per group)

**Endpoints**: Primary endpoints
Titres for anti-HBs antibodies at month 7.

Secondary endpoints
At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP)*** for anti-HBs antibodies
At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample

**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.

***SP is defined as anti-HBs titre ≥ 10 mIU/ml

Solicited signs and symptoms during a three day follow-up period. Unsolicited signs and symptoms experienced within 30 days of vaccination.
TABLE OF CONTENTS

1. INTRODUCTION 3
   1.1 Title 3
   1.2 Background 3
   1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine 4

2. STUDY CENTRES 6

3. STUDY OBJECTIVES 6

4. STUDY POPULATION 7
   4.1 Number of subjects 7
   4.2 Enrollment strategy/plan 7
   4.3 Inclusion criteria 7
   4.4 Exclusion criteria 7

5. VACCINE AND VACCINE ADMINISTRATION 8

6. STUDY DESIGN 9
   6.1 Study design 9
   6.2 Randomisation 9
   6.3 Replacement of individual vaccine doses 9

7. STUDY PROCEDURES 10

8. CLINICAL SIGNS AND SYMPTOMS 14

9. ADVERSE EXPERIENCES 15
   9.1 Eliciting and Documenting Adverse Experiences 15
   9.2 Serious Adverse Experiences 16
      9.2.1 Reporting 16
      9.2.2 Definitions 17
   9.3 Treatment of adverse experiences 18
   9.4 Assessment of severity and outcome 19
   9.5 Assessment of Causality 19
   9.6 Following up of adverse experiences 20
   9.7 Pregnancy 20

10. LABORATORY ASSAYS 20

11. STATISTICAL ANALYSIS 20
   11.1 Sample size estimation 21
   11.2 Demographics 22
   11.3 Immunogenicity 22
   11.4 Reactogenicity 22
   11.5 Interim analyses 22

Approved: July 3, 1997
SmithKline Beecham Biologicals' combined hepatitis A/hepatitis B vaccine 208127/075 (HAB-075)

12. REFERENCES 23

APPENDIX A: VACCINATION RELATED SEROLOGY 24

APPENDIX B: VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY 25

APPENDIX C: ETHICAL CONSIDERATIONS AND RESPECT OF LOCAL RULES AND REGULATIONS 27

APPENDIX D: ETHICAL AND REGULATORY CONSIDERATIONS IN ACCORDANCE WITH GOOD CLINICAL PRACTICE FOR CLINICAL STUDIES 32

APPENDIX E: CONFIDENTIALITY AND PUBLICATION 36

APPENDIX F: HANDLING OF THE SERUM SAMPLES COLLECTED BY THE INVESTIGATOR 37

APPENDIX G: INSTRUCTIONS FOR SHIPMENT OF SAMPLES 40

APPENDIX H: DESCRIPTION OF SERA LABELS 41

Approved: July 3, 1997
1. INTRODUCTION

1.1 Title

A double-blind study to compare the immunogenicity, safety and reactogenicity of two dose levels of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

1.2 Background

Hepatitis A
HAV is classified in the family *Picornaviridae*, genus *Heparnavirus*. Seven genotypes of the virus have been identified but only one serotype comprises all of these. Early researchers found that suspensions of fecal samples remained infectious after treatment with acids, ether, high temperatures and even after being frozen for more than a year. HAV can be inactivated by autoclaving, boiling, exposure to high levels of formalin and ultraviolet radiation. The serological marker for previous infection with HAV (anti-HAV) can be detected early in the course of the illness and usually remains detectable in slowly declining titres for years and confers immunity to repeat infection for a lifetime.

The most common route of HAV infection is simply through swallowing food or water contaminated with small amounts of infected fecal material. Most of the viral particles are shed in feces before any symptoms of infection appear so infected individuals may unwittingly pass on the disease to many others before they fall ill themselves.

The epidemiology of hepatitis A is highly influenced by personal and public hygiene. In areas of the world where there is inadequate or non-existent provision for sewage disposal, infection occurs early in life and is almost always subclinical. In developing countries, exposure, infection and subsequent immunity are virtually universal in childhood. In areas where the hepatitis A virus is not in wide circulation, the population is not immune and is therefore more vulnerable to infection occurring later in life. One of the most important factors for disease severity is the age of the patient. Childhood infections can be asymptomatic, while almost all adults suffer from the overt disease with symptoms ranging from mild flu-like symptoms to severe gastrointestinal symptoms, fever, prolonged jaundice and severe weight loss. Nearly two-thirds of adult patients with clinically apparent disease experience complete clinical recovery within two months. Fulminant hepatitis A can occur, although rarely, and is frequently fatal particularly in the older patient. Estimates of the risk of developing fulminant hepatitis A vary. One study estimates occurrence as less than 1% and another estimates it at 6.9%. There appears to be a positive association between mortality and age, with the death rate from symptomatic disease increasing from 0.3% for all ages to 1.8% for those aged over 50 years. Chronic hepatitis A does not occur but a relapsing form of the disease has been observed.
described \(^7\): relapse occurs 2-18 weeks after the primary infection and affects 3-20% of patients with acute hepatitis A infection - after a clinical phase and subsequent recovery, including normalisation of liver enzymes, a second clinical phase with an elevation of liver enzymes occurs, persisting for up to 40 weeks.

**Hepatitis B**

HBV is classified in the family *Hepadnaviridae*, genus *Orthohepadnavirus*. Five genotypes of the virus have been identified but only one serotype comprises all of these. The outer coat of the virus or nucleocapsid is a complex structure containing several proteins including the surface antigen, HBsAg, which is recognised by the antibodies raised by the immune system to combat the virus: the anti-HBs antibody. Natural infection with hepatitis B virus leads to life-long detectable anti-HBs antibody in most individuals. Two other antibodies are also produced by the immune system - anti-HBc and anti-HBe which target the core and e antigens respectively. The presence of HBsAg indicates that the host has been infected and is contagious. Anti-HBc is the first antibody to appear after infection and remains present in the serum even after recovery from the illness and can be detected for years up to the lifetime of the patient.

Blood has long been recognised as a major vehicle for the transmission of hepatitis B virus. Four major modes of transmission are recognised: vertical (also known as perinatal), horizontal, parenteral/percutaneous and sexual. The age of infection is the primary correlate for route of infection. In areas of intermediate and high endemicity of the disease, infection occurs early in life through mother-child transmission and through close personal contact among children \(^8\). In areas of low HBV endemicity, infection occurs primarily in adult life and by the sexual route. Individual response to the infection varies greatly. The age at which infection is acquired affects whether the infection is self-limiting or results in the chronic carrier state. Although the acute infection is more severe in adults, infections in infants and pre-school age children carry much greater risks of chronic carriage thereby increasing the risk of primary hepatocellular carcinoma and cirrhosis later in life \(^9\).

The precise mechanism by which carrier rates are influenced by age is unknown, but probably relates to the effect of age on the immune system's ability to eliminate a hepatitis B infection. The probability that an infant will become a chronic carrier if infected is about 90% in the first two years, about 50% at 3 years of age, and 6% to 10% from 6 years of age to adulthood \(^10\).

Up to one-third of individuals with laboratory evidence of infection, *i.e.*, serological markers, experience no symptoms, and so exhibit subclinical infection \(^11\). One-third of patients experience a mild flu-like illness without jaundice and another third develop full-blown jaundice with dark urine, extreme fatigue, anorexia and abdominal pain \(^12\). Individuals infected with hepatitis B may either proceed to full recovery or may become chronic carriers of virus. About 5% of the world's population (around 350 million persons) are chronic carriers of hepatitis B \(^13\). About a quarter of these carriers will develop serious liver disease, including chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma \(^14\).

### 1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine

There is currently no specific treatment for either of these infections. It has been recognised that vaccination is the only method of conferring long-term protection against clinical disease and/or infection. SB Biologicals has a licensed combined hepatitis A / hepatitis B (HAB) vaccine, Twinrix™, which facilitates the provision of
concurrent protection against the two diseases. The increased convenience provided by the use of combined vaccines will improve compliance with vaccination schedules. Studies performed with different lots of the combined vaccine have shown that the combination is safe and immunogenic. This vaccine is administered according to a three vaccination course (0, 1, 6-month schedule). Current studies performed by SB Biologicals are focusing on a high-dose HAB candidate vaccine consisting of a two dose vaccination course (0, 6-month schedule). This candidate high-dose HAB vaccine would offer added convenience and enhance the acceptance of immunisation by both the general public and the medical community. In order to achieve this shorter vaccination schedule the composition of the candidate high-dose HAB candidate vaccine has been modified. The antigen content has been doubled and the adjuvant content has been increased. SB Biologicals uses aluminium compounds, the only adjuvants used in routine human vaccines. These compounds are known to enhance the humoral immune response.

This study is undertaken to determine which is the optimal dose of the HAB 2-dose vaccine in adolescents (11-18 years of age) by comparing immunogenicity and reactogenicity & safety in this age category elicited by the vaccine containing 1440 EL.U of inactivated hepatitis A antigen and 40 µg of recombinant hepatitis B surface antigen to that of Twinrix™, (containing 720 EL.U of inactivated hepatitis A antigen and 20 µg of recombinant hepatitis B surface antigen), both administered according to a 0, 6-month schedule.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of the combined hepatitis A / hepatitis B vaccine.
2. STUDY CENTRES

Principal Investigators: Dr. Dr

Study site:

Australia

3. STUDY OBJECTIVES

The objectives of the present study are:

a) Primary objective
   To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™, (720/20) vaccine one month after the last dose (month 7).

b) Secondary objectives
   To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti-Hbs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
   To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies, seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
   To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

The endpoints of the present study are:

Primary endpoints
   Titres for anti-HBs antibodies at month 7.

Secondary endpoints
   At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP) for anti-HBs antibodies
   At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample

**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.

***SP is defined as anti-HBs titre ≥10 mIU/ml

Approved: July 3, 1997
Solicited signs and symptoms during a three day follow-up period. Unsolicited signs and symptoms experienced within 30 days of vaccination.

4. STUDY POPULATION

4.1 Number of subjects

The study population will be composed of adolescent volunteers arbitrarily defined as males and females between the ages of 11 and 18 years. In order to be included in the study, subjects will have completed their 11th birthday and will have not yet attained their 18th birthday at the time of the first vaccine dose. There will be 150 subjects enrolled (75 subjects/group).

4.2 Enrollment strategy/plan

The enrollment period, e.g. the period between the first and the last enrolled subject, is maximum 12 weeks. This will be followed up by monitoring.

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.

4.3 Inclusion criteria

- Age : from 11 to 18 years of age.
- Good physical condition as established by clinical examination and history taking at the time of entry.
- Sexually active female participants will avoid becoming pregnant during the study period and they will have been on a contraceptive program for at least 2 months before entry.
- Written informed consent will have been obtained from the parents/guardians of the subjects and/or from subjects themselves depending upon local regulations.

4.4 Exclusion criteria

- History of hepatitis.
- History of previous vaccination against hepatitis A or B.
- History of significant and persisting hematologic, hepatic, renal, cardiac or respiratory disease.
- Any acute disease at the moment of entry.
- Chronic alcohol consumption.
- Hepatomegaly, right upper quadrant abdominal pain or tenderness.

Approved: July 3, 1997
- Any chronic drug treatment, including any treatment with immunosuppressive drugs, which in the investigator's opinion, precludes inclusion into the study.
- History of allergic disease likely to be stimulated by any component of the vaccine.
- Administration of immunoglobulins within six months of the first vaccination or planned during the study period.
- Receipt of any other vaccine within 1 week of a dose of the study vaccine (period extending from 1 week before to 1 week after a dose of vaccine).
- Simultaneous participation in any other clinical trial, the only exception being involvement in long-term follow-up in another vaccine trial.

5. VACCINE AND VACCINE ADMINISTRATION

The vaccines employed in the present study will be:

**SmithKline Beecham Biologicals' combined hepatitis A - hepatitis B vaccine**

- **Hepatitis A (Strain HM 175 - RIT 4380)**: at least 1440 ELISA units
- **Hepatitis B (recombinant HBsAg)**: 40 µg.
- **Aluminium salt**: 0.85 mg.

**SmithKline Beecham Biologicals' combined hepatitis A - hepatitis B vaccine Twinrix™**

- **Hepatitis A (Strain HM 175 - RIT 4380)**: at least 720 ELISA units
- **Hepatitis B (recombinant HBsAg)**: 20 µg.
- **Aluminium salt**: 0.45 mg.

The Quality Control Standards and Requirements for the study vaccines are described in separate release protocols and the required approvals have been obtained.

The vaccines will be supplied as a single 1.0 ml monodose vials for intramuscular injection in the deltoid region.

The vaccine is to be injected intramuscularly in the deltoid muscle using a 25G 1” needle. Subjects will be closely observed for at least 15 minutes post-vaccination with resuscitation facilities readily available in case of any anaphylactic reaction.

**ALL VACCINES MUST BE STORED IN THE REFRIGERATOR (+2 to +8°C) AND MUST NOT BE FROZEN.** Storage temperature should be monitored at least once per week.

The investigator is further referred to the Investigator's Brochure for further information regarding the combined hepatitis A and hepatitis B vaccine.
6. STUDY DESIGN

6.1 Study design

This will be a double-blind, randomised study. Subjects will be randomly allocated to one of two groups to receive one of the two dose levels of the combined hepatitis A / hepatitis B vaccine in the order in which they are enrolled into the study.

6.2 Randomisation

Each monodose vial will be coded according to a randomisation list prepared by the sponsor. The randomisation will be made using an algorithm of pseudo random numbers (given by RS/1 from BBN).

The vaccines, which will be packed and supplied by the sponsor, will be labelled with the subject number, the study number and the name of the sponsor. Each subject will be given only the vaccines carrying his/her number.

6.3 Breaking the Study Blind

A set of sealed envelopes, one for each subject number and containing the identity of the vaccine given to the subject will be stored at SmithKline Beecham (sponsor). In case of a serious adverse experience, the investigator needs to notify the sponsor immediately. The sponsor will then break the code and transmit the information to the investigator. The reason for breaking the code must be recorded by the sponsor on the corresponding envelope and by the investigator in the subject’s case report form (CRF) and the medical record.

6.4 Replacement of individual vaccine doses

In addition to the vials numbered from number 1 up to the planned number of subjects, 5 % additional doses from the Twinrix™ (720/20) lot will be provided to replace broken or lost vials. Subjects who shall receive replacement vials will be eliminated from reactogenicity and serology analysis.

Approved: July 3, 1997
7. STUDY PROCEDURES

As the incidence of hepatitis A and hepatitis B is very low in Australia and in order to save an additional visit for the participants, blood sampling for screening and first vaccination will be performed on the same day\(^{17,18}\). In addition, vaccination of seropositive subjects has proven to be safe and results in a boost in antibody titre\(^{19}\).

**IMPORTANT:** An interval of 30 days + 7 days is planned between day 0 and month 1
- month 1 and month 2
- month 6 and month 7

An interval of 180 days + 14 days between day 0 and month 6.

The intervals indicated here will serve as a target and not as an absolute criteria for inclusion or exclusion from the study but should be followed as much as possible. However, if circumstances dictate other intervals, this will not necessarily lead to the exclusion of the subject(s) from analysis.

Details of the study procedures are as follows:

**DAY 0:** Screening of volunteers/Vaccine dose 1

- Visit 1
  - Informed consent obtained from parents/guardians of subjects and/or from subjects themselves depending upon local regulations.
  - Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HBs, anti-HBc, anti-HAV antibody and HBsAg measurement in SmithKline Beecham Biologicals’ laboratory (SB Biologicals), storage (at -20°C).
  - History taking and physical examination (including axillary body temperature). Include documentation of baseline symptomatology.
  - Inclusion/exclusion criteria.
  - Individual Case Report Forms will be filled in by the investigator.
  - IM administration of the first vaccine dose (coded monodose vial) in the deltoid region.
  - Each vaccinee will be closely observed for 15 minutes following vaccination.
  - Provision and explanation of diary card.
  - Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

* DAYS 1 TO 3 AFTER VISIT 2

- In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs.
and symptoms on a diary card provided by the sponsor (see also section 8).

MONTH 1 : Follow-up visit
(30±7 days vs Day 0)
Visit 2
* Checking and collection of diary cards (completion of data concerning the local and/or general symptoms).
  * Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
  * Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 2 : Follow-up visit
(60±7 days vs Day 0)
Visit 3
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 6 : Second vaccination
(180± 14d. vs Day 0)
Visit 4
* Physical examination (if deemed necessary by the investigator).
* Documentation of baseline symptomatology.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C
* IM administration of the last dose (coded monodose vial) in the deltoid region
* Each vaccinee will be closely observed for 15 minutes after vaccination.
* Provision and explanation of diary card.
* Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

Approved:July 3, 1997
SmithKline Beecham Biologicals

SmithKline Beecham Biologicals’ combined hepatitis A/hepatitis B vaccine 208127/075 (HAB-075)

-12-

♦ DAYS 1 TO 3 AFTER VISIT 4

* In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs and symptoms on a diary card provided by the sponsor (see also section 8).

MONTH 7 : Closure of the study
(30 ± 7 d. vs Month 6)
Visit 5

* Checking and collection of diary cards (completion of data concerning the local and/or general symptoms).
* Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.

Approved: July 3, 1997
### FLOW SHEET

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 Day 0</th>
<th>v 2 Month 1</th>
<th>v 3 Month 2</th>
<th>v 4 Month 6</th>
<th>v 5 Month 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening visit</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td></td>
<td></td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td>Recording of baseline</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diary card checking</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>anti-HBc, HBsAg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>anti-HAV</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>anti-HBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sera Labels</td>
<td>Pre</td>
<td>Post Vacc 1</td>
<td>Post Vacc 1</td>
<td>Post Vacc 1</td>
<td>Post Vacc 2</td>
</tr>
<tr>
<td></td>
<td>Study day 0</td>
<td>Study month 1</td>
<td>Study month 2</td>
<td>Study month 6</td>
<td>Study month 7</td>
</tr>
</tbody>
</table>

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.
8. CLINICAL SIGNS AND SYMPTOMS

After each vaccination, the subject will record on diary cards the local reactions and general symptoms, including axillary body temperature in the evening 5-9 hours post vaccination and thereafter every morning for 3 days.

The following signs and symptoms will be solicited:

**General symptoms:**
- Temperature*
- Headache*
- Fatigue*
- Gastrointestinal symptoms*
- Others (please specify)*

**Local reactions:**
- Soreness*
- Redness **
- Swelling **
- Others (please specify)*

* Signs and symptoms will be scored as:

0:  No adverse experience.
1:  Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2:  Adverse experience sufficiently discomforting to interfere with daily activities.
3:  Adverse experience which prevents normal everyday activities and necessitates medical advice. (In an adult, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

(see also section 9.4)

** The size of redness and swelling will be obtained by measuring their largest diameter and scored at SmithKline Beecham Biologicals as follows:

1:  1 ≥30mm
2:  > 30 mm
3:  > 30 mm and persisting more than 24 hours.

° The temperature will be recorded only when it is 37.5°C or above and will be scored at SmithKline Beecham Biologicals as follows:

1:  37.5°C-38.0°C
2:  >38.0°C-39.0°C
3:  >39.0°C

The vaccinees will be instructed to return the completed diary card with signs/symptoms on the next visit.
On that occasion, the forms completed by the vaccinee will be transcribed into the CRF by the clinical investigator after checking for completion and accuracy.

The relationship of any solicited or unsolicited symptom (those listed under “Others”) to the study vaccine will be assessed by the investigator and recorded in the CRF (see section 9.5).

Medication

Any concomitant medication administered during the period extending from 1 month prior until 1 month after each vaccination will be recorded in the medication section of the Case Report Form including: name, medical condition, code, start and end dates of treatment. Medications which do not need to be recorded include any homeopathic remedies, vitamins and contraceptives.

For antipyretics/analgesics, it should be specified whether they were given prophylactically or to treat an existing symptom (therapeutic use). If used prophylactically in anticipation of vaccine’s reaction, please code as "P" within the "medical indication" field of the Case Report Form.

9. ADVERSE EXPERIENCES

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out hereafter.

9.1 Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur within 30 days after each dose administration of the study vaccine.

An adverse experience includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic function as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with vaccine and whether or not considered vaccine related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or vaccine or drug interaction, or (if applicable) the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study (if applicable), that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

All adverse experiences which occur within thirty days after each dose either observed by the investigator or one of his clinical collaborators, or reported by the patient spontaneously or in response to a direct question, will be evaluated by the investigator and noted in the adverse experience section of the subject's case record form (CRF).

Ask the subject a non-leading question such as: "Do you feel different in any way since receiving the vaccine / within 30 days after receiving the vaccine".

Approved: July 3, 1997
The nature of each experience, time of onset after vaccine administration, duration, severity and relationship to vaccination should be established. Details of changes to the vaccination schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Symptomatology should be documented at baseline. It is important to collect baseline information in order to interpret data from subsequent assessments.

9.2 **Serious Adverse Experiences**

9.2.1 **Reporting**

Any serious adverse experiences which occur during the clinical trial or within 30 days of receiving the last dose of study vaccine, whether or not related to the study vaccine, must be reported by the investigator to the SB clinical trial monitor by telephone, telex or telefax, within 24 hours of his becoming aware of the occurrence.

This initial notification should include:

- Study protocol number + name of principal investigator
- Vaccine study number, initials, age, sex
- Date of onset of the experience and date of administration of the study vaccine(s)
- Relationship to the study vaccine (see section 9.5.)
All information should be sent promptly to the SmithKline Beecham monitors:

Dr. [name]
Medical Director
SmithKline Beecham Pharmaceuticals
300, Frankston Road
Dandenong Victoria 3175 AUSTRALIA
Tel office:
Fax:

or

Dr. [name]
Project Manager
SmithKline Beecham Biologicals
89, Rue de l’Institut
B-1330 Rixensart - Belgium
Tel office:
Tel home:
Telex:
Fax:

or also

Investigators should not wait to collect additional information to fully document the event before notifying SmithKline Beecham of a serious adverse experience. The telephone report should be followed by a full written report to include copies of relevant hospital case records, autopsy reports and other documents where applicable.

Moreover, instances of death, cancer or congenital abnormality if brought to the attention of the investigator AT ANY TIME after the cessation of study vaccine AND considered by the investigator to be probably associated to study vaccine or to have a reasonable possibility of an association to study vaccine, should be reported to the SmithKline Beecham Monitor.

9.2.2 Definitions
A serious adverse experience is defined as follows:

ANY experience that, in the investigator’s opinion, suggests a significant hazard to the vaccinee and will always include any event that is:

1. Fatal
2. Life-threatening
3. Disabling or incapacitating
4. Results in hospitalisation or prolongation of hospitalisation

or is:

5. A congenital abnormality (in offspring)
6. A cancer

Approved: July 3, 1997
7. An overdose of the vaccine or an adverse experience associated with an overdose (either accidental or intentional)

In addition, any adverse experience which suggests a significant hazard, contraindication, side effect or precaution that may be associated with the use of the vaccine will be considered a serious adverse experience.

Life threatening - definition:

An adverse experience is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death.

Disability/incapacitating - definition:

An adverse experience is incapacitating or the patient has suffered a temporary or permanent disability if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Hospitalisation - definition:

In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalisation' occurred or was necessary, the adverse experience should be considered serious.

9.3 Treatment of adverse experiences

Treatment of any adverse experience is at the sole discretion of the investigator and according to current Good Clinical Practice. The applied measures should be reported in the Case Report Form of the vaccinee.
9.4 Assessment of severity and outcome

Maximum intensity should be scored according to one of the following categories:

0: No adverse experience
1: Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
2: Adverse experience sufficiently discomforting to interfere with normal everyday activities
3: Adverse experience which prevents normal everyday activities and necessitates medical advice. (In adults, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

The outcome of adverse experiences should be indicated as follows:

1: Recovered
2: Recovered with sequelae
3: Ongoing
4: Died
5: Unknown

9.5 Assessment of Causality

Every effort should be made by the investigator to explain each general adverse experience and assess its relationship, if any, to study vaccine. Causality should be assessed using the following categories:

NR: Not related       The adverse experience is definitely not related to the study vaccine.

UL: Unlikely         There are other more likely causes and the study vaccine is not suspected as a cause.

SU: Suspected (reasonable possibility) A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.

PB: Probable         There is probably a direct cause and effect relationship between the adverse experience and the study vaccine.

The degree of certainty with which an adverse experience is attributed to the study vaccine (or alternative causes, e.g. diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of:

a) Known toxico-pharmacology of the vaccine, in preclinical and clinical experience.
b) Reaction of similar nature previously observed with this vaccine.
c) The experience having been reported in the literature for similar vaccines.
d) The experience being related by time to vaccine administration or reproduced on re-challenge.

9.6 Following up of adverse experiences

Investigators should follow-up patients with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the patient's subsequent course must be submitted to the clinical trial monitor.

9.7 Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately. Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, either during the treatment phase of the study or within 30 days after the (last) vaccination. Whenever possible, a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

10. LABORATORY ASSAYS

Blood samples obtained at the first visit (Day 0) will be tested at SmithKline Beecham Biologicals' laboratory for:
- Anti-HAV, anti-HBs and anti-HBc antibodies
- HBsAg

At each next visit serum will be collected for measurement of anti-HBs and anti-HAV antibodies in SmithKline Beecham Biologicals' laboratory. Radioimmunoassay technique (RIA technique) will be used to test the presence of HBsAg (AUSAB - Abbott) and anti-HBc (Corab-Abbott).

Antibody titres (anti-HAV and anti-HBs) will be expressed in mIU/ml, with reference to World Health Organisation (WHO) standard seras. Anti-HAV antibodies will be measured at day 0, months 1, 2, 6 and 7, using Enzymun (Boehringer Mannheim) kit. The cut-off level of this test is 33 mIU/ml. Measurements of anti-HBs antibodies at day 0, months 1, 2, 6 and 7 will be performed using a commercial radioimmunoassay kit (AUSAB-Abbott). The cut-off level of this test is 1 mIU/ml.

All serum samples should be kept at -20°C.

11. STATISTICAL ANALYSIS

Taking into consideration a 10 % dropout potential and the seroprevalence of hepatitis A (there is no screening and we will exclude the HAV positive subjects from the immunogenicity analysis) 150 subjects (75/group) will be enrolled to have at least 90 (45/group) evaluable subjects.

Approved: July 3, 1997
11.1 Sample size estimation

Primary objective

A sample size of 45 evaluable subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HBs between groups if the difference exceed 50%. The calculation has been made with a type I error = 5% and a type II error of 20%. For these calculation, a variability of log titres of 0.7441 for anti-HBs has been used. The variability used came from data generated from a previous study with the combined hepatitis A and B vaccine.

Secondary objectives

A sample size of 45 subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HAV between groups if the difference exceed 50%. With a type error of 5% and variability of log titres of 0.1299 for anti-HAV, we will reach a power of 97.6%. The variability used came from data generated on a previous study with the combined hepatitis A and vaccine.

For reactogenicity analysis, with the sample size of 45 subjects, we will be allowed to detect differences mentioned in the table hereafter with a type error of 5% and a power of 80% and a reference rate of a symptom or combination of symptoms reported by 1,2,5,10,20 and 50% of subjects.

<table>
<thead>
<tr>
<th>Reference rate (in %)</th>
<th>Detectable difference (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>21.7</td>
</tr>
<tr>
<td>5</td>
<td>24.1</td>
</tr>
<tr>
<td>10</td>
<td>26.8</td>
</tr>
<tr>
<td>20</td>
<td>29.9</td>
</tr>
<tr>
<td>50</td>
<td>29.9</td>
</tr>
</tbody>
</table>
11.2 Demographics

The demographic characteristics (age, sex) of the study cohort will be tabulated. The mean age, plus the range and standard deviation, by sex of the enrolled subjects, will be calculated. Similar analysis will be performed for those subjects who are included in the different analysis of reactogenicity and immunogenicity. Mean ages of groups will be compared using a Student’s t test. Ratio of males to females will be compared using either a Chi-square test or a Fisher’s exact test.

11.3 Immunogenicity

Two analyses will be performed: a first one will include only subjects corresponding to criteria defined in the protocol and a second one, called "Intention-to-treat", will include all data available from all subjects.

Seropositivity rates, seroconversion rates and geometric mean titres (GMTs) for anti-HBs and anti-HAV antibodies and seroprotection rates for anti-HBs antibodies, with 95% confidence intervals for each antigen, will be calculated for all time points for which blood samples are taken. Seropositivity is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay. Seroconversion is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample. Seroprotection is defined as anti-HBs titre ≥10 mIU/ml. The GMT will be calculated using the log-transformation of seropositive titres and taking the anti-log of the mean of these transformed values. GMTs will be compared using either a Student’s t test or a Mann-Whitney test. Seroconversion rates will be compared between groups using a Chi-square test or Fisher’s exact test.

11.4 Reactogenicity

The incidence of any symptom reported, local, general and local and general symptoms after each injection and overall will be evaluated, in addition to the frequency, intensity, duration (≤ or >1 day) and relationship of each individual solicited symptoms. The incidence is calculated on the number of documented diary cards. Chi-square test or Fisher’s exact test will be used to compare the proportion of subjects reporting any symptoms, local symptoms, general symptoms, local and general symptoms between groups.

11.5 Interim analyses

An exploratory analysis will be performed at month 2 for immunogenicity and for reactogenicity

Approved: July 3, 1997
12. REFERENCES

6. ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
17. ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
APPENDIX A: VACCINATION RELATED SEROLOGY

Serology

All of the serum samples will be tested in SmithKline Beecham Biologicals’ laboratory at the end of the study.

Anti-HBs antibodies will be tested using radio immunoassay (Ausab-Abbott). The anti-HBs titres will be expressed in international units (mIU/ml). The lowest sensitivity limit of this assay is 1 mIU/ml.

Anti-HAV antibodies will be tested by a commercially available test, Enzymun (Boehringer Mannheim). The lowest sensitivity limit of this assay is 33 mIU/ml.

Radio immunoassay (RIA technique) will be used to test the presence of HBsAg (Austria II - Abbott) and anti-HBc (Corab-Abbott) should it be necessary to validate screening results obtained in the investigator’s laboratory.
APPENDIX B: VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY

1. **Vaccine supplies**

380 single monodose vials, including 5 % dose replacement from Twinrix™ (720/20) will be provided. Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titres ≥ 10 mIU/ML and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.

It is at no time permitted to use the supplies for other purposes than those specified in the present protocol.

2. **Vaccine packaging**

Each vaccine dose will be labelled and placed in a plastic pack with 25 holes. A group label will be stuck on the top of each pack.

The vials will be placed in numerical order from left to right starting from the lower left hand corner, as shown:

<table>
<thead>
<tr>
<th></th>
<th>21</th>
<th>16</th>
<th>11</th>
<th>6</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

**Labeling**

The vial label will contain the following details:

- Study number
- Investigator's name
- Subject number
- Study vaccine name
- Lot number
- Storage conditions
- Expiry date
- "For investigational use only"
- Mode of administration
- Dose number
- MFD SmithKline Beecham Biologicals, Belgium

The group label will be similar to the vial label. It will also include the pack number and total number of packs, e.g. 3/7 = 3rd pack of 7, containing vials numbered 51-75.

**Storage**

Approved: July 3, 1997
The vaccines should be stored at 2 to 8°C in a safe and locked place with no access for unauthorised personnel.

3. Vaccine accountability

All vaccines need to be accounted for on the appropriate forms provided by the sponsor. At any time the figures on supplied, used and remaining vaccine should match.

All remaining product will be collected by the sponsor for destruction after the study. Unused supplies will be collected by the sponsor on completion of the study.

4. Other supplies provided by the sponsor

Additionally to the vaccines and the different documents, the investigator will receive the following supplies:

- tubes with screw caps for serum specimens
- labels for serum identification
- racks for the tubes of serum

No supplies should be used outside the scope of the protocol.
APPENDIX C: ETHICAL CONSIDERATIONS AND RESPECT OF LOCAL RULES AND REGULATIONS

1. Declaration of Helsinki
   
   The study will be conducted in accordance with the Declaration of Helsinki, enclosed with this protocol.

2. Ethics Review Committee
   
   The study will have been approved by the appropriate Ethics Review Committee and documentation of this approval will be submitted to SmithKline Beecham Biologicals prior to the start of the study.

3. Informed consent
   
   The investigators will inform the volunteers in a language which they clearly understand about the aims and the possible side effects of the research trial prior to enrollment; written consent will be obtained unless local law or customs preclude this. Under the circumstances, an oral witnessed consent will be obtained. Subjects have to be informed of the fact that their data will be stored in a coded fashion in an electronic database and may be subject to an internal or external audit. (See SOP SB Bio 06). Information should be given in both oral and written form.

4. Local rules and regulations
   
   The study will be conducted in accordance with the local rules and regulations of the country and respecting the European Commission Directive 91/507/EEC issued July 19, 1991 and effective January 1, 1992 on Good Clinical Practice.

5. Insurance
   
   All study participants are insured according to the SmithKline Beecham Insurance policy. The study participants (or their parents or guardians) may consult this contract at any time at the investigator site.

6. Withdrawals
   
   Subjects are free to withdraw from the study for any reason at any time. A subject will be withdrawn from the study by the investigator in case of serious adverse experience or suspected health hazard. In all cases the reason of the withdrawal must be recorded in the Case Report Form by the investigator.

   Attention should be paid to proper classification of reason for withdrawal. Subjects being withdrawn while presenting on adverse experience not related to the study and not responsible for withdrawal should not be included in the listing of subjects withdrawn for adverse experiences.
7. Current edition of declaration of Helsinki

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 fulfillment 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 etiology
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 recognized 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.

Approved: July 3, 1997
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 minimize 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.

Approved: July 3, 1997
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 judgment 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 (1, 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.

Approved: July 3, 1997
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 judgment 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 D: ETHICAL AND REGULATORY CONSIDERATIONS IN ACCORDANCE WITH GOOD CLINICAL PRACTICE FOR CLINICAL STUDIES

I. ETHICS REVIEW COMMITTEE (ERC) / INSTITUTIONAL REVIEW BOARD (IRB)

Ethics Committees must be constituted according to the local laws/customs of each participating country.

- This protocol will be submitted to an appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study.

- SB will supply relevant data for the investigator to submit to the hospital/university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB’s unconditional approval of the protocol and either written informed consent or oral consent with written information to be given to the subjects/patients will be transmitted to the SB Clinical Monitor prior to shipment of drug supplies and case record forms to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

- The ERC must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or the conduct of the trial. Approval for such changes must be transmitted in writing to the SB Clinical Monitor.

II. INFORMED CONSENT

Information should be given in both oral and written form.

Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

- WRITTEN INFORMED CONSENT

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the Ethics Review Committee and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Where appropriate, informed consent shall be documented by the use of a written consent form approved by the Ethics Review Committee and signed by the subject or the subject’s legally authorised representative.

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

Approved: July 3, 1997
Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event 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 SB professional and regulatory compliance persons.

- **WITNESSED ORAL CONSENT**

In countries where written informed consent contravenes local law or custom, informed consent may be gained orally. Full and comprehensive information must be communicated to the potential subject (or his legal representative) in the presence of a witness. The witness will be an independent third party i.e. not a nominated co-investigator. The witness will sign the Informed Consent document (testifying that informed consent has been given orally) along with the investigator (or his/her nominated representative).

### III. 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 to not divert essential subjects/patients 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.

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

- Preparing and maintaining adequate case histories designed to record observations and other data pertinent to the study.

### IV. STUDY DRUGS

1) **STORAGE OF STUDY DRUGS**

Specify clearly the site where (e.g. pharmacy or safely locked place), and conditions under which the study drugs are to be stored, as it is essential that the sponsor can be certain that the drugs will retain their safety and potency for the duration of their assigned shelf life.

2) **DRUG ACCOUNTABILITY**

The investigator or pharmacist must sign that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products are handled and stored safely and properly; that investigational products are only dispensed to study subjects/patients in accordance with the protocol; that any unused products (including placebo) will be returned to SB. 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 used and unused investigational drugs (including placebo) for the stated study have been returned.

Approved: July 3, 1997
3) ASSESSMENT OF COMPLIANCE

A record of the amount dispensed, taken (and returned for out-patient studies) for each patient/subject must be recorded in the CRF. The means of assessing compliance will be described.

V. SPONSOR'S TERMINATION OF TRIAL

SmithKline Beecham 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.

VI. Protocol Amendments

No modification to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Medical Monitor and filed as an amendment to this protocol.

Any modifications to the protocol will be adhered to by the study centre (or all participating centres) and will apply to all subjects/patients following approval by the Ethical Review Committee or Institutional Review Board.

VII. CASE REPORT FORMS (CRFs)

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 patient diary cards, if applicable), will be supplied by SB for recording all data. It is the responsibility of the investigator to ensure that CRFs (and patient diary cards) are legible and completely filled in.

Principal investigators or designated physicians under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to ensure that they have reviewed the data and that the data are complete and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a section conclusion signature is required.

An original case report form must be submitted for all patients who have given informed consent and who have undergone protocol specific procedures, whether or not the patient completed the study.

For each form on which information is entered, the patient's identification (2-3 alphabet letters representing initials or first letters of patient's name), allocation number and the date of the visit number and the date of the visit must be neatly hand-written with black ink ball-point 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 initialed, dated and justified by the authorised individual making the change if it is significant. Do not obliterate, write over, or erase the original entry when making a correction.

Approved: July 3, 1997
While completed CRFs will be reviewed by an SB professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

When a patient completes a study, it is anticipated that all CRFs pages will be completed as soon as possible and that they can be submitted to SB at the time of the next monitoring visit. This also applies to forms for potential study participants who were not randomised to a treatment group.

Any questions or comments related to the CRF should be directed to the assigned Study Monitor.

VIII. 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 patient, during the study at appropriate intervals and after the last patient is completed.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the Case Report Forms (CRF) and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits should be made available by the investigator.

IX. ARCHIVING OF DATA

The investigator must retain patient records and case report forms as well as drug disposition records at a maximum period of time permitted by the hospital, institution or private practice. The subject identification codes should be kept at least 15 years in accordance with Good Clinical Practices. The investigator must have a “key” linking the patient’s trial identification number (i.e. treatment number) to the patient’s clinical file. If the investigator moves or retires, he/she should nominate someone in writing to be responsible for record keeping. Archived data may be held on a microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it if require.

SmithKline Beecham agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out and to provide copies to the investigator should he/she wish another copy.

X. AUDITS

For the purpose of compliance with Good Clinical Practice and regulatory agency guidelines it may be necessary for SmithKline Beecham or a drug regulatory agency to conduct a site audit.

When an investigator signs the protocol, he agrees to allow drug regulatory agency and SB auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.
SB has a substantial investment in clinical trials. Having the highest quality data and studies are essential aspects of drug development. SB 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 SB sponsored studies are in accordance with 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 SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Visits from the sponsor's representatives
- Ethical Review Committee approval
- Study vaccine accountability
- Study protocol and amendments
- Informed consent of the patients
- Medical records supportive of case report form data
- Reports to the ERC/IRB and the sponsor
- Record retention

SB will gladly help investigators prepare for an inspection.

**APPENDIX E: CONFIDENTIALITY AND PUBLICATION**

You agree that all information communicated to you by SmithKline Beecham Biologicals/Pharmaceuticals is the exclusive property of SmithKline Beecham Biologicals/Pharmaceuticals 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 by your or such person to any third party without the prior written consent of SmithKline Beecham Pharmaceuticals. You shall communicate the results of the work promptly to SmithKline Beecham Pharmaceuticals.

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 study monitor. SmithKline Beecham will undertake to comment on such documents within four weeks.

All rights and interests world-wide 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 trial 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.

Approved: July 3, 1997
APPENDIX F: HANDLING OF THE SERUM SAMPLES COLLECTED BY THE INVESTIGATOR

1. COLLECTION

The whole blood (by capillary or venous route) will be collected observing appropriate aseptic conditions. It is recommended to use Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood medical) to minimise hemolysis risks and to avoid blood cell contamination of the sera when transferring serum in standard tubes.

2. RECOMMENDED PROCEDURE FOR SERUM SEPARATION

These guideline’s aim is to insure a good quality of the serum by minimising hemolysis risks, blood cell contamination of the sera or serum adverse cell toxicity at testing.

◊ Vacutainer® tubes with integrated serum separator

- Invert gently the tube several times to allow close contact with clot activator.

- Keep at room temperature (18 - 20°C) for minimum 30 minutes and maximum 2 hours. If necessary due to extenuating circumstances, the room temperature incubation period may be increased beyond 2 hours but shall never exceed 24 hours.

- Centrifuge at 1100 G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).

- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.

- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.

- Identify the standard tubes with the appropriate standard label - as described here below in point 3.

Approved: July 3, 1997
SmithKline Beecham Biologicals’ combined hepatitis A/hepatitis B vaccine 208127/075 (HAB-075)

-38-

Vacutainer® tubes without separator

- PRELIMINARY NOTE: NEVER USE SILICONIZED TUBES (cell toxicity!)

- Keep at room temperature (18 - 20°C) for minimum 2 hours and ideally overnight.

- Centrifuge at 2000G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).

- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.

- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.

- Identify the standard tubes with the appropriate standard label - as described here below

3. LABELLING (see the diagram hereafter)

- Use the standard labels provided by SmithKline Beecham Biologicals.

- Attach the label on the tube, first by its written paper part and than turn around the tube with the plastic transparent part so that the clear plastic part will protect the text and codification.

- To be readable, the bar code must be vertical on the tube.

- Please, do not stick the label on caps.

Approved: July 3, 1997
4. **SORTING and STORAGE**

- Tubes should be placed in the SB racks in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, than with the post vaccination sample series.

  *When impossible as with new sealed bag/box (IATA regulation), samples should be sorted by numeric order per batch of 20 packed in plastic bags, all those plastic bags packed together in the sealed box.*

- The tubes of serum will be stored at temperature between -20°C and -70°C in a vertical position until sent to SmithKline Beecham Biologica尔斯.
APPENDIX G: INSTRUCTIONS FOR SHIPMENT OF SAMPLES

- Serum samples should always be sent by air unless otherwise requested by the sponsor and must be made on Mondays, Tuesdays and Wednesdays preferably.

- Serum samples should be placed in a container complying with IATA requirements with dry ice (-20°C). The completed standard serum listing form should always accompanied the shipment.

- The Air Way Bill form should mention ‘-20°C storage’.

- ‘A “proforma” invoice, stating a value for customs purposes only should be prepared and attached to the parcel, the mention : store at -20°C should be add on this document

- ‘Details of the shipment, including airway bill number, flight number, flight departure and arrival times should be sent by fax, two days before the shipment to: SmithKline Beecham Biologicals

- Shipment and fax to be addressed to:
  SmithKline Beecham Biologicals
  Attn. Dr [Redacted]
  Clinical Immunology
  R&D Department / Building 44
  Rue de l’institut, 89
  B - 1330 Rixensart - Belgium
  Telephone: [Redacted]
  Fax: [Redacted]
  c/o MSAS Nedlloyd
  Brussels National Airport
  Zaventem - Belgium

- The box should be clearly identified by using stickers provided by SBBio mentioning the shipment address as well as with red stickers ‘STORE AT -20°C’
### APPENDIX H: DESCRIPTION OF SERA LABELS

<table>
<thead>
<tr>
<th>Pre</th>
<th>Study day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post vacc 1</td>
<td>Study month 1</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 2</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 6</td>
</tr>
<tr>
<td>Post vacc 2</td>
<td>Study month 7</td>
</tr>
</tbody>
</table>

Approved: July 3, 1997
SMITHKLINE BEECHAM BIOLOGICALS

ADDENDUM TO SUBJECT/PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR THE STUDY
208127/075 (HAB-075)

Study title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Investigator: Dr. [Redacted] Australia

Sponsor: SmithKline Beecham Biologicals

CPMS Protocol no.: 208127/099 (EXT HAB-075) – Month 36 follow-up
208127/100 (EXT HAB-075) – Month 48 follow-up
208127/101 (EXT HAB-075) – Month 60 follow-up

Date of approval:

Prepared by: [Redacted]

This document should be presented to the subject and parents/guardians of the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the participant and the parents/guardians of the participant.
Introduction

The main objective of this document is to provide the potential study participants and parents/guardians of the participants with the information necessary to help them in deciding to participate in the long-term follow-up of the HAB-075 study. The document provides a full but simple understanding of the scientific reasons, the likely effects and benefits of this long-term follow-up of the HAB-075 study. This document also informs subjects and parents/guardians of subjects about their rights, benefits, risks and responsibilities in participating in this follow-up trial.

Hepatitis A and B are diseases caused by viruses that infect the liver. The symptoms of both infections may be quite similar - characterised by fever, ill- feeling, loss of appetite, abdominal discomfort, jaundice and liver damage. Both diseases are transmitted by person-to-person contact.

There are no effective therapies against hepatitis A or hepatitis B. Vaccination, resulting in protection against both the diseases, is the best method of reducing the incidence of infection. SmithKline Beecham Biologicals has developed vaccines against both hepatitis A (Havrix™) and hepatitis B (Engerix™-B) which have shown to be protective and are available on the world market. SmithKline Beecham Biologicals has also developed a combination hepatitis A / hepatitis B vaccine (Twinrix™) which is also available on the market. This combination is known to provide simultaneous protection against both diseases.

You have / your son/daughter/ward has already received a course of SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine in the original HAB-075 study. In this long-term follow-up study, the long-term protection against hepatitis A and hepatitis B achieved by this combined hepatitis A/hepatitis B vaccine is being determined.
Approval

This addendum to subject information sheet has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

All volunteers in this long-term follow-up study-extension have received SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine (given according to 0, 6 months schedule), in HAB-075 study. This long-term follow-up study is designed to assess the immune response 36, 48 and 60 months after the first dose of the primary vaccination course.

Your/your son’s/daughter’s/ward’s participation in this follow-up period will require 3 visits (one visit per year) to the investigator. At each visit, 7 ml (approximately 3 ½ tablespoons) of blood will be collected to determine antibody titres.

Risks associated with the study

You/your son/daughter/ward may experience momentary mild discomfort during the blood collection. The amount to be taken will not cause any symptoms or anaemia.

Benefits of the study

The principal benefit of you/your son/daughter/ward participating in this long-term follow-up study, is the evaluation of your/your son’s/daughter’s/ward’s long-term protection against hepatitis A and hepatitis B.

Voluntary participation

Your/your son’s/daughter’s/ward’s participation is voluntary. Refusal to take part or continue with this long-term follow-up study will involve no penalty or loss of benefits or attention to which you/your son/daughter/ward is otherwise entitled to
receive from your healthcare provider. You are entitled to receive a signed copy of this form.

**Alternative measures of prevention**

Not applicable.

**Confidentiality and data access**

This section ensures that you/your son/daughter/ward benefits from the protection and the rights granted by the European Union Data Protection Directive and other national laws on the protection of your son’s/daughter’s/ward’s personal data.

You understand and consent to the following:

I. Your/your son’s/daughter’s/ward’s data, including data relating to your/your son’s/daughter’s/ward’s health, will be recorded and processed for the purpose of 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/your son’s/daughter’s/ward’s data may also be processed for product registration and for notification to organisations monitoring the safety and effectiveness of medicines. Your/your son’s/daughter’s/ward’s data may also be processed in order to add to scientific knowledge;

II. Your/your son’s/daughter’s/ward’s participation in the study will be treated as confidential. You/your son/daughter/ward will not be referred to by name in any report on the study and your/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical data or study samples (e.g. 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 access your/your son’s/daughter’s/ward’s personal data and 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/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical records may be accessed by representatives of SB Bio or regulatory bodies for medicines.

**Right to ask questions and/or withdraw from the long-term study follow-up**

You may ask questions about the study. Although your continuous support is appreciated, you have the right to withdraw yourself/your son/daughter/ward from this long-term study-extension at any time and you/your son/daughter/ward will be under no further obligation for blood samplings.

If you have any questions, please contact:

**Name of investigator:** Dr.

**Address of investigator:** Australia

**Telephone number of investigator:**
Compensation

If you become/your son/daughter/ward 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 you have/your son/daughter/ward has experienced a research-related illness or injury, please contact:

Name of investigator: Dr.
Address of investigator: Australia

Telephone number of investigator: [Redacted]
Informed Consent for the long-term follow-up (adolescents/minors)

The 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 study.

Participant’s Name: ________________________________
(First Name, Family Name)

Participant’s signature (where applicable): ________________________________

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)
Subject Information Sheet
& Informed Consent

CPMS Protocol No.
208127/099 (EXT HAB-075) – Month 36 follow-up
208127/100 (EXT HAB-075) – Month 48 follow-up
208127/101 (EXT HAB-075) – Month 60 follow-up

Subject No._____________________ Date: Protocol dated July 3, 1997
First Amendment dated June 23, 2000

Witness:

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 consent form.

Name: ____________________________________________

Signature: __________________________________________

Designation: __________________________________________

Date: ___________________________ Time: ___________________________

(DD-MM-YY)
Informed Consent for the long-term follow-up (adults)

The aims and procedures of the study have been clearly explained to me and I have read the preceding information sheet and understood the information provided. I agree to be enrolled in the study. I understand that I have the right to decline to enter the study and to withdraw from it at any time for any reasons, without consequence to my present or future health care and attention, which I receive from my healthcare provider. I have been made aware of my right to access and request correction of my personal data. I acknowledge that I have received a copy of this form for future reference.

I, ________________________________,
(subject’s first name and family name)

hereby freely give my consent to take part in this [clinical/vaccine] study.

Participant’s signature: ________________________________

Participant’s main address: ________________________________

Participant’s phone number: ________________________________

Date: ____________________ Time: ____________________
(DD-MM-YY)

Witness: ________________________________
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 consent form.

Name: 

Signature: 

Designation: 

Date: 

Time: 

(DD-MM-YY)
<table>
<thead>
<tr>
<th>Centre</th>
<th>Subject identification</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SmithKline Beecham**

CONFIDENTIAL

CASE REPORT FORM

208127/075 (HAB-075)
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: 01 JAN 97 = 1st January 1997

**TIME**

Unless specified otherwise, use the 24 hour clock: 00:00-23:59

Example: 15 30 = 3.30 PM

The **Medication** section, the **Concomitant Vaccination** section, the **Non-Serious Adverse Experiences** section and the **Serious Adverse Experience (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 EXPERIENCE DEFINITIONS

INTENSITY
0: No adverse experience (applicable only for solicited symptoms).
1: An adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2: An adverse experience which is sufficiently discomforting to interfere with normal everyday activities.
3: An adverse experience which prevents normal, everyday activities.
   (In adults/adolescents, such an adverse experience would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy).

RELATIONSHIP
NR : Not Related The adverse experience 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 A direct cause and effect relationship between administration of the study vaccine(s) and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by administration of the study vaccine(s).
PB : Probable There probably is a direct cause and effect relationship between the adverse experience 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 EXPERIENCE
A serious adverse experience is defined as follows:
ANY experience that, in the investigator’s opinion, suggests a significant hazard to the study vaccinee and is:

1. Fatal
2. Life threatening
3. Disabling/incapacitating
4. Results in hospitalisation (excluding elective surgery or routine clinical procedures that are not the result of an adverse experience)
5. Results in prolonged hospitalisation
6. Associated with congenital abnormality in offspring
7. Associated with cancer
8. Associated with overdose
9. Any event which is regarded by the investigator as serious or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the study vaccine should be reported as a serious adverse experience.

For each serious adverse experience, please fill in the Serious Adverse Experience (SAE) form and contact SmithKline Beecham within 24 hours.
### Exploratory Analysis

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 Day 0</th>
<th>v2 Month 1 30±7D/D0</th>
<th>v3 Month 2 60±7D/D0</th>
<th>v4 Month 6 180±14D/D0</th>
<th>v5 Month 7 30±7D/M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening visit</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recording of baseline symptoms</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vaccination</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Diary card checking</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>anti-HBc, HBsAg</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>anti-HAV</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sera Labels</td>
<td>Pre Study day 0</td>
<td>Post Vac 1 Study month 1</td>
<td>Post Vac 1 Study month 2</td>
<td>Post Vac 1 Study month 6</td>
<td>Post Vac 2 Study month 7</td>
</tr>
</tbody>
</table>

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.
Informed Consent has to be obtained prior to any study procedure
ELIGIBILITY CHECKLIST

INCLUSION CRITERIA

1. Age: from 11 to 18 years of age.
2. Good physical condition as established by clinical examination and history taking at the time of entry.
3. Sexually active female participants will avoid becoming pregnant during the study period and they will have been on a contraceptive program for at least 2 months before entry.
4. Written informed consent will have been obtained from the parents/guardians of the subjects and/or from subjects themselves depending upon local regulations.

EXCLUSION CRITERIA

5. History of hepatitis.
6. History of previous vaccination against hepatitis A or B.
7. History of significant and persisting hematologic, hepatic, renal, cardiac or respiratory disease.
8. Any acute disease at the moment of entry.
9. Chronic alcohol consumption.
10. Hepatomegaly, right upper quadrant abdominal pain and tenderness.
11. Any chronic drug treatment, including any treatment with immunosuppressive drugs, which in the investigator's opinion, precludes inclusion into the study.
12. History of allergic disease likely to be stimulated by any component of the vaccine.
13. Administration of immunoglobulins within six months of the first vaccination or planned during the study period.
14. Receipt of any other vaccine within 1 week of a dose of the study vaccine (period extending from 1 week before to 1 week after a dose of vaccine).
15. Simultaneous participation in any other clinical trial, the only exception being involvement in long-term follow-up in another vaccine trial.
Protocol | Centre | Visit | Date of visit | Subject number
---|---|---|---|---
208127/075 (HAB-075) | | VISIT 1 | | |

I certify that the subject has given Informed Consent before 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 ☐ WH
Black ☐ BL
Oriental ☐ OR
Other ☐ OT 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 relevant medical history/medical condition?

NO □ YES ☐  Please tick appropriate box and give diagnosis

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>99</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td></td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CUTANEOUS</td>
<td>EYES</td>
<td>EARS-NOSE-THROAT</td>
<td>CARDIOVASCULAR</td>
<td>RESPIRATORY</td>
<td>GASTROINTESTINAL</td>
<td>MUSCULO-SKELETAL</td>
<td>NEUROLOGICAL</td>
<td>ALLERGIES</td>
<td>ENDOCRINE</td>
<td>GENITO-URINARY</td>
<td>HAEMATOLOGY</td>
<td>OTHER (specify)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
<td>.................................................................</td>
</tr>
</tbody>
</table>

Please report any medication as specified in the protocol and fill in the Medication section.
LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken?  YES ☐  NO ☐

BASELINE ASSESSMENT

GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms just before injection?

For each symptom, please tick a No/Yes box. Please give intensity for any experience observed.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No</th>
<th>Yes</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BASELINE TEMPERATURE

Temperature:  ___. __℃  Route:  ☐ Axillary  ☐ Oral  ☐ Rectal
SmithKline Beecham Biologicals s.a.

### Protocol

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>208127/075 (HAB-075)</td>
<td>VISIT 1 DOSE 1</td>
<td></td>
</tr>
</tbody>
</table>

### 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>HAB Vaccine</td>
<td>DELTOID IM</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

Please tick appropriate box:

- Side:
  - Left ☐
  - Right ☐

- Route:
  - Deltoid ☐
  - Thigh ☐
  - Buttock ☐

**NB:** any other vaccines administered during the study period must be recorded in the **Concomitant Vaccination section**.

### POST VACCINATION OBSERVATION

If any **adverse experience** occurred during the immediate post-vaccination time specified in the protocol, ➔ please fill in the **Solicited Adverse Experiences section**, the **Non-Serious Adverse Experiences section** or the **Serious Adverse Experience section**, as appropriate.

### MEDICATION

If any **prophylactic** medication has been administered in anticipation of study vaccine reactions, ➔ please complete the **Medication section**.
### SOLICITED ADVERSE EXPERIENCES - SINGLE INJECTION

Has the Diary Card been returned?  

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

**LOCAL SYMPTOMS**

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

- **NO**
- **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 (at the injection site)</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
</tr>
<tr>
<td>Soreness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➤ intensity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➤ size in mm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>➤ size in mm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
</tbody>
</table>

Intensity:  

- 0  
- 1  
- 2  
- 3

If any of these adverse experiences is serious according to protocol definition,  

➤ ➤ please report experience to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Experience form**.
### SOLICITED ADVERSE EXPERIENCES - GENERAL SYMPTOMS

Has the subject experienced any of the following general solicited signs or symptoms during the solicited period?

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>RELATIONSHIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>15 min</td>
<td>5-9 hours post injection</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
</tr>
<tr>
<td>Fever No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral ≥ 37.5°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axillary ≥ 37.5°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal ≥ 38°C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If any of these adverse experiences is serious according to protocol definition, please report experience to SB monitor by telephone or fax within 24 hours (see protocol) and complete the Serious Adverse Experience form.

If ongoing after Day 3:

- Relationship: NR: Not related
- UL: Unlikely
- SU: Suspected
- PB: Probable

**Intensity:**
- 0
- 1
- 2
- 3
VISIT 2

Month 1

(30 ± 7 days vs day 0)
Before any vaccine administration, please review the Contraindications as specified in the protocol.

REMARKS

ADVERSE EXPERIENCES

- Please report any adverse experiences as specified in the protocol and fill in the Non-Serious Adverse Experiences section or the Serious Adverse Experience (SAE) form, as appropriate.

MEDICATION

- Please report any 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.
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visit</th>
<th>Date of visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>208127/075 (HAB-075)</td>
<td>VISIT 2</td>
<td>[day] [month] [year]</td>
<td>[ ] [ ] [ ]</td>
</tr>
</tbody>
</table>

LABORATORY TESTS

BLOOD SAMPLE

Has a blood sample been taken?  YES ☐  NO ☐
VISIT 3

Month 2

$(60 \pm 7 \text{ days vs day } 0)$
REMINDER

ADVERSE EXPERIENCES

► Please report any adverse experiences as specified in the protocol and fill in the Non-Serious Adverse Experiences section or the Serious Adverse Experience (SAE) form, as appropriate.

MEDICATION

► Please report any 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.
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visits</th>
<th>Date of visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>208127/075 (HAB-075)</td>
<td>VISIT 3</td>
<td>______ ______ ______</td>
<td>______ ______ ______</td>
</tr>
</tbody>
</table>

**LABORATORY TESTS**

**BLOOD SAMPLE**

Has a blood sample been taken?  YES ☐  NO ☐
VISIT 4

Month 6
(180 ± 14 days vs day 0)
REMINDER

ADVERSE EXPERIENCES

➢ Please report any adverse experiences as specified in the protocol and fill in the Non-Serious Adverse Experiences section or the Serious Adverse Experience (SAE) form, as appropriate.

MEDICATION

➢ Please report any 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.
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visit</th>
<th>Date of visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>208127/075</td>
<td>VISIT 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LABORATORY TESTS**

**BLOOD SAMPLE**

Has a blood sample been taken?  YES [ ]  NO [ ]
## BASELINE ASSESSMENT

### GENERAL SYMPTOMS

Does the subject experience any of the following general solicited signs or symptoms just before injection?

- **Headache**
  - No [ ]
  - Yes [ ]
  - Intensity: [ ]

- **Fatigue**
  - No [ ]
  - Yes [ ]
  - Intensity: [ ]

- **Gastrointestinal Symptoms**
  - No [ ]
  - Yes [ ]
  - Intensity: [ ]

### BASeline TEMPERATURE

Temperature: [ ] [ ] °C  
Route: [ ] Axillary  [ ] Oral  [ ] Rectal
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>DELTOID I.M.</td>
<td>Yes [ ]  No [ ] Site [ ] Route: Deltoid [ ] IM [ ] Thigh [ ] SC [ ] Buttock [ ]</td>
</tr>
</tbody>
</table>

Please tick appropriate box

Side:
Left [ ] Right [ ]

NB: any other vaccines administered during the study period must be recorded in the Concomitant Vaccination section.

POST VACCINATION OBSERVATION

If any adverse experience occurred during the immediate post-vaccination time specified in the protocol, please fill in the Solicited Adverse Experiences section, the Non-Serious Adverse Experiences section or the Serious Adverse Experience section, as appropriate.

MEDICATION

If any prophylactic medication has been administered in anticipation of study vaccine reactions, please complete the Medication section.
SOLICITED ADVERSE EXPERIENCES - SINGLE INJECTION

Has the Diary Card been returned?  YES ☐  NO ☐

LOCAL SYMPTOMS

Has the subject experienced any of the following local (at injection site) solicited signs/symptoms during the solicited period?

☐ NO
☐ YES ➤ Please tick a No/Yes box for each symptom.

If Yes is ticked, please fill in the complete line.

If ongoing after Day 3 ➤

<table>
<thead>
<tr>
<th>LOCAL SYMPTOMS</th>
<th>DAY 0</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(at the injection site)</td>
<td>15 min post injection</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
</tr>
<tr>
<td>Soreness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Yes</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>intensity :</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Yes</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>size in mm :</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Yes</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>size in mm :</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Date of last day of symptoms

If any of these adverse experiences is serious according to protocol definition,

➤ please report experience to SB monitor by telephone or fax within 24 hours (see protocol) and complete the Serious Adverse Experience form.
### SOLICITED ADVERSE EXPERIENCES - GENERAL SYMPTOMS

Has the subject experienced **any of the following general** solicited signs or symptoms during the solicited period?

- [ ] NO
- | 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>Date of last day of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>5-9 hours post injection</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
<td>Relationship</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Date of last day of symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>day</td>
</tr>
</tbody>
</table>

- [ ] NO
- [ ] Yes ➤ intensity:

**Intensity**: 0  1  2  3  

**Relationship**: NR: Not related  
UL: Unlikely  
SU: Suspected  
PB: Probable

⇒ If any of these adverse experiences is **serious** according to protocol definition,

⇒⇒ please report experience to SB monitor by telephone or fax within 24 hours (see protocol) and complete the **Serious Adverse Experience form**.
VISIT 5
Month 7
(30 ± 7 days vs Month 6)
REMINDER

ADVERSE EXPERIENCES

- Please report any adverse experiences as specified in the protocol and fill in the Non-Serious Adverse Experiences section or the Serious Adverse Experience (SAE) form, as appropriate.

MEDICATION

- Please report any medication as specified in the protocol and fill in the Medication section.
- Please report concomitant vaccination in the Concomitant Vaccination section.
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Visit</th>
<th>Date of visit</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>208127/075 (HAB-075)</td>
<td>VISIT 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LABORATORY TESTS**

**BLOOD SAMPLE**

Has a blood sample been taken?  YES [ ]  NO [ ]
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>For SB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>For SB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>For SB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>For SB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>For SB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>For SB</td>
<td></td>
</tr>
</tbody>
</table>

Please report below any other vaccine(s) administered during the study period which are not recorded on the Vaccine Administration page.
MEDICATION
### MEDICATION

Please report all medications except vitamins, mineral supplements, homeopathic remedies, contraceptives.

<table>
<thead>
<tr>
<th>Trade / Generic Name</th>
<th>Medical Indication</th>
<th>Code</th>
<th>Start Date at end of study</th>
<th>End date, or tick (√) box if continuing</th>
</tr>
</thead>
<tbody>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
<tr>
<td>For SB</td>
<td></td>
<td></td>
<td>day</td>
<td>month</td>
</tr>
</tbody>
</table>

Enter appropriate code:
- P: Prophylactic medication in anticipation of study vaccine reactions
- T: Therapeutic
- C: Chronic
NON-SERIOUS
ADVERSE
EXPERIENCES
NON-SERIOUS ADVERSE EXPERIENCES

Please report below all **non-serious adverse experiences** that occurred within 30 days post vaccination, excluding those recorded on the Solicited Adverse Experiences pages.

Please report all **serious adverse experiences** only on the Serious Adverse Experience (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 Experiences</td>
<td>.................................................</td>
<td>.................................................</td>
<td>.................................................</td>
</tr>
<tr>
<td>Description</td>
<td>.................................................</td>
<td>.................................................</td>
<td>.................................................</td>
</tr>
</tbody>
</table>

Local (injection site) | General (non injection site) | Local (injection site) | General (non injection site) | Local (injection site) | General (non injection site)

**For SB**

<table>
<thead>
<tr>
<th>Date Started</th>
<th>Date Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>day</td>
<td>month</td>
</tr>
</tbody>
</table>

- **Intensity**
  - 1
  - 2
  - 3

- **Relationship**
  - NR: Not related
  - UL: Unlikely
  - SU: Suspected
  - PB: Probable

- **Outcome**
  - 1: Recovered
  - 2: Recovered with sequelae
  - 3: Ongoing at subject study conclusion
  - 4: Died
  - 5: Unknown
# NON-SERIOUS ADVERSE EXPERIENCES - CONTINUED

<table>
<thead>
<tr>
<th>Non-Serious Adverse Experiences</th>
<th>AE No.</th>
<th>AE.4</th>
<th>AE.5</th>
<th>AE.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Local (injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] General (non injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Local (injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] General (non injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] Local (injection site)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[ ] General (non injection site)</td>
<td></td>
<td></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

<table>
<thead>
<tr>
<th>Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

### Relationship

<table>
<thead>
<tr>
<th>Description</th>
<th>NR: Not related</th>
<th>UL: Unlikely</th>
<th>SU: Suspected</th>
<th>PB: Probable</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE No.</td>
<td>NR [ ]</td>
<td>UL [ ]</td>
<td>SU [ ]</td>
<td>PB [ ]</td>
</tr>
<tr>
<td>AE No.</td>
<td>NR [ ]</td>
<td>UL [ ]</td>
<td>SU [ ]</td>
<td>PB [ ]</td>
</tr>
<tr>
<td>AE No.</td>
<td>NR [ ]</td>
<td>UL [ ]</td>
<td>SU [ ]</td>
<td>PB [ ]</td>
</tr>
</tbody>
</table>

### Outcome

<table>
<thead>
<tr>
<th>Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td></td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE No.</th>
<th>AE.4</th>
<th>AE.5</th>
<th>AE.6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SERIOUS ADVERSE EXPERIENCE
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 minimise the time you spend dealing with data queries.

   If the SAE is still ongoing at the time of reporting, please leave "Experience 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 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 EXPERIENCE (SAE)

Person Reporting SAE :
(Please print clearly) ............................................................

Serious Adverse Experience ............................................................
(Please print clearly) ............................................................

For SB
AEGIS Number : [__] [__] [__] [__] [__] [__]. [__]

Specify reason(s) for considering this a serious adverse experience. Mark all that apply.

1. Fatal ✅ Autopsy ✅ Yes
   ✅ No
   Please send autopsy report

2. Life threatening

3. Disabling/incapacitating

4. Results in hospitalisation (excluding elective surgery or routine clinical procedures that are not the result of an adverse experience)

5. Results in prolonged hospitalisation

6. Congenital abnormality in offspring

7. Associated with cancer

8. Associated with overdose

9. Any event which is regarded by the investigator as serious or which would suggest any significant hazard, contra-indication, side effect or precaution that may be associated with the use of the study vaccine should be reported as a serious adverse experience.

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 : ...............................................................

Experience Course

- Intermittent ✅ No. of episodes ✅
- Constant

Was subject withdrawn ✅ Yes due to this specific SAE ? ✅ No

1. Fatal

2. Life threatening

3. Disabling/incapacitating

4. Results in hospitalisation (excluding elective surgery or routine clinical procedures that are not the result of an adverse experience)

5. Results in prolonged hospitalisation

6. Congenital abnormality in offspring

7. Associated with cancer

8. Associated with overdose

9. Any event which is regarded by the investigator as serious or which would suggest any significant hazard, contra-indication, side effect or precaution that may be associated with the use of the study vaccine should be reported as a serious adverse experience.

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 : ...............................................................
## 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[day] [month] [year]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[day] [month] [year]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[day] [month] [year]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Remarks** *(please provide a brief narrative description of the serious adverse experience, 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**: [_____ _____ _____]  **day**  **month**  **year**

**Please PRINT name**: .................................................................

**For SB**

**SB Medical Monitor Signature**: ....................................................  **Date**: [_____ _____ _____]  **day**  **month**  **year**

**Please PRINT name**: .................................................................
STUDY CONCLUSION
Has the code been broken?  
YES ☐  NO ☐

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 experience  
SAE  (complete the Serious Adverse Experience section)
    ➤  please specify AEGIS No.: ...........................................................

☐  Non-serious adverse experience  
AEX  (complete the Non-Serious Adverse Experiences section)
    ➤  please specify AE No.: ..............................................................

☐  Protocol violation  
PTV  ➤  please specify: .................................................................

☐  Consent withdrawal, not due to adverse experiences  
CWS

☐  Migration from study area  
MIG

☐  Lost to follow-up  
LFU

☐  Others  
OTH  ➤  please specify: .................................................................

Date of last contact:   |   |   |
    day          month        year

Was the subject in good condition at date of last contact?  

YES ☐

NO ☐  ➤  Please give details within the Adverse Experiences 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:   |   |   |
    day          month        year

Investigator Signature:  

CV Investigator
This section contained Principal Investigator’s Curriculum Vitae and has been excluded to protect Principal Investigator privacy.
Verification and approval:

Scientific Writer

Associate Director,
Clinical Development Adult Vaccines

Il 9 April, 1999
Date (day/month/year)

3/4/99
Date (day/month/year)
Final Study Report 208127/075 (HAB-075)

An integrated clinical/statistical report

A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologics’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Report prepared by:

Scientific Writer

Biometrician

Clinical Research Associate

Clinical Development Manager

Verification and Approval:

Clinical Regulatory

Associate Director,
Clinical Development Adult Vaccines
Study Report 208127/099 (HAB-075) Annex-1 to Study Report 208127/075 (HAB-075)

An Integrated Clinical/Statistical Report

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Study Vaccine: GlaxoSmithKline Biologicals’ combined hepatitis A / hepatitis B vaccine (Twinrix™)

CPMS Study No.: 208127/099 (Ext.HAB-075)

Indication: To protect healthy adolescents against hepatitis A and B.

Principal Investigator: Dr. [Redacted]
Date of First Visit: 12 August 1997
Primary Study End Date: 14 March 1998
Primary Study Report Date: 26 March 1999
Long-term Follow-up End Date: 19 September 2000

Co-ordinating Author: [Redacted]

Other Contributing Authors: [Redacted] Associate Director Clinical Development
[Redacted] Clinical Development Manager
[Redacted] Clinical Study Management Statistician

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

Annex 1 Report Date: 28 August 2001

This annex report provides results of long-term follow-up to and including Month 36.

Verification and approval

Dr. [Redacted]

15 Oct 2001
Date (day/month/year)
An Integrated Clinical/Statistical Report

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Study Vaccine: GlaxoSmithKline Biologicals’ combined hepatitis A / hepatitis B vaccine (Twinrix™)

CPMS Study No.: 208127/099 (Ext.HAB-075)

Indication: To protect healthy adolescents against hepatitis A and B.

Principal Investigator: Dr. [Redacted]

Date of First Visit: 12 August 1997

Primary Study End Date: 14 March 1998

Primary Study Report Date: 26 March 1999

Long-term Follow-up End Date: 19 September 2000

Co-ordinating Author: [Redacted]

Other Contributing Authors: [Redacted] - Associate Director Clinical Development
[Redacted] - Clinical Development Manager
[Redacted] - Clinical Study Management Statistician

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

Annex 1 Report Date: 28 August 2001

This annex report provides results of long-term follow-up to and including Month 36.
Synopsis of Study Report 208127/099 Annex-1

to Study Report 208127/075 (HAB-075)

Name of Company: GlaxoSmithKline Biologicals, Rixensart, Belgium
Name of Finished Product: Hepatitis A / Hepatitis B
Name of active substance: Hepatitis A (Strain HM 175 - RIT 4380)
Hepatitis B (Recombinant HBsAg)

TABULAR FORMAT
REFERRING TO PART
OF THE DOSSIER
Volume:
Page:
(for national authority only)

Title of the study: Clinical Trial: 208127/099 (HAB-075) Annex-1
A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigator: Dr.
Study Centers: Australia
Publication (reference): None published as of 28 August 2001
Study period: Start of main study: 12 August 1997
Completed (up to Month 36): 19 September 2000
Clinical phase: III

Objectives:
Objective of this long-term follow-up was to evaluate the long-term anti-HAV and anti-HBs antibody persistence from blood samples taken 36 months after the first dose of the primary vaccination (0, 6 month schedule) with GlaxoSmithKline Biologicals’ (GSK Biologicals’) high-dose combined hepatitis A - hepatitis B (HAB) vaccine, or GSK Biologicals’ combined hepatitis A - hepatitis B vaccine (Twinrix™), in healthy adolescents.

Methodology:
Study design: The primary study was a comparative, double-blind and randomized study with two groups. The long-term follow-up at Month 36 was an open study with two groups. At this time point, a blood sampling was done and any serious adverse events (SAEs) which the subject might have experienced since the last study visit was documented. Written informed consent was obtained prior to the blood sampling at Month 36 from all subjects who returned.

Population Group: Healthy male and female subjects between 11 to 18 years of age inclusive at the time of primary vaccination.

Number of subjects enrolled and vaccinated: 150 (75 /group)
Number of subjects who completed the primary study: 149 (Group 1 = 75, Group 2 = 74)
Number of subjects who returned at Month 36: 139 (Group 1 = 67, Group 2 = 72)
Number of subjects included in the long-term ATP immunogenicity analysis at Month 36: 112 (Group 1 = 59, Group 2 = 53)
Number of subjects included in the long-term kinetics analysis at Month 36: 112 (Group 1 = 59, Group 2 = 53)
**Name of Company:** GlaxoSmithKline Biologicals, Rixensart, Belgium  
**Name of Finished Product:** Hepatitis A / Hepatitis B  
**Name of active substance:** Hepatitis A (Strain HM 175 - RIT 4380)  
Hepatitis B (Recombinant HBsAg)

**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER**

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine received:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contents</td>
</tr>
<tr>
<td></td>
<td>Combined Hep A-</td>
</tr>
<tr>
<td></td>
<td>Hep B (Twinrix™)</td>
</tr>
<tr>
<td>Group 1</td>
<td>at least 720 EL U</td>
</tr>
<tr>
<td>Hepatitis A (Strain HM 175 - RIT 4380 44380)</td>
<td>20 mcg</td>
</tr>
<tr>
<td>Hepatitis B (recombinant HBsAg)</td>
<td>0.45 mg</td>
</tr>
<tr>
<td>Aluminium salt</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>Volume/dose</td>
<td>HAB116C4/M</td>
</tr>
<tr>
<td>Lot number</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>Combined high-dose</td>
</tr>
<tr>
<td>Hepatitis A - Hep B vaccine</td>
<td>at least 1440 EL U</td>
</tr>
<tr>
<td></td>
<td>40 mcg</td>
</tr>
<tr>
<td></td>
<td>0.85 mg</td>
</tr>
<tr>
<td></td>
<td>1.0 ml</td>
</tr>
<tr>
<td></td>
<td>DHAB404A4</td>
</tr>
</tbody>
</table>

**Test product, dose, mode of administration, lot No.:**  
*Vaccination schedule/site:* 0, 6 month schedule administered intramuscularly in the deltoid region for both groups.  
*Vaccine/composition/dose/lot number:*

- **Group 1:** Combined Hep A-Hep B (Twinrix™) vaccine  
  - Hepatitis A (Strain HM 175 - RIT 4380)  
  - Hepatitis B (recombinant HBsAg)  
  - Aluminium salt  
  - Volume: 1.0 ml  
  - Lot number: HAB116C4/M DHAB404A4

- **Group 2:** Combined high-dose Hep A - Hep B vaccine  
  - Hepatitis A (Strain HM 175 - RIT 4380)  
  - Hepatitis B (recombinant HBsAg)  
  - Aluminium salt  
  - Volume: 1.0 ml  
  - Lot number: DHAB404A4

**Reference therapy, dose and mode of administration, lot number:** NA

**Duration of treatment:**  
*Primary Study:* 7 months.  
*Long-term follow-up:* 36 months

**Criteria for evaluation:**  
*Immunogenicity:* Measurement of anti-HAV and anti-HBs antibody titers 36 months after the first of the two doses of primary vaccination (0, 6 month schedule). Anti-HAV antibody titers were measured using enzyme immunoassay (EIA) and anti-HBs antibody titers were measured using enzyme-linked immunoassay. Subjects with anti-HAV antibody titers ≥ 15 mIU/ml were considered seropositive for anti-HAV antibodies. Subjects with anti-HBs antibody titers ≥ 3.3 mIU/ml were considered seropositive and those with anti-HBs antibody titers ≥ 10 mIU/ml were considered seroprotected.

**Statistical methods:**  
Descriptive analyses were performed on the according-to-protocol cohort (ATP), total cohort and kinetics cohort.  
The long-term ATP cohort included all subjects who were in the ATP analysis of immunogenicity in the primary study and who were not eliminated from the ATP analysis during the long-term follow-up at Month 36. The total cohort included all subjects with assay results available for anti-HAV and/or anti-HBs antibodies at Month 36. The kinetic cohort included all subjects who were in the long-term ATP immunogenicity analysis at Month 36 and who had serology results available at Months 7 and 36.  
Seropositivity rates, GMTs with 95% confidence interval (CI) for anti-HAV and anti-HBs antibodies and seroprotection rates with 95% CI for anti-HBs antibodies was calculated.

**SUMMARY-Results:**  
*Immunogenicity Results:* New serological assay kits (EIA) for anti-HAV and enzyme-linked immunoassay for anti-HBs antibodies were used for Month 36 blood samples in addition to the assay kits used in the primary study. Blood samples at Month 7 (i.e., the last primary blood sampling time point) were re-tested with the new assay kits in order to evaluate the kinetics of decline of antibody titers. Only results at these time points have been presented.  
Three years after the first dose of the primary vaccination (i.e., at Month 36):  
- All subjects in the long-term ATP immunogenicity cohort remained seropositive for anti-HAV antibodies.  
- The decrease in anti-HAV GMTs between Months 7 and 36 was approximately 90% in Group 1 (7360.2 vs 710.2 mIU/ml) and approximately 93% in Group 2 (14559.2 vs 1023.4 mIU/ml).  
- In Group 1, 84.7% (50/59) of subjects and in Group 2, 86.8% (46/53) of subjects in the
long-term ATP immunogenicity cohort remained seroprotected for anti-HBs antibodies.
- The decrease in anti-HBs GMTs between Months 7 and 36 was approximately 96% in both groups (Group 1: 3840.7 vs. 148.4 mIU/ml; Group 2: 4748.3 vs. 175.9 mIU/ml).

GMTs and seropositivity (S+) rates of anti-HAV and anti-HBs antibodies and seroprotection (SP) rates of anti-HBs antibodies, for the long-term ATP immunogenicity cohort are as follows:

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>Anti-HBs antibodies</th>
<th>Anti-HAV antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>PII(M7)</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>59</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>PII(M7)</td>
<td>55</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>53</td>
<td>50</td>
</tr>
</tbody>
</table>

N = number of subjects tested
S+ = seropositive for anti-HBs antibodies (titers ≥ 3.3 mIU/ml) or for anti-HAV antibodies (titers ≥ 15 mIU/ml)
SP = seroprotected for anti-HBs antibodies (titers ≥ 10 mIU/ml)
n, % = number, percent of subjects who were seropositive for anti-HAV/anti-HBs antibodies/seroprotected for anti-HBs antibodies
PII (M7) = post-vaccination Dose 2, blood sampling at Month 7
PII (M36) = post-vaccination Dose 2, blood sampling at Month 36

Retrospective follow-up for Serious Adverse Events: (SAEs)
At Month 36, five SAEs were reported by three subjects (2/Group 1 and 1/Group 2), all of which were determined by the investigator to be ‘unrelated’ to vaccination.

SUMMARY-Conclusion:
GlaxoSmithKline Biologicals’ Twinrix™ 2-dose and Hepatitis A - Hepatitis B combined high-dose (1440/40) vaccines induced a satisfactory immune response in terms of anti-HAV and anti-HBs antibodies that persisted for at least 36 months after the first dose of the primary vaccination course (0, 6 month schedule) in the majority of vaccinees of 11-18 years of age. This was evident by the fact that 36 months after the first dose of the primary vaccination course, all subjects remained seropositive for anti-HAV antibodies and 84.7% (50/59) and 86.8% (46/53) of subjects in Groups 1 and 2, respectively, remained seroprotected for anti-HBs antibodies.

Date of report: 28 August, 2001
NOTE

This report updates the results of the previous study report 208127/075 (HAB-075) by including the results of blood sampling and retrospective safety follow-up 36 months after administration of the first dose.

The sections on INTRODUCTION, OBJECTIVES AND METHODOLOGY have not been repeated in this annex report as no change occurred in either section. Please refer to the main report of this study (HAB-075) for information regarding these sections.
CONTENTS: TEXT

1. RATIONALE
2. STUDY OBJECTIVES
3. METHODOLOGY
   3.1 STUDY DESIGN
   3.2 ETHICS
   3.3 STUDY VACCINE COMPOSITION
   3.4 STUDY PROCEDURES
       3.4.1 Intervals between study visits
       3.4.2 Laboratory assays and time points
   3.5 ASSESSMENT OF SAFETY VARIABLES
   3.6 DATA QUALITY ASSURANCE
   3.7 STATISTICAL METHODS
       3.7.1 Study cohorts/data sets analyzed
       3.7.2 Analysis of demographics
       3.7.3 Analysis of immunogenicity
       3.7.4 Analysis of safety
   3.8 SUBJECT ELIGIBILITY AND ATTRITION FROM STUDY
       3.8.1 Eligibility for analysis
   3.9 DEMOGRAPHIC CHARACTERISTICS
       3.9.1 Total cohort
       3.9.2 ATP cohort
4. ANALYSIS OF IMMUNOGENICITY
   4.1 DATA SETS ANALYZED
   4.2 ACCORDING-TO-PROTOCOL ANALYSIS
       4.2.1 Anti-HAV antibody persistence
       4.2.2 Anti-HBs antibody persistence
   4.3 ANALYSIS OF TOTAL COHORT
       4.3.1 Anti-HAV antibody persistence
       4.3.2 Anti-HBs antibody persistence
5. RETROSPECTIVE FOLLOW-UP FOR SERIOUS ADVERSE EVENTS
6. OVERALL CONCLUSIONS
CONTENTS: REPORT TABLES AND FIGURES

Table 1 The number of subjects, enrolled into the study as well as the number excluded from analyses .................................................................16
Table 2 Demographics at Month 36 for long-term total cohort .........................17
Table 3 Demographics: at Month 36 for long-term ATP and kinetics cohort........17
Table 4 Seropositivity rates and Geometric Mean Titers (GMT) of Anti-HAV antibody titers (long-term ATP cohort for immunogenicity) .........................19
Table 5 Seropositivity rates, seroprotection rates and Geometric Mean Titers (GMT) of anti-HBs antibody titers (long-term ATP cohort for immunogenicity) ..................................................................................20
Table 6 Seropositivity rates and Geometric Mean Titers (GMT) of anti-HAV antibody titers (long-term total cohort for immunogenicity)..........................21
Table 7 Seropositivity rates, seroprotection rates and Geometric Mean Titers (GMT) of anti-HBs antibody titers (long-term total cohort for immunogenicity) ..................................................................................22
Table 8 Serious adverse events reported during the long-term follow-up at Month 36........................................................................................................23
APPENDICES

Clintrial Elimination Codes........................................................................................................ 24
Notes for appendix tables........................................................................................................ 26

Appendices: Individual Listings

I A ELIMINATION CODES........................................................................................................ 27
I C DATES OF BLOOD SAMPLING AND DATE OF BIRTHS................................................. 29
III A IMMUNOGENICITY........................................................................................................... 34

Appendices: Serious Adverse Events

− CIOMS
− SERIOUS ADVERSE EVENTS TABLE

Appendices: Study Information

− PROTOCOL AMENDMENT
− REPRESENTATIVE SUBJECT INFORMATION SHEET
− ONE PAGE CV OF PRINCIPAL INVESTIGATOR
List of Abbreviations and Definitions of Terms

Anti-HAV : Antibodies to hepatitis A virus
Anti-HBs : Antibodies to hepatitis B surface antigen
ATP : According-to-protocol analysis
EIA : Enzyme immunoassay
GMT : Geometric mean antibody titre
GSK Biologicals : GlaxoSmithKline Biologicals
HA : Hepatitis A
HAB : Hepatitis A / hepatitis B viruses
HBsAg : Hepatitis B surface antigen
HBV : Hepatitis B virus
ICH : International Committee on Harmonization
IEC : Independent Ethical Committee
IRB : Institutional Review Board
IU : International Units
mcg : microgram
mg : milligram
mIU/ml : milli-International Units per milliliter
ml : milliliter
SAE : Serious Adverse Events
SARR : Suspect Adverse Reaction Report
Glossary of Terms

ATP cohort for long-term analysis of immunogenicity: The long-term ATP cohort included all subjects who were in the ATP analysis of immunogenicity in the primary study except for the subjects who received elimination code(s) during the long-term follow-up.

Total cohort The total cohort included all subjects for whom serological results were available for anti-HAV and/or anti-HBs antibodies at Month 36.

Kinetic cohort The kinetic cohort included all subjects who were in the long-term ATP immunogenicity analysis at Month 36 and who had serology results available at Months 7 and 36.

Serious Adverse Event A serious adverse event was any event which was fatal, life threatening *, disabling/incapacitating † or resulted in hospitalisation ‡, prolonged a hospital stay or was associated with congenital abnormality in offspring, cancer or overdose (either accidental or intentional). In addition any event which the investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the vaccine was documented as a serious adverse event.

Seroprotection: Subjects with anti-HBs antibody titers ≥ 10 mIU/ml were considered seroprotected.

Seropositive: Subjects with anti-HBs antibody titers ≥ 3.3 mIU/ml, anti-HAV antibody titers ≥ 15 mIU/ml were considered seropositive for that antibody.

Subjects: Term used throughout the report for the enrolled individuals in the study.
1. Rationale

To evaluate the long-term anti-HAV and anti-HBs antibody persistence 36 months after the first dose of the primary vaccination course (0, 6 month schedule). Blood samples were taken from all available subjects who received the primary vaccination.

2. Study Objectives

Objective of this long-term follow-up was to evaluate the long-term anti-HAV and anti-HBs antibody persistence from blood samples taken 36 months after the first of the two doses of primary vaccination (0, 6 month schedule) with GlaxoSmithKline (GSK) Biologicals’ high-dose (1440) combined hepatitis A – hepatitis B (HAB) vaccine or Twinrix™ in healthy volunteers 11 to 18 years of age (inclusive) at the time of primary vaccination.

3. Methodology

A protocol amendment dated 23 June 2000 required the collection of blood samples at 36, 48, and 60 months after the first of the two doses of primary vaccination (0, 6 months). The amendment also required the documentation of any serious adverse events (SAE), which the subject might have experienced since the last study visit (Month 7).

This annex report details the results of the study from the last visit of the primary study (Month 7) up to and including Month 36.

3.1 Study design

The primary study was a double blind, randomized 1:1 study with two groups. The long-term follow-up at Month 36 was an open study with the same two groups.

At this time point, one blood sampling was done and Serious Adverse Events (SAEs) from the last visit of the primary study up to Month 36 were documented.

The blood sampling visits at Month 36 were conducted between 7 August 2000 and 19 September 2000.
3.2 Ethics

The protocol amendment dated 23 June 2000 and the amended statement of informed consent were approved by the
Australia on 21 July 2000.

Written informed consent was obtained from the parent/guardian and/or the subject (if required by local legislation, written informed consent was obtained from the subjects in addition to the parent/guardian), prior to entry into the long-term follow-up study at Month 36.

3.3 Study vaccine composition

The study vaccine used in the primary study was developed and manufactured by GlaxoSmithKline Biologicals.

The Quality Control Standards and Requirements for the study vaccine were described in separate release protocol and the required approvals were obtained. The vaccine release protocol was archived in the study file and was available upon request.

Group 1 received combined hepatitis A / hepatitis B vaccine (Twinrix™) and Group 2 received combined high-dose hepatitis A / hepatitis B vaccine. Antigen content in the vaccine lots used in this study were as follows:

<table>
<thead>
<tr>
<th>Group: Vaccine received:</th>
<th>Group 1 Combined hep A/hep B vaccine (Twinrix™)</th>
<th>Group 2 Combined high-dose hep A/hep B vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated Hepatitis A antigen (Strain HM 175 - RIT 4380)</td>
<td>at least 720 EL.U</td>
<td>at least 1440 EL.U</td>
</tr>
<tr>
<td>Hepatitis B antigen (recombinant HBsAg)</td>
<td>20 mcg</td>
<td>40 mcg</td>
</tr>
<tr>
<td>Aluminium salt</td>
<td>0.45 mg</td>
<td>0.85 mg</td>
</tr>
<tr>
<td>Volume</td>
<td>1.0 ml</td>
<td>1.0 ml</td>
</tr>
<tr>
<td>Lot number</td>
<td>HAB116C4/M</td>
<td>DHAB404A4</td>
</tr>
</tbody>
</table>

Schedule: 0, 6 months for both groups

3.4 Study procedures

At Month 36 (Visit 6):

- Before each bleeding:
  The investigator asked each volunteer if he/she had received, since the last visit
  ➢ a dose of hepatitis A or hepatitis B vaccine and/or
a dose of hepatitis A or hepatitis B immunoglobulins. If so, subjects were excluded from this extended long-term follow-up study.

- **Bleeding:**
  From each subject, 7 ml of whole venous blood was collected for testing anti-HAV and anti-HBs antibodies. Serum was stored at – 20°C until transported to GSK Biologicals for testing.

- **Recording of serious adverse events (SAEs):**
  Documentation of SAEs, which the subject might have experienced since the last study visit.

### 3.4.1 Intervals between study visits

The interval to be respected for the long-term time point was as follows:

<table>
<thead>
<tr>
<th>Interval between visits</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0 – Month 36</td>
<td>36 months ± 6 weeks</td>
</tr>
</tbody>
</table>

### 3.4.2 Laboratory assays and time points

All laboratory assays were conducted in GSK Biologicals.

**Serology**

- The presence of anti-HAV antibodies was determined using an enzyme immunoassay (EIA) using the Enzygnost® Kit from DADE Behring and expressed in milli-International Units per milliliter (mIU/ml).

- Anti-HBs antibodies were tested using enzyme-linked immunoassay Test-Kit from Ausab®, Abbott Laboratories, North Chicago IL, USA. The anti-HBs antibody titers were expressed in milli-international units per milliliter (mIU/ml).

New serological assay kits (EIA) for anti-HAV and enzyme-linked immunoassay for anti-HBs antibodies were used for Month 36 blood samples in addition to the assay kits used in the primary study. Blood samples at Month 7 (i.e., the last primary blood sampling time point) were re-tested with the new assay kits in order to evaluate the kinetics of decline of antibody titers. Only results at these time points have been presented.

Subjects with anti-HAV antibody titers ≥ 15 mIU/ml were considered seropositive for anti-HAV antibodies. Subjects with anti-HBs antibody titers ≥ 3.3 mIU/ml were considered seropositive for anti-HBs antibodies. Seroprotection rate for anti-
HBs antibodies was defined as the percentage of subjects with anti-HBs antibody titers ≥ 10 mIU/ml.

3.5 Assessment of safety variables

Serious adverse events (SAE), which were experienced since the last study visit at Month 7 were documented.

3.6 Data quality assurance

To ensure that study procedures conformed across all investigator sites, the amendment, blood sampling and safety reporting were reviewed with the investigator and his/her 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 GlaxoSmithKline Standard Operating Procedures (SOPs).

3.7 Statistical methods

Only descriptive analysis was performed for immunology results at Month 36. Analyses were performed on three study cohorts: the according-to-protocol (ATP) cohort, the total cohort and the kinetics cohort.

3.7.1 Study cohorts/data sets analyzed

The long-term ATP cohort included all subjects who were in the ATP analysis of immunogenicity in the primary study except for the subjects who received the elimination code(s) during the long-term follow-up.

The total cohort included all subjects for whom serological results were available for anti-HAV and/or anti-HBs antibodies at Month 36.

The kinetics cohort included subjects who were included in the long-term ATP cohort at Month 36 and who had serology results of the previous time point (i.e., Month 7) available.

3.7.2 Analysis of demographics

The demographic data were tabulated for the long-term total, ATP and kinetics cohort.
3.7.3 Analysis of immunogenicity

This annex report describes serology results of blood sampling done at Month 36. Only descriptive analyses for immunology results were performed at this time point.

Seropositivity (S+) rates and GMTs of anti-HAV and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies were calculated with 95% confidence interval (CI).

Seropositivity rate was defined as the percentage of subjects with titers $\geq 3.3$ mIU/ml for anti-HBs antibodies and titers $\geq 15$ mIU/ml for anti-HAV antibodies. Seroprotection rate for anti-HBs antibodies was defined as the percentage of subjects with titers $\geq 10$ mIU/ml. Geometric Mean Titers (GMT) of anti-HAV antibodies and anti-HBs antibodies were calculated by taking the anti-log of the mean of the log titre transformations.

3.7.4 Analysis of safety

SAEs, which the subject experienced since the last study visit at Month 7, were documented.

3.8 Subject eligibility and attrition from study

3.8.1 Eligibility for analysis

The number of subjects enrolled and excluded (with reasons for exclusion) from the long-term ATP and kinetics analyses is presented in Table 1. Elimination codes are defined on the first page of the Appendix Tables. See Appendix Table I A for individual subject data on elimination codes.

In the primary study, 150 subjects were enrolled. Three years after the first dose of the primary vaccination at Month 36, 139 (92.6% compliance) subjects returned for the blood sampling visit.

Of these 139 subjects who returned at Month 36, 27 subjects were eliminated in the primary ATP analysis and none were eliminated during the long-term follow-up. Thus, 112 subjects (59 in Group 1 and 53 in Group 2) were included in the long-term ATP immunogenicity analysis at Month 36 and all these subjects were also in the kinetics cohort.
Table 1 The number of subjects, enrolled into the study as well as the number excluded from analyses

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects planned and enrolled in the primary study</td>
<td>150</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Number of subjects in the primary ATP immunogenicity analysis</td>
<td>122</td>
<td>67</td>
<td>55</td>
</tr>
<tr>
<td>Number of subjects who returned at Month 36</td>
<td>139</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>Administration of vaccine(s) forbidden in the protocol (code 1040)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Protocol violation (inclusion/exclusion criteria) (code 2010)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Initially seropositive or initially unknown antibody status (code 2020)</td>
<td>23</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080 )</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Essential serological data missing (code 2100 )</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>*Number of subjects in long-term ATP cohort for immunogenicity at Month 36</td>
<td>112</td>
<td>59</td>
<td>53</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4
Subjects may have more than one elimination code assigned (see Appendix Table I A), in which case the primary code is listed in this flow chart. The elimination code numbers are given in parentheses next to the code description (see the first page of Appendix Tables for details of code numbers).

All subjects were eliminated in primary study and none of the subjects were eliminated during the long-term follow-up at Month 36.

* Also the kinetics cohort in this study (i.e., subjects who were included in the long-term ATP immunogenicity analysis and who had serology results available for Months 7 and 36).

3.9 Demographic characteristics

3.9.1 Total cohort

The demographics of the total cohort at Month 36 are presented in Table 2.

The demographic profile of the 2 groups of subjects who came back at Month 36 was comparable with respect to mean age and gender. The mean age was 17.8 years with a standard deviation of 1.51 years, the male: female ratio was 69:70 and all except two subjects were white.
**Table 2 Demographics at Month 36 for long-term total cohort**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>N</th>
<th>Mean age (in years)</th>
<th>SD age (in years)</th>
<th>Min. age (in years)</th>
<th>Max. age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>32</td>
<td>18.1</td>
<td>1.41</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>35</td>
<td>17.6</td>
<td>1.63</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>67</td>
<td>17.8</td>
<td>1.54</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>38</td>
<td>17.9</td>
<td>1.57</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>34</td>
<td>17.7</td>
<td>1.41</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>72</td>
<td>17.8</td>
<td>1.49</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Both</td>
<td>Female</td>
<td>70</td>
<td>18.0</td>
<td>1.49</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>69</td>
<td>17.6</td>
<td>1.51</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>139</td>
<td>17.8</td>
<td>1.51</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4
N = number of subjects
SD = standard deviation
Min, Max age = minimum, maximum age in years

### 3.9.2 ATP cohort

The demographics of subjects who were included in the long-term ATP analysis of immunogenicity at Month 36 are shown in Table 3. (Note: As all subjects included in the long-term ATP analysis of immunogenicity, had serology results available at Months 7 and 36, this is also the kinetics cohort).

The demographics of the ATP cohort were similar to that of the total cohort.

**Table 3 Demographics: at Month 36 for long-term ATP and kinetics cohort**

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>N</th>
<th>Mean age (in years)</th>
<th>SD age (in years)</th>
<th>Min. age (in years)</th>
<th>Max. age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>30</td>
<td>18.0</td>
<td>1.45</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>29</td>
<td>17.6</td>
<td>1.72</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>59</td>
<td>17.8</td>
<td>1.60</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>24</td>
<td>17.7</td>
<td>1.49</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>29</td>
<td>17.7</td>
<td>1.49</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>53</td>
<td>17.7</td>
<td>1.48</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Both</td>
<td>Female</td>
<td>54</td>
<td>17.9</td>
<td>1.47</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>58</td>
<td>17.6</td>
<td>1.60</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>112</td>
<td>17.7</td>
<td>1.53</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4
N = number of subjects
SD = standard deviation
Min, Max age = minimum, maximum age in years
4. **Analysis of immunogenicity**

4.1 **Data sets analyzed**

Two analyses were performed for immunogenicity. The total cohort, which included all subjects with assay results available for anti-HAV and/or anti-HBs antibodies at Month 36. The long-term ATP cohort, which was regarded as the principal analysis for this report included all subjects who were in the ATP analysis of immunogenicity in the primary study and who were not eliminated from the analysis during the long-term follow-up at Month 36.

4.2 **According-To-Protocol analysis**

Data from 112 subjects (59 in Group 1 and 53 in Group 2) were included in this long-term according-to-protocol immunogenicity analysis.

Note: As all subjects included in the long-term ATP analysis of immunogenicity, had serology results available at Months 7 and 36, this is also the kinetics cohort.

4.2.1 **Anti-HAV antibody persistence:**

Table 4 presents the seropositivity rates and GMTs of anti-HAV antibodies up to Month 36 for the long-term ATP immunogenicity cohort.

Three years after the first dose of the primary vaccination (i.e., at Month 36), all subjects in both groups included in the long-term ATP immunogenicity analysis and who were tested at Month 36 remained seropositive for anti-HAV antibodies.

The decrease in anti-HAV GMTs between Months 7 and 36 was approximately 90% in Group 1 (7360.2 vs 710.2 mIU/ml) and approximately 93% in Group 2 (14559.2 vs 1023.4 mIU/ml).
Table 4 Seropositivity rates and Geometric Mean Titers (GMT) of Anti-HAV antibody titers (long-term ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI GMT (mIU/ml)</th>
<th>95% CI GMT (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>L.L. U.L.</td>
<td>L.L. U.L.</td>
</tr>
<tr>
<td>1</td>
<td>PII(M7)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>7360.2</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>59</td>
<td>59</td>
<td>100.0</td>
<td>710.2</td>
</tr>
<tr>
<td>2</td>
<td>PII(M7)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>14559.2</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>53</td>
<td>53</td>
<td>100.0</td>
<td>1023.4</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4
N = number of subjects tested
S+ = seropositive for anti-HAV antibodies (titres ≥ 15 mIU/ml)
n, % = number, percent of subjects who were seropositive for anti-HAV antibodies
GMTs (Geometric Mean Titer) calculated on subjects with titers greater than assay cut-off
PII (M7) = post-vaccination Dose 2, blood sampling at Month 7
PII (M36) = post-vaccination Dose 2, blood sampling at Month 36
95% CI, L.L and U.L = 95% confidence intervals, lower and upper limit

4.2.2 Anti-HBs antibody persistence

Table 5 presents the seropositivity rates, seroprotection rates and GMTs of anti-HBs antibodies, up to Month 36, for long-term ATP immunogenicity cohort.

Three years after the first dose of the primary vaccination (i.e., at Month 36), 84.7% (50/59) of subjects in Group 1 and 86.8% (46/53) of subjects in Group 2 included in the long-term ATP immunogenicity analysis and who were tested at Month 36 remained seroprotected for anti-HBs antibodies.

The decrease in anti-HBs GMTs between Months 7 and 36 was approximately 96% in both groups (Group 1: 3840.7 vs. 148.4 mIU/ml; Group 2: 4748.3 vs. 175.9 mIU/ml).
Table 5 Seropositivity rates, seroprotection rates and Geometric Mean Titers (GMT) of anti-HBs antibody titers (long-term ATP cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI L.L.</th>
<th>100.0</th>
<th>U.L.</th>
<th>SP</th>
<th>95% CI L.L.</th>
<th>100.0</th>
<th>U.L.</th>
<th>GMT</th>
<th>95% CI L.L.</th>
<th>100.0</th>
<th>U.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PII(M7)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>3840.7</td>
<td>2667.9</td>
<td>5529.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>59</td>
<td>54</td>
<td>91.5</td>
<td>81.3</td>
<td>97.2</td>
<td>50</td>
<td>84.7</td>
<td>73.0</td>
<td>92.8</td>
<td>148.4</td>
<td>94.3</td>
<td>233.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PII(M7)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>4748.3</td>
<td>2815.1</td>
<td>8009.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>53</td>
<td>50</td>
<td>94.3</td>
<td>84.3</td>
<td>98.8</td>
<td>46</td>
<td>86.8</td>
<td>74.7</td>
<td>94.5</td>
<td>175.9</td>
<td>103.8</td>
<td>298.2</td>
<td></td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1 received Twinrix™ lot HAB116C4/M

Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4

N = number of subjects tested

S+ = seropositive for anti-HBs antibodies (titres ≥ 3.3 mIU/ml)

SP = seroprotected for anti-HBs antibodies (titres ≥ 10 mIU/ml)

n, % = number, percent of subjects who were seropositive/seroprotected for anti-HBs antibodies

GMTs (Geometric Mean Titer) calculated on subjects with titers greater than assay cut-off

PII (M7) = post-vaccination Dose 2, blood sampling at Month 7

PII (M36) = post-vaccination Dose 2, blood sampling at Month 36

95% CI, L.L and U.L = 95% confidence intervals, lower and upper limit

4.3 Analysis of total cohort

4.3.1 Anti-HAV antibody persistence

Table 6 presents the seropositivity rates and GMTs of anti-HAV antibodies up to Month 36, for the total cohort.

All subjects in the total cohort analysis remained seropositive for anti-HAV antibodies up to Month 36. Seropositivity rates for the total cohort were similar to that observed in the long-term ATP immunogenicity cohort.
Table 6 Seropositivity rates and Geometric Mean Titers (GMT) of anti-HAV antibody titers (long-term total cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+ n</th>
<th>%</th>
<th>95% CI L.L.</th>
<th>U.L.</th>
<th>GMT (mIU/ml)</th>
<th>95% CI L.L.</th>
<th>U.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PII(M7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>7206.8</td>
<td>5492.6</td>
<td>9456.1</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>688.3</td>
<td>527.7</td>
<td>897.7</td>
</tr>
<tr>
<td>2</td>
<td>PII(M7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
<td>13574.9</td>
<td>10504.6</td>
<td>17542.6</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>72</td>
<td>72</td>
<td>100.0</td>
<td>95.0</td>
<td>100.0</td>
<td>1002.2</td>
<td>786.0</td>
<td>1277.8</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4

N = number of subjects tested
S+ = seropositive for anti-HAV antibodies (titres ≥ 15 mIU/ml)
n, % = number, percent of subjects who were seropositive for anti-HAV antibodies
GMTs (Geometric Mean Titer) calculated on subjects with titers greater than assay cut-off
PII (M7) = post-vaccination Dose 2, blood sampling at Month 7
PII (M36) = post-vaccination Dose 2, blood sampling at Month 36
95% CI, L.L and U.L = 95% confidence intervals, lower and upper limit

4.3.2 Anti-HBs antibody persistence

Table 7 presents the seropositivity, seroprotection rates and GMTs of anti-HBs antibodies up to Month 36, for the total cohort.

In the total cohort analysis, 85.1% and 86.1% of subjects in Groups 1 and 2, respectively, remained seroprotected for anti-HBs antibodies up to Month 36. Anti-HBs seropositivity and seroprotection rates for the total cohort were similar to that observed in the long-term ATP immunogenicity cohort.
Table 7 Seropositivity rates, seroprotection rates and Geometric Mean Titers (GMT) of anti-HBs antibody titers (long-term total cohort for immunogenicity)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI L.L.</th>
<th>U.L.</th>
<th>SP</th>
<th>95% CI L.L.</th>
<th>U.L.</th>
<th>GMT</th>
<th>95% CI L.L.</th>
<th>U.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PII(M7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td></td>
<td>75</td>
<td>100.0</td>
<td></td>
<td>3543.2</td>
<td>2516.8</td>
<td>4988.2</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>67</td>
<td>61</td>
<td>91.0</td>
<td></td>
<td>57</td>
<td>85.1</td>
<td></td>
<td>135.9</td>
<td>89.5</td>
<td>206.3</td>
</tr>
<tr>
<td>2</td>
<td>PII(M7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td></td>
<td>73</td>
<td>100.0</td>
<td></td>
<td>135.9</td>
<td>89.5</td>
<td>206.3</td>
</tr>
<tr>
<td></td>
<td>PII(M36)</td>
<td>72</td>
<td>67</td>
<td>93.1</td>
<td></td>
<td>62</td>
<td>86.1</td>
<td></td>
<td>157.2</td>
<td>102.7</td>
<td>240.8</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1 received Twinrix™ lot HAB116C4/Ms
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4
N = number of subjects tested
S+ = seropositive for anti-HBs antibodies (titres ≥ 3.3 mIU/ml)
SP = seroprotected for anti-HBs antibodies (titres ≥ 10 mIU/ml)
n, % = number, percent of subjects who were seropositive/seroprotected for anti-HAV/anti-HBs antibodies
GMTs (Geometric Mean Titer) calculated on subjects with titers greater than assay cut-off
PII (M7) = post-vaccination Dose 2, blood sampling at Month 7
PII (M36) = post-vaccination Dose 2, blood sampling at Month 36
95% CI, L.L and U.L = 95% confidence intervals, lower and upper limit

5. Retrospective Follow-up for Serious Adverse Events

Five serious adverse events (SAEs) were reported by three subjects, which occurred since the last study visit (Month 7). All the five SAEs were determined by the investigator to be ‘not related’ to vaccination. Refer Table 8 for details.
Table 8 Serious adverse events reported during the long-term follow-up at Month 36

Group 1 received Twinrix™ lot HAB116C4/M
Group 2 received high-dose combined hepatitis A-hepatitis B vaccine lot DHAB404A4

Suspect Adverse Reaction Report (SARR) and serious adverse events table can be found in the Appendices for Serious Adverse Events.

6. Overall Conclusions

The long term ATP analysis demonstrated the following:

GlaxoSmithKline Biologicals’ Twinrix™ 2-dose and Hepatitis A - Hepatitis B combined high-dose (1440/40) vaccines induced a satisfactory immune response in terms of anti-HAV and anti-HBs antibodies that persisted for at least 36 months after the first dose of the primary vaccination course (0, 6 month schedule) in the majority of vaccinees aged 11-18 years old. This was evident by the fact that 36 months after the first dose of the primary vaccination course, all subjects remained seropositive for anti-HAV antibodies and 84.7% (50/59) and 86.8% (46/53) of subjects in Groups 1 and 2, respectively, remained seroprotected for anti-HBs antibodies.
GLAXOSMITHKLINE BIOLOGICALS VACCINES

CLINTRIAL ELIGIBILITY CODES

Elimination from reactogenicity and serology analysis

1010 Subject or vaccine number not allocated
   Vaccine not administered at all
   Only screening
   No subject attributed for the number randomized or for the vaccine number

1030 Study vaccine dose not administered
   Vaccine dose not given but not drop-out

1040 Administration of vaccine not specified, or forbidden, in the protocol
   Administration of a vaccine different from the trial vaccine

1050 Randomisation failure
   Wrong vaccine vial given

1060 Randomisation code broken
   Code open for any reason

1070 Site of study vaccine administration unknown

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

Elimination from serology analysis

2010 Demographics protocol violation
   Too young
   Too old
   Unknown age, sex
   Gender not according to the protocol

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

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

2040 Medication forbidden by the protocol
   Any medication forbidden

2050 Underlying medical condition

2060 Concomitant infection related to the vaccine
   Infection with any of the vaccine components
GLAXOSMITHKLINE BIOLOGICALS VACCINES
CLINTRIAL ELIGIBILITY CODES

(continued)

2070 Concomitant infection not related to the vaccine
   Any viral infection

2080 Non compliance with vaccination schedule (including wrong and
   unknown dates)

2090 Non compliance with blood sampling schedule (including wrong and
   unknown dates)

2100 Blood sample lost or unable to test (haemolysis, insufficient volume, etc.)
   Absence of parallelism
   Essential serological data missing

2110 Blood sample available but not yet tested (interim analysis)

2120 Obvious incoherence or abnormality or error in data
   Wrong labeling in BS
   Abnormal serology evolution

2500 Others
GLAXOSMITHKLINE BIOLOGICALS VACCINES

NOTES TO APPENDIX TABLES

Sub. No. : subject number
Ctr : centre
Elig : eligibility
Elim : eliminated from analysis (es)
I : indicative of elimination for serological reason
F : female
M : male

Appendix table I C
Pre : pre vaccination blood sampling
PII(M7), etc. : post-vaccination Dose 2, blood sampling at Month 7, etc.
VAC ND : vaccination administration not documented
VIS ND : visit not documented
BS ND : blood sampling not documented

Appendix table III A
PII (M7) = post-vaccination Dose 2, blood sampling at Month 7
PII (M36) = post-vaccination Dose 2, blood sampling at Month 36
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.
Protocol Amendment 1
SmithKline Beecham Biologicals’ combined Hepatitis A/Hepatitis B vaccine.

**Protocol Number:** 208127/075 (HAB-075)

**Protocol Title:** A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

**FIRST AMENDMENT**

CPMS No. 208127/099 (EXT HAB-075) – Month 36 Follow-up
CPMS No. 208127/100 (EXT HAB-075) – Month 48 Follow-up
CPMS No. 208127/101 (EXT HAB-075) – Month 60 Follow-up

**DATE:** JUNE 23, 2000

Protocol HAB-075 dated July 3, 1997

**Coordinating Author:**

**BACKGROUND FOR CHANGES:**

The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile. To follow-up the long term antibody persistence, it was decided to bleed the volunteers at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, and to determine their anti-HAV and anti-HBs antibody titres.

**THE FOLLOWING SECTIONS WERE AMENDED ON JUNE 23, 2000:**

- Section 4.2: Enrolment strategy/plan
- Section 7: Study Procedures
- Section 10: Laboratory Assays
- Section 11.3: Immunogenicity
Approved by:

Associate Director,
Clinical Development

Dr. [redacted] dd-mm-yyyy

Principal Investigator

Dr. [redacted] dd-mm-yyyy
Study Vaccine: SmithKline Beecham Biologicals' combined Hepatitis A/Hepatitis B vaccine.

CPMS Protocol No: 208127/075 (HAB-075)

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

FIRST AMENDMENT

CPMS NO. 208127/099 (EXT HAB-075) – MONTH 36 FOLLOW-UP
CPMS NO. 208127/100 (EXT HAB-075) – MONTH 48 FOLLOW-UP
CPMS NO. 208127/101 (EXT HAB-075) – MONTH 60 FOLLOW-UP
DATE: JUNE 23, 2000

Protocol HAB-075 dated July 3, 1997

1) RATIONALE

The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile.

Present Rationale:
Open follow-up study to evaluate the long term anti-HAV and anti-HBs antibody persistence in both groups (720/20 and 1440/40), at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, by drawing blood samples from all available subjects who received the primary vaccination schedule.

2) SECTIONS AMENDED

4.2 Enrolment strategy/plan

Signed informed consent (for this amendment) will be obtained from each subject before the blood sampling.
7 Study Procedures

The intervals to be respected for the long-term time points are as summarised below.

<table>
<thead>
<tr>
<th>Interval between visits</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0 – Month 36</td>
<td>36 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 48</td>
<td>48 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 60</td>
<td>60 months ± 6 weeks</td>
</tr>
</tbody>
</table>

The intervals between visits are indicative and should be followed as closely as possible. These intervals may determine evaluation of the subjects.

**Detailed description of study stages/visits are as follows:** At month 36 (Visit 6), month 48 (Visit 7) and month 60 (Visit 8):

- **Before each bleeding:**
  The investigator will ask each volunteer if he/she has received, since the last visit
  - a dose of hepatitis A or hepatitis B vaccine and/or
  - a dose of hepatitis A or hepatitis B immunoglobulin.
  If so, subjects will be excluded from this extended long-term follow-up study.

- **Bleeding:**
  From each subject, 7 ml of whole venous blood will be collected for testing anti-HAV and anti-HBs antibodies. Serum will be stored at −20 °C until transported to SB Bio for testing.

- **Recording of serious adverse events (SAEs):**
  Documentation of any SAE, which the subject may have experienced since the last study visit.

10 Laboratory Assays

- The presence of anti-HAV antibodies will be determined using an ELISA (Boehringer Manheim Enzymun Kit® or equivalent assay) calibrated by the use of WHO international standard reference serum and expressed in milli-International Units per milliliter (mIU/ml). The assay cut-off is 33 mIU/ml.

- Anti-HBs antibodies will be tested by radio immunoassay (RIA) using the Test-Kit from AUSAB, Abbott Laboratories, North Chicago IL, USA, or equivalent assay. The anti-HBs titres will be expressed in milli-international units per milliliter (mIU/ml). The assay cut-off is 1 mIU/ml.
• Subjects with anti-HAV antibody titres \( \geq 33 \) mIU/ml, will be considered to be seropositive for anti-HAV antibodies. Subjects with anti-HBs antibody titres \( \geq 1 \) mIU/ml, will be considered to be seropositive for anti-HBs antibodies. Seroprotection rate for anti-HBs is defined as the percentage of subjects with anti-HBs antibody titres \( \geq 10 \) mIU/ml.

• All serology assays will be performed in SmithKline Beecham Biologicals’ central laboratory or in a validated laboratory designated by SmithKline Beecham Biologicals.

11.3 Immunogenicity

The elimination code for an abnormal increase in antibody titres will be assigned for the long-term follow-up. The definition of abnormal increase will depend on the magnitude of the titre reached at the first time point considered (reference value). Abnormal increase in antibody titres is defined as a two-fold increase or more in antibody titres (when the antibody titre at the reference time point is \( \geq 100 \) mIU/ml) or a four-fold increase or more in antibody titres (when the antibody titre at the reference time point is < 100 mIU/ml). This code will be assigned to give a more realistic evaluation of the long-term persistence of antibodies.

The immunogenicity analysis will be performed on two study cohorts: the according-to-protocol study cohort (study cohort eligible for the long-term ATP analysis of immunogenicity) and the total cohort (ITT).

The long-term ATP immunogenicity analysis will include all subjects who are in the ATP immunogenicity analysis in the main study report (except for the subjects who receive the elimination code for abnormal increase in anti-HAV and/or HBs antibody titres during the long-term follow-up). The ITT analysis will be on the total cohort, which will include all subjects for whom assay results are available for anti-HAV and/or anti-HBs antibodies at long term blood sampling time point (months 36, 48 or 60).

Seropositivity rates and GMTs with 95% confidence interval (CI) for anti-HAV and anti-HBs antibodies, seroprotection rates with 95% CI for anti-HBs antibodies will be calculated. Kinetics of anti-HAV and anti-HBs GMTs will be graphically represented.
SB
SmithKline Beecham Biologicals
SmithKline Beecham Pharmaceuticals
89, rue de l’Institut
1330 Rixensart, Belgium

CONFIDENTIAL

Study vaccines: SmithKline Beecham Biologicals’ high-dose combined hepatitis A / hepatitis B candidate vaccine

Protocol n°: 208127/075 (HAB-075)

Date of approval: July 3, 1997

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author: Science Writer
Clinical Research & Development

SB Responsible Physician: Project Manager

Principal Investigators: Dr. Dr. Australia
AGREEMENT

SmithKline Beecham Biologicals
89, rue de l'Institut
1330 Rixensart, Belgium

Study vaccine
SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°
208127 / 075 (HAB-075)

Date
July 3, 1997

Title:
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author

Investigator:
Dr.

Study site address:
Australia

SB responsible physician:
Dr.

Approvals
SmithKline Beecham Biologicals
Dr. Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator's Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date

Signature

(Day-month-year)

Dr.
AGREEMENT

SmithKline Beecham Biologicals
89, rue de l’Institut
1330 Rixensart, Belgium

Study vaccine
SmithKline Beecham Biologicals’ high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°
208127 / 075 (HAB-075)

Date
July 3, 1997

Title :
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author

Investigator :
Dr. [redacted]

Study site address:
Australia

SB responsible physician
Dr. [redacted]

Approvals
SmithKline Beecham Biologicals
Dr. [redacted]
Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator’s Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date Signature
_____________________
(Day-month-year) Dr [redacted]

SYNOPSIS OF PROTOCOL 208127/075 (HAB-075)
**Vaccine under study**: SmithKline Beecham Biologicals’ combined high-dose hepatitis A / hepatitis B vaccine

**Title**: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

**Rationale for the study**: To determine which is the optimal dose of the high-dose HAB 2-dose vaccine, with respect to immunogenicity and reactogenicity & safety in this age category.

**Indication/Study population**: To protect healthy adolescents between the ages of 11 and 18 years against hepatitis A and B.

**Objectives of the study**:

- **Primary objective**: To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine one month after the last dose (month 7).

- **Secondary objectives**: To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
  To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies; seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
  To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

**Study design**: Double blind, randomised study with two groups.

**Schedule**: 0, 6 months.

**Number of subjects**: 150 enrolled (75 subjects per group)

**Endpoints**:

- **Primary endpoints**: Titres for anti-HBs antibodies at month 7.
Secondary endpoints
At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP)*** for anti-HBs antibodies
At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample

**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.

***SP is defined as anti-HBs titre ≥10 mIU/ml

Solicited signs and symptoms during a three day follow-up period. Unsolicited signs and symptoms experienced within 30 days of vaccination.
TABLE OF CONTENTS

1. INTRODUCTION 3
   1.1 Title 3
   1.2 Background 3
   1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine 4

2. STUDY CENTRES 6

3. STUDY OBJECTIVES 6

4. STUDY POPULATION 7
   4.1 Number of subjects 7
   4.2 Enrollment strategy/plan 7
   4.3 Inclusion criteria 7
   4.4 Exclusion criteria 7

5. VACCINE AND VACCINE ADMINISTRATION 8

6. STUDY DESIGN 8
   6.1 Study design 8
   6.2 Randomisation 9
   6.3 Replacement of individual vaccine doses 10

7. STUDY PROCEDURES 10

8. CLINICAL SIGNS AND SYMPTOMS 14

9. ADVERSE EXPERIENCES 15
   9.1 Eliciting and Documenting Adverse Experiences 15
   9.2 Serious Adverse Experiences 16
      9.2.1 Reporting 16
      9.2.2 Definitions 17
   9.3 Treatment of adverse experiences 18
   9.4 Assessment of severity and outcome 19
   9.5 Assessment of Causality 19
   9.6 Following up of adverse experiences 20
   9.7 Pregnancy 20

10. LABORATORY ASSAYS 20

11. STATISTICAL ANALYSIS 20
   11.1 Sample size estimation 21
   11.2 Demographics 22
   11.3 Immunogenicity 22
   11.4 Reactogenicity 22
   11.5 Interim analyses 22

Approved: July 3, 1997
1. INTRODUCTION

1.1 Title

A double-blind study to compare the immunogenicity, safety and reactogenicity of two dose levels of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 μg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 μg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

1.2 Background

Hepatitis A

HAV is classified in the family Picornaviridae, genus Heparnavirus. Seven genotypes of the virus have been identified but only one serotype comprises all of these. Early researchers found that suspensions of fecal samples remained infectious after treatment with acids, ether, high temperatures and even after being frozen for more than a year. HAV can be inactivated by autoclaving, boiling, exposure to high levels of formalin and ultraviolet radiation. The serological marker for previous infection with HAV (anti-HAV) can be detected early in the course of the illness and usually remains detectable in slowly declining titres for years and confers immunity to repeat infection for a lifetime.

The most common route of HAV infection is simply through swallowing food or water contaminated with small amounts of infected fecal material. Most of the viral particles are shed in feces before any symptoms of infection appear so infected individuals may unwittingly pass on the disease to many others before they fall ill themselves.

The epidemiology of hepatitis A is highly influenced by personal and public hygiene. In areas of the world where there is inadequate or non-existent provision for sewage disposal, infection occurs early in life and is almost always subclinical. In developing countries, exposure, infection and subsequent immunity are virtually universal in childhood. In areas where the hepatitis A virus is not in wide circulation, the population is not immune and is therefore more vulnerable to infection occurring later in life. One of the most important factors for disease severity is the age of the patient. Childhood infections can be asymptomatic, while almost all adults suffer from the overt disease with symptoms ranging from mild flu-like symptoms to severe gastrointestinal symptoms, fever, prolonged jaundice and severe weight loss. Nearly two-thirds of adult patients with clinically apparent disease experience complete clinical recovery within two months. Fulminant hepatitis A can occur, although rarely, and is frequently fatal particularly in the older patient. Estimates of the risk of developing fulminant hepatitis A vary. One study estimates occurrence as less than 1% and another estimates it at 6.9%. There appears to be a positive association between mortality and age, with the death rate from symptomatic disease increasing from 0.3% for all ages to 1.8% for those aged over 50 years. Chronic hepatitis A does not occur but a relapsing form of the disease has been observed.

Approved: July 3, 1997
described \(^7\); relapse occurs 2-18 weeks after the primary infection and affects 3-20% of patients with acute hepatitis A infection - after a clinical phase and subsequent recovery, including normalisation of liver enzymes, a second clinical phase with an elevation of liver enzymes occurs, persisting for up to 40 weeks.

**Hepatitis B**

HBV is classified in the family *Hepadnaviridae*, genus *Orthohepadnavirus*. Five genotypes of the virus have been identified but only one serotype comprises all of these. The outer coat of the virus or nucleocapsid is a complex structure containing several proteins including the surface antigen, HBsAg, which is recognised by the antibodies raised by the immune system to combat the virus: the anti-HBs antibody. Natural infection with hepatitis B virus leads to life-long detectable anti-HBs antibody in most individuals. Two other antibodies are also produced by the immune system - anti-HBc and anti-HBe which target the core and e antigens respectively. The presence of HBsAg indicates that the host has been infected and is contagious. Anti-HBc is the first antibody to appear after infection and remains present in the serum even after recovery from the illness and can be detected for years up to the lifetime of the patient.

Blood has long been recognised as a major vehicle for the transmission of hepatitis B virus. Four major modes of transmission are recognised: vertical (also known as perinatal), horizontal, parenteral/percutaneous and sexual. The age of infection is the primary correlate for route of infection. In areas of intermediate and high endemicity of the disease, infection occurs early in life through mother-child transmission and through close personal contact among children \(^8\). In areas of low HBV endemicity, infection occurs primarily in adult life and by the sexual route. Individual response to the infection varies greatly. The age at which infection is acquired affects whether the infection is self-limiting or results in the chronic carrier state. Although the acute infection is more severe in adults, infections in infants and pre-school age children carry much greater risks of chronic carriage thereby increasing the risk of primary hepatocellular carcinoma and cirrhosis later in life \(^9\). The precise mechanism by which carrier rates are influenced by age is unknown, but probably relates to the effect of age on the immune system's ability to eliminate a hepatitis B infection. The probability that an infant will become a chronic carrier if infected is about 90% in the first two years, about 50% at 3 years of age, and 6% to 10% from 6 years of age to adulthood \(^10\).

Up to one-third of individuals with laboratory evidence of infection, *i.e.*, serological markers, experience no symptoms, and so exhibit subclinical infection \(^11\). One-third of patients experience a mild flu-like illness without jaundice and another third develop full-blown jaundice with dark urine, extreme fatigue, anorexia and abdominal pain \(^12\). Individuals infected with hepatitis B may either proceed to full recovery or may become chronic carriers of virus. About 5% of the world's population (around 350 million persons) are chronic carriers of hepatitis B \(^13\). About a quarter of these carriers will develop serious liver disease, including chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma \(^14\).

### 1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine

There is currently no specific treatment for either of these infections. It has been recognised that vaccination is the only method of conferring long-term protection against clinical disease and/or infection. SB Biologicals has a licensed combined hepatitis A / hepatitis B (HAB) vaccine, Twinrix™, which facilitates the provision of
concurrent protection against the two diseases. The increased convenience provided by the use of combined vaccines will improve compliance with vaccination schedules. Studies performed with different lots of the combined vaccine have shown that the combination is safe and immunogenic. This vaccine is administered according to a three vaccination course (0, 1, 6-month schedule). Current studies performed by SB Biologicals are focusing on a high-dose HAB candidate vaccine consisting of a two dose vaccination course (0, 6-month schedule). This candidate high-dose HAB vaccine would offer added convenience and enhance the acceptance of immunisation by both the general public and the medical community. In order to achieve this shorter vaccination schedule the composition of the candidate high-dose HAB candidate vaccine has been modified. The antigen content has been doubled and the adjuvant content has been increased. SB Biologicals uses aluminium compounds, the only adjuvants used in routine human vaccines. These compounds are known to enhance the humoral immune response.

This study is undertaken to determine which is the optimal dose of the HAB 2-dose vaccine in adolescents (11-18 years of age) by comparing immunogenicity and reactogenicity & safety in this age category elicited by the vaccine containing 1440 EL.U of inactivated hepatitis A antigen and 40 µg of recombinant hepatitis B surface antigen to that of Twinrix™, containing 720 EL.U of inactivated hepatitis A antigen and 20 µg of recombinant hepatitis B surface antigen), both administered according to a 0, 6-month schedule.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of the combined hepatitis A / hepatitis B vaccine.
2. STUDY CENTRES

Principal Investigators: 
Dr. [Name] 
Dr. [Name]

Study site: 
Australia

3. STUDY OBJECTIVES

The objectives of the present study are:

a) **Primary objective**
To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™, (720/20) vaccine one month after the last dose (month 7).

b) **Secondary objectives**
To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti Hbs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies, seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

The endpoints of the present study are:

**Primary endpoints**
Titres for anti-HBs antibodies at month 7.

**Secondary endpoints**
At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP) for anti-HBs antibodies.
At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies.

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample

**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.

***SP is defined as anti-HBs titre ≥10 mIU/ml
4. STUDY POPULATION

4.1 Number of subjects

The study population will be composed of adolescent volunteers arbitrarily defined as males and females between the ages of 11 and 18 years. In order to be included in the study, subjects will have completed their 11th birthday and will have not yet attained their 18th birthday at the time of the first vaccine dose. There will be 150 subjects enrolled (75 subjects/group).

4.2 Enrollment strategy/plan

The enrollment period, e.g. the period between the first and the last enrolled subject, is maximum 12 weeks. This will be followed up by monitoring.

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.

4.3 Inclusion criteria

- Age: from 11 to 18 years of age.
- Good physical condition as established by clinical examination and history taking at the time of entry.
- Sexually active female participants will avoid becoming pregnant during the study period and they will have been on a contraceptive program for at least 2 months before entry.
- Written informed consent will have been obtained from the parents/guardians of the subjects and/or from subjects themselves depending upon local regulations.

4.4 Exclusion criteria

- History of hepatitis.
- History of previous vaccination against hepatitis A or B.
- History of significant and persisting hematologic, hepatic, renal, cardiac or respiratory disease.
- Any acute disease at the moment of entry.
- Chronic alcohol consumption.
- Hepatomegaly, right upper quadrant abdominal pain or tenderness.

Approved: July 3, 1997
- Any chronic drug treatment, including any treatment with immunosuppressive drugs, which in the investigator's opinion, precludes inclusion into the study.
- History of allergic disease likely to be stimulated by any component of the vaccine.
- Administration of immunoglobulins within six months of the first vaccination or planned during the study period.
- Receipt of any other vaccine within 1 week of a dose of the study vaccine (period extending from 1 week before to 1 week after a dose of vaccine).
- Simultaneous participation in any other clinical trial, the only exception being involvement in long-term follow-up in another vaccine trial.

5. VACCINE AND VACCINE ADMINISTRATION

The vaccines employed in the present study will be:

SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine containing per dose (1.0 ml):
- Hepatitis A (Strain HM 175 - RIT 4380) : at least 1440 ELISA units
- Hepatitis B (recombinant HBsAg) : 40 µg.
- Aluminium salt : 0.85 mg.

SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine Twinrix™ containing per dose (1.0 ml):
- Hepatitis A (Strain HM 175 - RIT 4380) : at least 720 ELISA units
- Hepatitis B (recombinant HBsAg) : 20 µg.
- Aluminium salt : 0.45 mg.

The Quality Control Standards and Requirements for the study vaccines are described in separate release protocols and the required approvals have been obtained.

The vaccines will be supplied as a single 1.0 ml monodose vials for intramuscular injection in the deltoid region.

The vaccine is to be injected intramuscularly in the deltoid muscle using a 25G 1" needle. Subjects will be closely observed for at least 15 minutes post-vaccination with resuscitation facilities readily available in case of any anaphylactic reaction.

ALL VACCINES MUST BE STORED IN THE REFRIGERATOR (+2 to +8°C) AND MUST NOT BE FROZEN. Storage temperature should be monitored at least once per week.

The investigator is further referred to the Investigator’s Brochure for further information regarding the combined hepatitis A and hepatitis B vaccine.

6. STUDY DESIGN

6.1 Study design

Approved: July 3, 1997
This will be a double-blind, randomised study. Subjects will be randomly allocated to one of two groups to receive one of the two dose levels of the combined hepatitis A / hepatitis B vaccine in the order in which they are enrolled into the study.

6.2 Randomisation

Each monodose vial will be coded according to a randomisation list prepared by the sponsor. The randomisation will be made using an algorithm of pseudo random numbers (given by RS/1 from BBN).

The vaccines, which will be packed and supplied by the sponsor, will be labelled with the subject number, the study number and the name of the sponsor. Each subject will be given only the vaccines carrying his/her number.

6.3 Breaking the Study Blind

A set of sealed envelops, one for each subject number and containing the identity of the vaccine given to the subject will be stored at SmithKline Beecham (sponsor). In case of a serious adverse experience, the investigator needs to notify the sponsor immediately. The sponsor will then break the code and transmit the information to the investigator. The reason for breaking the code must be recorded by the sponsor on the corresponding envelope and by the investigator in the subject's case report form (CRF) and the medical record.
6.4 Replacement of individual vaccine doses

In addition to the vials numbered from number 1 up to the planned number of subjects, 5% additional doses from the Twinrix™ (720/20) lot will be provided to replace broken or lost vials. Subjects who shall receive replacement vials will be eliminated from reactogenicity and serology analysis.

7. STUDY PROCEDURES

As the incidence of hepatitis A and hepatitis B is very low in Australia and in order to save an additional visit for the participants, blood sampling for screening and first vaccination will be performed on the same day. In addition, vaccination of seropositive subjects has proven to be safe and results in a boost in antibody titre.

IMPORTANT: An interval of 30 days ± 7 days is planned between day 0 and month 1, month 1 and month 2, month 6 and month 7. An interval of 180 days ± 14 days between day 0 and month 6.

The intervals indicated here will serve as a target and not as an absolute criteria for inclusion or exclusion from the study but should be followed as much as possible. However, if circumstances dictate other intervals, this will not necessarily lead to the exclusion of the subject(s) from analysis.

Details of the study procedures are as follows:

DAY 0 : Screening of volunteers/Vaccine dose 1
Visit 1
* Informed consent obtained from parents/guardians of subjects and/or from subjects themselves depending upon local regulations.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HBs, anti-HBc, anti-HAV antibody and HBsAg measurement in SmithKline Beecham Biologicals’ laboratory (SB Biologicals), storage (at -20°C).
* History taking and physical examination (including axillary body temperature). Include documentation of baseline symptomatology.
* Inclusion/exclusion criteria.
* Individual Case Report Forms will be filled in by the investigator.
* IM administration of the first vaccine dose (coded monodose vial) in the deltoid region.
* Each vaccinee will be closely observed for 15 minutes following vaccination.
* Provision and explanation of diary card.

Approved: July 3, 1997
* Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

♦ DAYS 1 TO 3 AFTER VISIT 2

* In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs and symptoms on a diary card provided by the sponsor (see also section 8).

MONTH 1 : Follow-up visit
(30±7 days vs Day 0)
Visit 2
* Checking and collection of diary cards (completion of data concerning the local and/or general symptoms).
* Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 2 : Follow-up visit
(60±7 days vs Day 0)
Visit 3
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 6 : Second vaccination
(180±14d. vs Day 0)
Visit 4
* Physical examination (if deemed necessary by the investigator).
* Documentation of baseline symptomatology.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C
* IM administration of the last dose (coded monodose vial) in the deltoid region
* Each vaccinee will be closely observed for 15 minutes after vaccination.
* Provision and explanation of diary card.
* Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

♦ DAYS 1 TO 3 AFTER VISIT 4

* In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs and symptoms on a diary card provided by the sponsor (see also section 8).

Approved: July 3, 1997
MONTH 7 : Closure of the study
(30 ± 7 d. vs Month 6)
Visit 5
* Checking and collection of diary cards
  (completion of data concerning the local and/or general symptoms).
* Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.

Approved: July 3, 1997
### FLOW SHEET

<table>
<thead>
<tr>
<th></th>
<th>Visit 1 Day 0</th>
<th>v 2 Month 1</th>
<th>v 3 Month 2</th>
<th>v 4 Month 6</th>
<th>v 5 Month 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening visit</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td>X</td>
<td></td>
<td></td>
<td>(X)</td>
<td></td>
</tr>
<tr>
<td><strong>Recording of baseline symptoms</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaccination</strong></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diary card checking</strong></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>anti-HBc, HBsAg</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>anti-HAV</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>anti-HBs</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Sera Labels</strong></td>
<td>Pre</td>
<td>Post Vacc 1</td>
<td>Post Vacc 1</td>
<td>Post Vacc 1</td>
<td>Post Vacc 2</td>
</tr>
<tr>
<td></td>
<td>Study day 0</td>
<td>Study month 1</td>
<td>Study month 2</td>
<td>Study month 6</td>
<td>Study month 7</td>
</tr>
</tbody>
</table>

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.

---

Approved: July 3, 1997
8. CLINICAL SIGNS AND SYMPTOMS

After each vaccination, the subject will record on diary cards the local reactions and general symptoms, including axillary body temperature in the evening 5-9 hours post vaccination and thereafter every morning for 3 days.

The following signs and symptoms will be solicited:

**General symptoms:**
- Temperature*
- Headache*
- Fatigue*
- Gastrointestinal symptoms*
- Others (please specify)*

**Local reactions:**
- Soreness*
- Redness **
- Swelling **
- Others (please specify)*

* Signs and symptoms will be scored as:

0 : No adverse experience.
1 : Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : Adverse experience sufficiently discomforting to interfere with daily activities.
3 : Adverse experience which prevents normal everyday activities and necessitates medical advice. (In an adult, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

(see also section 9.4)

**The size of redness and swelling will be obtained by measuring their largest diameter and scored at SmithKline Beecham Biologicals as follows:

1 : 1 ≥30mm
2 : > 30 mm
3 : > 30 mm and persisting more than 24 hours.

°The temperature will be recorded only when it is 37.5°C or above and will be scored at SmithKline Beecham Biologicals as follows:

1 : 37.5°C-38.0°C
2 : >38.0°C-39.0°C
3 : >39.0°C

The vaccinees will be instructed to return the completed diary card with signs/symptoms on the next visit.

Approved: July 3, 1997
On that occasion, the forms completed by the vaccinee will be transcribed into the CRF by the clinical investigator after checking for completion and accuracy.

The relationship of any solicited or unsolicited symptom (those listed under “Others”) to the study vaccine will be assessed by the investigator and recorded in the CRF (see section 9.5).

Medication

Any concomitant medication administered during the period extending from 1 month prior until 1 month after each vaccination will be recorded in the medication section of the Case Report Form including: name, medical condition, code, start and end dates of treatment. Medications which do not need to be recorded include any homeopathic remedies, vitamins and contraceptives.

For antipyretics/analgesics, it should be specified whether they were given prophylactically or to treat an existing symptom (therapeutic use). If used prophylactically in anticipation of vaccines reaction, please code as “P” within the “medical indication” field of the Case Report Form.

9. ADVERSE EXPERIENCES

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out hereafter.

9.1 Eliciting and Documenting Adverse Experiences

It is the responsibility of the investigator to document all adverse experiences which occur within 30 days after each dose administration of the study vaccine.

An adverse experience includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic function as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with vaccine and whether or not considered vaccine related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or vaccine or drug interaction, or (if applicable) the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study (if applicable), that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

All adverse experiences which occur within thirty days after each dose either observed by the investigator or one of his clinical collaborators, or reported by the patient spontaneously or in response to a direct question, will be evaluated by the investigator and noted in the adverse experience section of the subject's case record form (CRF).

Ask the subject a non-leading question such as: “Do you feel different in any way since receiving the vaccine / within 30 days after receiving the vaccine”.

Approved: July 3, 1997
The nature of each experience, time of onset after vaccine administration, duration, severity and relationship to vaccination should be established. Details of changes to the vaccination schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Symptomatology should be documented at baseline. It is important to collect baseline information in order to interpret data from subsequent assessments.

9.2 Serious Adverse Experiences

9.2.1 Reporting

Any serious adverse experiences which occur during the clinical trial or within 30 days of receiving the last dose of study vaccine, whether or not related to the study vaccine, must be reported by the investigator to the SB clinical trial monitor by telephone, telex or telefax, within 24 hours of his becoming aware of the occurrence.

This initial notification should include:
- Study protocol number + name of principal investigator
- Vaccine study number, initials, age, sex
- Date of onset of the experience and date of administration of the study vaccine(s)
- Relationship to the study vaccine (see section 9.5.)
SmithKline Beecham Biologicals

SmithKline Beecham Biologicals’ combined hepatitis A/hepatitis B vaccine 208127/075 (HAB-075)

-17-

All information should be sent promptly to the SmithKline Beecham monitors:

Dr. [Name]
Medical Director
SmithKline Beecham Pharmaceuticals
300, Frankston Road
Dandenong
Victoria 3175 AUSTRALIA

Tel office: [Number]
Fax: [Number]

or

Dr. [Name]
Project Manager
SmithKline Beecham Biologicals
89, Rue de l'Institut
B-1330 Rixensart - Belgium

Tel office: [Number]
Tel home: [Number]
Telex: [Number]
Fax: [Number]

Investigators should not wait to collect additional information to fully document the event before notifying SmithKline Beecham of a serious adverse experience. The telephone report should be followed by a full written report to include copies of relevant hospital case records, autopsy reports and other documents where applicable.

Moreover, instances of death, cancer or congenital abnormality if brought to the attention of the investigator AT ANY TIME after the cessation of study vaccine AND considered by the investigator to be probably associated to study vaccine or to have a reasonable possibility of an association to study vaccine, should be reported to the SmithKline Beecham Monitor.

9.2.2 Definitions

A serious adverse experience is defined as follows:

ANY experience that, in the investigator's opinion, suggests a significant hazard to the vaccinee and will always include any event that is:

1. Fatal
2. Life-threatening
3. Disabling or incapacitating
4. Results in hospitalisation or prolongation of hospitalisation

or is:

5. A congenital abnormality (in offspring)
6. A cancer

Approved: July 3, 1997
7. An overdose of the vaccine or an adverse experience associated with an overdose (either accidental or intentional)

In addition, any adverse experience which suggests a significant hazard, contraindication, side effect or precaution that may be associated with the use of the vaccine will be considered a serious adverse experience.

Life threatening - definition:

An adverse experience is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death.

Disability/incapacitating - definition:

An adverse experience is incapacitating or the patient has suffered a temporary or permanent disability if the experience results in a substantial and/or permanent disruption of the patient’s ability to carry out normal life functions.

Hospitalisation - definition:

In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or out-patient setting. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the adverse experience should be considered serious.

9.3 Treatment of adverse experiences

Treatment of any adverse experience is at the sole discretion of the investigator and according to current Good Clinical Practice. The applied measures should be reported in the Case Report Form of the vaccinee.
9.4 Assessment of severity and outcome

Maximum intensity should be scored according to one of the following categories:

0:   No adverse experience
1:   Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
2:   Adverse experience sufficiently discomforting to interfere with normal everyday activities
3:   Adverse experience which prevents normal everyday activities and necessitates medical advice. (In adults, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

The outcome of adverse experiences should be indicated as follows:

1: Recovered
2: Recovered with sequelae
3: Ongoing
4: Died
5: Unknown

9.5 Assessment of Causality

Every effort should be made by the investigator to explain each general adverse experience and assess its relationship, if any, to study vaccine. Causality should be assessed using the following categories:

NR: Not related  The adverse experience is definitely not related to the study vaccine.
UL: Unlikely  There are other more likely causes and the study vaccine is not suspected as a cause.
SU: Suspected (reasonable possibility)  A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.
PB: Probable  There is probably a direct cause and effect relationship between the adverse experience and the study vaccine.

The degree of certainty with which an adverse experience is attributed to the study vaccine (or alternative causes, e.g. diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of:

a) Known toxico-pharmacology of the vaccine, in pre clinical and clinical experience.
b) Reaction of similar nature previously observed with this vaccine.

Approved: July 3, 1997
c) The experience having been reported in the literature for similar vaccines.
d) The experience being related by time to vaccine administration or reproduced on re-challenge.

9.6 Following up of adverse experiences

Investigators should follow-up patients with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the patient's subsequent course must be submitted to the clinical trial monitor.

9.7 Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately. Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, either during the treatment phase of the study or within 30 days after the (last) vaccination. Whenever possible, a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

10. LABORATORY ASSAYS

Blood samples obtained at the first visit (Day 0) will be tested at SmithKline Beecham Biologicals' laboratory for:
- Anti-HAV, anti-HBs and anti-HBc antibodies
- HBsAg
At each next visit serum will be collected for measurement of anti-HBs and anti-HAV antibodies in SmithKline Beecham Biologicals' laboratory.
Radioimmunoassay technique (RIA technique) will be used to test the presence of HBsAg (AUSAB - Abbott) and anti-HBc (Corab-Abbott).

Antibody titres (anti-HAV and anti-HBs) will be expressed in mIU/ml, with reference to World Health Organisation (WHO) standard sera. Anti-HAV antibodies will be measured at day 0, months 1, 2, 6 and 7, using Enzymun (Boehringer Mannheim) kit. The cut-off level of this test is 33 mIU/ml. Measurements of anti-HBs antibodies at day 0, months 1, 2, 6 and 7 will be performed using a commercial radioimmunoassay kit (AUSAB-Abbott). The cut-off level of this test is 1 mIU/ml.

All serum samples should be kept at -20°C.

11. STATISTICAL ANALYSIS

Taking into consideration a 10% dropout potential and the seroprevalence of hepatitis A (there is no screening and we will exclude the HAV positive subjects from the immunogenicity analysis) 150 subjects (75/group) will be enrolled to have at least 90 (45/group) evaluable subjects

Approved: July 3, 1997
11.1 Sample size estimation

Primary objective

A sample size of 45 evaluable subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HBs between groups if the difference exceed 50%. The calculation has been made with a type I error = 5% and a type II error of 20%.

For these calculation, a variability of log titres of 0.7441 for anti-HBs has been used. The variability used came from data generated from a previous study with the combined hepatitis A and B vaccine.

Secondary objectives

A sample size of 45 subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HAV between groups if the difference exceed 50%. With a type error of 5% and variability of log titres of 0.1299 for anti-HAV, we will reach a power of 97.6%. The variability used came from data generated on a previous study with the combined hepatitis A and vaccine.

For reactogenicity analysis, with the sample size of 45 subjects, we will be allowed to detect differences mentioned in the table hereafter with a type error of 5% and a power of 80% and a reference rate of a symptom or combination of symptoms reported by 1,2,5,10,20 and 50% of subjects.

<table>
<thead>
<tr>
<th>Reference rate (in %)</th>
<th>Detectable difference (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>21.7</td>
</tr>
<tr>
<td>5</td>
<td>24.1</td>
</tr>
<tr>
<td>10</td>
<td>26.8</td>
</tr>
<tr>
<td>20</td>
<td>29.9</td>
</tr>
<tr>
<td>50</td>
<td>29.9</td>
</tr>
</tbody>
</table>
11.2 Demographics

The demographic characteristics (age, sex) of the study cohort will be tabulated. The mean age, plus the range and standard deviation, by sex of the enrolled subjects, will be calculated. Similar analysis will be performed for those subjects who are included in the different analysis of reactogenicity and immunogenicity. Mean ages of groups will be compared using a Student’s t test. Ratio of males to females will be compared using either a Chi-square test or a Fisher’s exact test.

11.3 Immunogenicity

Two analyses will be performed: a first one will include only subjects corresponding to criteria defined in the protocol and a second one, called "Intention-to-treat", will include all data available from all subjects.

Seropositivity rates, seroconversion rates and geometric mean titres (GMTs) for anti-HBs and anti-HAV antibodies and seroprotection rates for anti-HBs antibodies, with 95 % confidence intervals for each antigen, will be calculated for all time points for which blood samples are taken. Seropositivity is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay. Seroconversion is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample. Seroprotection is defined as anti-HBs titre ≥10 mIU/ml. The GMT will be calculated using the log-transformation of seropositive titres and taking the anti-log of the mean of these transformed values. GMTs will be compared using either a Student’s t test or a Mann-Whitney test. Seroconversion rates will be compared between groups using a Chi-square test or Fisher’s exact test.

11.4 Reactogenicity

The incidence of any symptom reported, local, general and local and general symptoms after each injection and overall will be evaluated, in addition to the frequency, intensity, duration (≤ or >1 day) and relationship of each individual solicited symptoms. The incidence is calculated on the number of documented diary cards. Chi-square test or Fisher’s exact test will be used to compare the proportion of subjects reporting any symptoms, local symptoms, general symptoms, local and general symptoms between groups.

11.5 Interim analyses

An exploratory analysis will be performed at month 2 for immunogenicity and for reactogenicity.

Approved:July 3, 1997
12. REFERENCES

6. ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
17. ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
APPENDIX A: VACCINATION RELATED SEROLOGY

Serology

All of the serum samples will be tested in SmithKline Beecham Biologicals’ laboratory at the end of the study.

Anti-HBs antibodies will be tested using radio immunoassay (Ausab-Abbott). The anti-HBs titres will be expressed in international units (mIU/ml). The lowest sensitivity limit of this assay is 1 mIU/ml.

Anti-HAV antibodies will be tested by a commercially available test, Enzymun (Boehringer Mannheim). The lowest sensitivity limit of this assay is 33 mIU/ml.

Radio immunoassay (RIA technique) will be used to test the presence of HBsAg (Austria II - Abbott) and anti-HBc (Corab-Abbott) should it be necessary to validate screening results obtained in the investigator’s laboratory.
APPENDIX B: VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY

1. Vaccine supplies

380 single monodose vials, including 5% dose replacement from Twinrix™ (720/20) will be provided. Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titres ≥ 10 mIU/ML and /or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine. It is at no time permitted to use the supplies for other purposes than those specified in the present protocol.

2. Vaccine packaging

Each vaccine dose will be labelled and placed in a plastic pack with 25 holes. A group label will be stuck on the top of each pack. The vials will be placed in numerical order from left to right starting from the lower left hand corner, as shown:

```
 21 0 0 0 0 0 25
 16 0 0 0 0 0 20
 11 0 0 0 0 0 15
  6 0 0 0 0 0 10
   1 0 0 0 0 0  5
```

Labeling

The vial label will contain the following details:

- Study number
- Investigator's name
- Subject number
- Study vaccine name
- Lot number
- Storage conditions
- Expiry date
- "For investigational use only"
- Mode of administration
- Dose number
- MFD SmithKline Beecham Biologicals, Belgium

The group label will be similar to the vial label. It will also include the pack number and total number of packs, e.g. 3/7 = 3rd pack of 7, containing vials numbered 51-75.

Storage

Approved: July 3, 1997
The vaccines should be stored at 2 to 8°C in a safe and locked place with no access for unauthorised personnel.

3. Vaccine accountability

All vaccines need to be accounted for on the appropriate forms provided by the sponsor. At any time the figures on supplied, used and remaining vaccine should match.

All remaining product will be collected by the sponsor for destruction after the study. Unused supplies will be collected by the sponsor on completion of the study.

4. Other supplies provided by the sponsor

Additionally to the vaccines and the different documents, the investigator will receive the following supplies:

- tubes with screw caps for serum specimens
- labels for serum identification
- racks for the tubes of serum

No supplies should be used outside the scope of the protocol.
APPENDIX C: ETHICAL CONSIDERATIONS AND RESPECT OF LOCAL RULES AND REGULATIONS

1. Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki, enclosed with this protocol.

2. Ethics Review Committee

The study will have been approved by the appropriate Ethics Review Committee and documentation of this approval will be submitted to SmithKline Beecham Biologicals prior to the start of the study.

3. Informed consent

The investigators will inform the volunteers in a language which they clearly understand about the aims and the possible side effects of the research trial prior to enrollment; written consent will be obtained unless local law or customs preclude this. Under the circumstances, an oral witnessed consent will be obtained. Subjects have to be informed of the fact that their data will be stored in a coded fashion in an electronic database and may be subject to an internal or external audit. (See SOP SB Bio 06). Information should be given in both oral and written form.

4. Local rules and regulations

The study will be conducted in accordance with the local rules and regulations of the country and respecting the European Commission Directive 91/507/EEC issued July 19, 1991 and effective January 1, 1992 on Good Clinical Practice.

5. Insurance

All study participants are insured according to the SmithKline Beecham Insurance policy. The study participants (or their parents or guardians) may consult this contract at any time at the investigator site.

6. Withdrawals

Subjects are free to withdraw from the study for any reason at any time. A subject will be withdrawn from the study by the investigator in case of serious adverse experience or suspected health hazard. In all cases the reason of the withdrawal must be recorded in the Case Report Form by the investigator.

Attention should be paid to proper classification of reason for withdrawal. Subjects being withdrawn while presenting on adverse experience not related to the study and not responsible for withdrawal should not be included in the listing of subjects withdrawn for adverse experiences.

Approved: July 3, 1997
7. **Current edition of declaration of Helsinki**

**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 fulfillment 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 etiology 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 recognized 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.

Approved: July 3, 1997
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 minimize 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.

Approved: July 3, 1997
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 judgment 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 (1, 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.

Approved: July 3, 1997
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 judgment 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 D: ETHICAL AND REGULATORY CONSIDERATIONS IN ACCORDANCE WITH GOOD CLINICAL PRACTICE FOR CLINICAL STUDIES

I. ETHICS REVIEW COMMITTEE (ERC) / INSTITUTIONAL REVIEW BOARD (IRB)

Ethics Committees must be constituted according to the local laws/customs of each participating country.

- This protocol will be submitted to an appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study.

- SB will supply relevant data for the investigator to submit to the hospital/university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB's unconditional approval of the protocol and either written informed consent or oral consent with written information to be given to the subjects/patients will be transmitted to the SB Clinical Monitor prior to shipment of drug supplies and case record forms to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

- The ERC must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or the conduct of the trial. Approval for such changes must be transmitted in writing to the SB Clinical Monitor.

II. INFORMED CONSENT

Information should be given in both oral and written form.

Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

- WRITTEN INFORMED CONSENT

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the Ethics Review Committee and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Where appropriate, informed consent shall be documented by the use of a written consent form approved by the Ethics Review Committee and signed by the subject or the subject’s legally authorised representative.

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

Approved: July 3, 1997
Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event 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 SB professional and regulatory compliance persons.

- **WITNESSED ORAL CONSENT**

In countries where written informed consent contravenes local law or custom, informed consent may be gained orally. Full and comprehensive information must be communicated to the potential subject (or his legal representative) in the presence of a witness. The witness will be an independent third party i.e. not a nominated co-investigator. The witness will sign the Informed Consent document (testifying that informed consent has been given orally) along with the investigator (or his/her nominated representative).

### III. 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 to not divert essential subjects/patients 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.

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

- Preparing and maintaining adequate case histories designed to record observations and other data pertinent to the study.

### IV. STUDY DRUGS

1) **STORAGE OF STUDY DRUGS**

Specify clearly the site where (e.g. pharmacy or safely locked place), and conditions under which the study drugs are to be stored, as it is essential that the sponsor can be certain that the drugs will retain their safety and potency for the duration of their assigned shelf life.

2) **DRUG ACCOUNTABILITY**

The investigator or pharmacist must sign that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products are handled and stored safely and properly; that investigational products are only dispensed to study subjects/patients in accordance with the protocol; that any unused products (including placebo) will be returned to SB. 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 used and unused investigational drugs (including placebo) for the stated study have been returned.

Approved: July 3, 1997
3) **ASSESSMENT OF COMPLIANCE**

A record of the amount dispensed, taken (and returned for out-patient studies) for each patient/subject must be recorded in the CRF. The means of assessing compliance will be described.

V. **SPONSOR'S TERMINATION OF TRIAL**

SmithKline Beecham 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.

VI. **Protocol Amendments**

No modification to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Medical Monitor and filed as an amendment to this protocol.

Any modifications to the protocol will be adhered to by the study centre (or all participating centres) and will apply to all subjects/patients following approval by the Ethical Review Committee or Institutional Review Board.

VII. **CASE REPORT FORMS (CRFs)**

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 patient diary cards, if applicable), will be supplied by SB for recording all data. It is the responsibility of the investigator to ensure that CRFs (and patient diary cards) are legible and completely filled in.

Principal investigators or designated physicians under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to ensure that they have reviewed the data and that the data are complete and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a section conclusion signature is required.

An original case report form must be submitted for all patients who have given informed consent and who have undergone protocol specific procedures, whether or not the patient completed the study.

For each form on which information is entered, the patient's identification (2-3 alphabet letters representing initials or first letters of patient's name), allocation number and the date of the visit number and the date of the visit must be neatly hand-written with black ink ball-point 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 initialed, dated and justified by the authorised individual making the change if it is significant. Do not obliterate, write over, or erase the original entry when making a correction.

Approved: July 3, 1997
While completed CRFs will be reviewed by an SB professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

When a patient completes a study, it is anticipated that all CRFs pages will be completed as soon as possible and that they can be submitted to SB at the time of the next monitoring visit. This also applies to forms for potential study participants who were not randomised to a treatment group.

Any questions or comments related to the CRF should be directed to the assigned Study Monitor.

VIII. 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 patient, during the study at appropriate intervals and after the last patient is completed.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the Case Report Forms (CRF) and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits should be made available by the investigator.

IX. ARCHIVING OF DATA

The investigator must retain patient records and case report forms as well as drug disposition records at a maximum period of time permitted by the hospital, institution or private practice. The subject identification codes should be kept at least 15 years in accordance with Good Clinical Practices. The investigator must have a “key” linking the patient’s trial identification number (i.e. treatment number) to the patient’s clinical file. If the investigator moves or retires, he/she should nominate someone in writing to be responsible for record keeping. Archived data may be held on a microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it if require.

SmithKline Beecham agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out and to provide copies to the investigator should he/she wish another copy.

X. AUDITS

For the purpose of compliance with Good Clinical Practice and regulatory agency guidelines it may be necessary for SmithKline Beecham or a drug regulatory agency to conduct a site audit.

When an investigator signs the protocol, he agrees to allow drug regulatory agency and SB auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.
SB has a substantial investment in clinical trials. Having the highest quality data and studies are essential aspects of drug development. SB 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 SB sponsored studies are in accordance with 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 SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Visits from the sponsor’s representatives
- Ethical Review Committee approval
- Study vaccine accountability
- Study protocol and amendments
- Informed consent of the patients
- Medical records supportive of case report form data
- Reports to the ERC/IRB and the sponsor
- Record retention

SB will gladly help investigators prepare for an inspection.

APPENDIX E: CONFIDENTIALITY AND PUBLICATION

You agree that all information communicated to you by SmithKline Beecham Biologicals/Pharmaceuticals is the exclusive property of SmithKline Beecham Biologicals/Pharmaceuticals 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 by your or such person to any third party without the prior written consent of SmithKline Beecham Pharmaceuticals. You shall communicate the results of the work promptly to SmithKline Beecham Pharmaceuticals.

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 study monitor. SmithKline Beecham will undertake to comment on such documents within four weeks.

All rights and interests world-wide 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 trial 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.

Approved: July 3, 1997
APPENDIX F: HANDLING OF THE SERUM SAMPLES COLLECTED BY THE INVESTIGATOR

1. COLLECTION

The whole blood (by capillary or venous route) will be collected observing appropriate aseptic conditions.

It is recommended to use Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or Corvac® Sherwood medical) to minimise hemolysis risks and to avoid blood cell contamination of the sera when transferring serum in standard tubes.

2. RECOMMENDED PROCEDURE FOR SERUM SEPARATION

These guideline’s aim is to insure a good quality of the serum by minimising hemolysis risks, blood cell contamination of the sera or serum adverse cell toxicity at testing.

◊ Vacutainer® tubes with integrated serum separator

- Invert gently the tube several times to allow close contact with clot activator

- Keep at room temperature (18 - 20°C) for minimum 30 minutes and maximum 2 hours. If necessary due to extenuating circumstances, the room temperature incubation period may be increased beyond 2 hours but shall never exceed 24 hours.

- Centrifuge at 1100 G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).

- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.

- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.

- Identify the standard tubes with the appropriate standard label - as described here below in point 3.
Vacutainer® tubes without separator

- PRELIMINARY NOTE: NEVER USE SILICONIZED TUBES (cell toxicity!)

- Keep at room temperature (18 - 20°C) for minimum 2 hours and ideally overnight.

- Centrifuge at 2000G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).

- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.

- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.

- Identify the standard tubes with the appropriate standard label - as described here below

3. LABELLING (see the diagram hereafter)

- Use the standard labels provided by SmithKline Beecham Biologicals.

- Attach the label on the tube, first by its written paper part and then turn around the tube with the plastic transparent part so that the clear plastic part will protect the text and codification.

- To be readable, the bar code must be vertical on the tube.

- Please, do not stick the label on caps.
4. **SORTING and STORAGE**

- Tubes should be placed in the SB racks in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, than with the post vaccination sample series.

  *When impossible as with new sealed bag/box (IATA regulation), samples should be sorted by numeric order per batch of 20 packed in plastic bags, all those plastic bags packed together in the sealed box.*

- The tubes of serum will be stored at temperature between -20°C and -70°C in a vertical position until sent to SmithKline Beecham Biologicals.
APPENDIX G: INSTRUCTIONS FOR SHIPMENT OF SAMPLES

- Serum samples should always be sent by air unless otherwise requested by the sponsor and must be made on Mondays, Tuesdays and Wednesdays preferably.

- Serum samples should be placed in a container complying with IATA requirements with dry ice (-20°C). The completed standard serum listing form should always accompanied the shipment. The Air Way Bill form should mention ‘-20°C storage’.

- A “proforma” invoice, stating a value for customs purposes only should be prepared and attached to the parcel, the mention : store at -20°C should be add on this document

- Details of the shipment, including airway bill number, flight number, flight departure and arrival times should be sent by fax, two days before the shipment to: SmithKline Beecham Biologicals

  Shipment and fax to be addressed to:
  SmithKline Beecham Biologicals
  Attn. Dr Clinical Immunology
  R&D Department / Building 44
  Rue de l’institut, 89
  B - 1330 Rixensart - Belgium
  Telephone: 
  Fax: 
  c/o MSAS Nedlloyd
  Brussels National Airport
  Zaventem - Belgium

- The box should be clearly identified by using stickers provided by SBBio mentioning the shipment address as well as with red stickers ‘STORE AT -20°C’

Approved: July 3, 1997
APPENDIX H: DESCRIPTION OF SERA LABELS

<table>
<thead>
<tr>
<th>Pre</th>
<th>Study day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post vacc 1</td>
<td>Study month 1</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 2</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 6</td>
</tr>
<tr>
<td>Post vacc 2</td>
<td>Study month 7</td>
</tr>
</tbody>
</table>

Approved: July 3, 1997
This section contained Principal Investigator’s Curriculum Vitae and has been excluded to protect Principal Investigator privacy.
Representative SIS/IC Amendment 1
SMITHKLINE BEECHAM BIOLOGICALS

ADDENDUM TO SUBJECT/PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR THE STUDY 208127/075 (HAB-075)

Study title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Investigator: Dr. [ ] Australia

Sponsor: SmithKline Beecham Biologicals

CPMS Protocol no.: 208127/099 (EXT HAB-075) – Month 36 follow-up
208127/100 (EXT HAB-075) – Month 48 follow-up
208127/101 (EXT HAB-075) – Month 60 follow-up

Date of approval:

Prepared by: [ ]

This document should be presented to the subject and parents/guardians of the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the participant and the parents/guardians of the participant.
Introduction

The main objective of this document is to provide the potential study participants and parents/guardians of the participants with the information necessary to help them in deciding to participate in the long-term follow-up of the HAB-075 study. The document provides a full but simple understanding of the scientific reasons, the likely effects and benefits of this long-term follow-up of the HAB-075 study. This document also informs subjects and parents/guardians of subjects about their rights, benefits, risks and responsibilities in participating in this follow-up trial.

Hepatitis A and B are diseases caused by viruses that infect the liver. The symptoms of both infections may be quite similar - characterised by fever, ill-feeling, loss of appetite, abdominal discomfort, jaundice and liver damage. Both diseases are transmitted by person-to-person contact.

There are no effective therapies against hepatitis A or hepatitis B. Vaccination, resulting in protection against both the diseases, is the best method of reducing the incidence of infection. SmithKline Beecham Biologicals has developed vaccines against both hepatitis A (Havrix™) and hepatitis B (Engerix™-B) which have shown to be protective and are available on the world market. SmithKline Beecham Biologicals has also developed a combination hepatitis A / hepatitis B vaccine (Twinrix™) which is also available on the market. This combination is known to provide simultaneous protection against both diseases.

You have / your son/daughter/ward has already received a course of SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine in the original HAB-075 study. In this long-term follow-up study, the long-term protection against hepatitis A and hepatitis B achieved by this combined hepatitis A/hepatitis B vaccine is being determined.
Approval

This addendum to subject information sheet has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

All volunteers in this long-term follow-up study-extension have received SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine (given according to 0, 6 months schedule), in HAB-075 study. This long-term follow-up study is designed to assess the immune response 36, 48 and 60 months after the first dose of the primary vaccination course.

Your/your son’s/daughter’s/ward’s participation in this follow-up period will require 3 visits (one visit per year) to the investigator. At each visit, 7 ml (approximately 3 ½ tablespoons) of blood will be collected to determine antibody titres.

Risks associated with the study

You/your son/daughter/ward may experience momentary mild discomfort during the blood collection. The amount to be taken will not cause any symptoms or anaemia.

Benefits of the study

The principal benefit of you/your son/daughter/ward participating in this long-term follow-up study, is the evaluation of your/your son’s/daughter’s/ward’s long-term protection against hepatitis A and hepatitis B.

Voluntary participation

Your/your son’s/daughter’s/ward’s participation is voluntary. Refusal to take part or continue with this long-term follow-up study will involve no penalty or loss of benefits or attention to which you/your son/daughter/ward is otherwise entitled to.
receive from your healthcare provider. You are entitled to receive a signed copy of this form.

**Alternative measures of prevention**

Not applicable.

**Confidentiality and data access**

This section ensures that you/your son/daughter/ward benefits from the protection and the rights granted by the European Union Data Protection Directive and other national laws on the protection of your son’s/daughter’s/ward’s personal data.

You understand and consent to the following:

I. Your/your son’s/daughter’s/ward’s data, including data relating to your/your son’s/daughter’s/ward’s health, will be recorded and processed for the purpose of 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/your son’s/daughter’s/ward’s data may also be processed for product registration and for notification to organisations monitoring the safety and effectiveness of medicines. Your/your son’s/daughter’s/ward’s data may also be processed in order to add to scientific knowledge;

II. Your/your son’s/daughter’s/ward’s participation in the study will be treated as confidential. You/your son/daughter/ward will not be referred to by name in any report on the study and your/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical data or study samples (e.g. 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 access your/your son’s/daughter’s/ward’s personal data and 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/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical records may be accessed by representatives of SB Bio or regulatory bodies for medicines.

**Right to ask questions and/or withdraw from the long-term study follow-up**

You may ask questions about the study. Although your continuous support is appreciated, you have the right to withdraw yourself/your son/daughter/ward from this long-term study-extension at any time and you/your son/daughter/ward will be under no further obligation for blood samplings.

If you have any questions, please contact:

**Name of investigator:** Dr.

**Address of investigator:** [Redacted]

**Telephone number of investigator:** [Redacted]
Compensation

If you become/your son/daughter/ward 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 you have/your son/daughter/ward has experienced a research-related illness or injury, please contact:

Name of investigator: Dr. [Redacted]
Address of investigator: [Redacted], Australia

Telephone number of investigator: [Redacted]
Informed Consent for the long-term follow-up
(adolescents/minors)

The 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 study.

Participant’s Name: ____________________________
(First Name, Family Name)

Participant’s signature (where applicable): ____________________________

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: ____________________________________________

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 consent form.

Name: ____________________________________________

Signature: ___________________________________________

Designation: ___________________________________________

Date: ___________________________ Time: _________________

(DD-MM-YY)
Informed Consent for the long-term follow-up  
(adults)

The aims and procedures of the study have been clearly explained to me and I have read the preceding information sheet and understood the information provided. I agree to be enrolled in the study. I understand that I have the right to decline to enter the study and to withdraw from it at any time for any reasons, without consequence to my present or future health care and attention, which I receive from my healthcare provider. I have been made aware of my right to access and request correction of my personal data. I acknowledge that I have received a copy of this form for future reference.

I, ____________________________,
(subject’s first name and family name)

hereby freely give my consent to take part in this [clinical/vaccine] study.

Participant’s signature: ____________________________

Participant’s main address: ____________________________

Participant’s phone number: ____________________________

Date: ____________ Time: ____________
(DD-MM-YY)

Witness: ____________________________
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 consent form.

Name: __________________________________________

Signature: ________________________________________

Designation: ______________________________________

Date: _______________ Time: _______________

(DD-MM-YY)
GSK Biologicals
GlaxoSmithKline Biologicals
Clinical Research and Development

Clinical Study Report Approval form

Report number: 208127/099(HAB-099) Annex-1

Study title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Report prepared by:
Scientific Writer: [Redacted] 03/09/01

Report reviewed by:
Statistician: [Redacted] 28.08.01
Clinical Study Management: [Redacted] 28.08.01
Scientific Writer: [Redacted] 28.08.01
Regulatory: [Redacted] 28.08.01

Report accepted by:
Clinical Development Manager: [Redacted] 2A.01.01

Report Approved by:
[Redacted] 30-08-01

Associate Director Clinical Development, Hepatitis and Traveller vaccines development (Hepatitis,Typhoid)

Signature/Date
Final Study Report
Annex 2

Ext-HAB-075
(208127/100 & 101)

7 December 2004
Final Study Report for 208127/100 and 208127/101
(Ext-HAB-075) Annex-2
An Integrated Clinical/Statistical Report

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of TWINRIX™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6 month schedule in healthy adolescents (11-18 years of age).

Development Phase: III
Study Vaccines: GlaxoSmithKline Biologicals’,
- combined hepatitis A/hepatitis B vaccine (TWINRIX™)
- high-dose combined hepatitis A/hepatitis B vaccine
CPMS Study No.: 208127/100 and 208127/101
Indication: To protect healthy adolescents against hepatitis A and B.
Principal Investigator: Prof. Dr. [Redacted]
Primary Study Start Date: 12 August 1997
Primary Study End Date: 14 March 1998
Primary Study Report Date: 26 March 1999
Long-term Follow-up End Date: (Upto Month 60) 15 September 2002
Co-ordinating Author: [Redacted] and [Redacted] Scientific Writer
Other Contributing Authors: [Redacted] and [Redacted] Clinical Development Managers
[Redacted] and [Redacted] Central Study Coordinators
[Redacted] and [Redacted] Statisticians

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

Annex 1 Report Date: 28 August 2001
Annex 2 Report Date: 7 December 2004 (Final)

This annex report provides results of long-term follow-up up to Month 60

Verification and approval

I agree with the conclusions based on the data contained in this report

Prof. Dr. [Redacted] 25.2.05

Date (day/month/year)

CARS Id : CLIN_200407_204/ Version : 1.4, Admin. QC/ Modify Date : 18/01/2005
Final Study Report for 208127/100 and 208127/101 (Ext-HAB-075) Annex-2

An Integrated Clinical/Statistical Report

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of TWINRIX™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6 month schedule in healthy adolescents (11-18 years of age).

Development Phase: III
Study Vaccines: GlaxoSmithKline Biologicals’,
• combined hepatitis A/hepatitis B vaccine (TWINRIX™)
• high-dose combined hepatitis A/hepatitis B vaccine

CPMS Study No.: 208127/100 and 208127/101
Indication: To protect healthy adolescents against hepatitis A and B.

Principal Investigator: Prof. Dr.
Primary Study Start Date: 12 August 1997
Primary Study End Date: 14 March 1998
Primary Study Report Date: 26 March 1999
Long-term Follow-up End Date: (Upto Month 60) 15 September 2002
Co-ordinating Author: Scientific Writer
Other Contributing Authors: Development Managers and Clinical
Central Study Coordinators and Statisticians

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

Annex 1 Report Date: 28 August 2001
Annex 2 Report Date: 7 December 2004 (Final)

This annex report provides results of long-term follow-up up to Month 60

CARS Id : CLIN_200407_204/ Version : 1.4,Admin. QC/ Modify Date : 18/01/2005
Synopsis of Final Study Report for 208127/100 and 208127/101 (Ext-HAB-075) Annex-2

Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium  
Name of finished product: Combined hepatitis A/hepatitis B vaccine  
Name of active substances: Inactivated hepatitis A antigen (Strain HM 175-RIT 4380) and recombinant Hepatitis B surface antigen (HBsAg)

Title of the study: 208127/100 and 208127/101 
A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of TWINRIX™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Principal Investigator: Prof. Dr.  
Study Centre: Australia  
Publication (reference): None published as of 7 December 2004

Objectives: The objectives of the primary study can be found in the primary HAB-075 study report. The objective of this long-term follow-up was to evaluate the long-term anti-HAV and anti-HBs antibody persistence through blood samples taken 48 and 60 months after the first of the two doses of primary vaccination course (0, 6 month schedule) with GSK Biologicals’ high-dose combined hepatitis A/hepatitis B (HAB) vaccine, or GSK Biologicals’ combined HAB vaccine (TWINRIX™), in healthy volunteers aged 11 to 18 years at the time of primary vaccination.

Note: Subjects in the primary study (HAB-075) who had previously shown seroprotection for anti-HBs antibodies but who had concentrations < 10 mIU/ml at Month 36 were offered an additional dose of GSK Biologicals’ TWINRIX™ (720/20) (See the objectives of the HAB-123 study report) given approximately 44 months after the last dose of primary vaccination.

Methodology:  
Study design: The primary study was a comparative, double-blind and randomized study with two groups. A blood sample was taken at Month 36 and results thereof are described in Annex 1 of the study report of HAB-075. The long-term follow-up at Month 48 and Month 60 was an open study with the same two groups. At these time points, a blood sampling was done and any serious adverse events (SAEs) which the subject might have experienced since the last study visit (i.e. Month 36) was documented. Written informed consent for blood sampling at Months 36, 48 and 60 was obtained prior to the blood sampling at Month 36 from all subjects who returned.

Population Group: Healthy male and female subjects aged between 11 to 18 years (inclusive) at the time of primary vaccination.

Number of subjects enrolled and vaccinated: 150 (75/group)  
Number of subjects who completed the primary study: 149 (Group 1: 75, Group 2: 74)  
Number of subjects who returned at Month 48 after adjustment with subjects from HAB-123: 141 (Group 1: 69, Group 2: 72)  
Number of subjects included in the long-term ATP immunogenicity cohort at Month 48: 92 (Group 1: 47, Group 2: 45)  
Number of subjects who returned at Month 60: 122 (Group 1: 59, Group 2: 63)  
Number of subjects included in the long-term ATP immunogenicity cohort at Month 60: 90 (Group 1: 46, Group 2: 44)
Name of company: GlaxoSmithKline Biologicals, Rixensart, Belgium
Name of finished product: Combined hepatitis A/hepatitis B vaccine
Name of active substances: Inactivated hepatitis A antigen (Strain HM 175-RIT 4380) and recombinant Hepatitis B surface antigen (HBsAg)

TABULAR FORMAT

<table>
<thead>
<tr>
<th>Test product, dose, mode of administration, lot number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination schedule/site: In the primary study, Group 2 received high-dose combined hepatitis A/hepatitis B vaccine as an intramuscular (IM) injection in the deltoid region according to a 0, 6 month schedule.</td>
</tr>
<tr>
<td>Vaccine/composition/dose/lot number: GlaxoSmithKline Biologicals’ high-dose combined hepatitis A/hepatitis B vaccine contained at least 1440 EL.U of inactivated hepatitis A antigen (Strain HM 175-RIT 4380), 40 mcg of recombinant Hepatitis B surface antigen (HBsAg) and 0.85 mg aluminium salt in 1 ml dose. Lot no.: DHAB404A4</td>
</tr>
</tbody>
</table>

Reference therapy, dose and mode of administration, lot number:

| Vaccination schedule/site: In the primary study, Group 1 received combined hepatitis A/hepatitis B vaccine as an intramuscular (IM) injection in the deltoid region according to a 0, 6 month schedule. |
| Vaccine/composition/dose/lot number: GlaxoSmithKline Biologicals’ combined hepatitis A/hepatitis B vaccine (TWINRIX™) contained at least 720 EL.U of inactivated hepatitis A antigen (Strain HM 175-RIT 4380), 20 mcg of recombinant HBsAg and 0.45 mg aluminium salt in 1 ml dose. Lot no.: HAB116C4/M |

Duration of treatment: Primary Study: 7 months
Long-term follow-up up to 60 months after the first dose of primary vaccination course

Criteria for evaluation:

| Immunogenicity: The serology results for Months 7, 36, 48 and 60 time points are presented in this annex report. The anti-HAV and anti-HBs antibody concentrations were expressed in milli-International Units per milliliter (mIU/ml). Subjects with antibody concentrations ≥ 15 mIU/ml were considered seropositive for anti-HAV antibodies. Subjects with antibody concentrations ≥ 3.3 mIU/ml were considered seropositive for anti-HBs antibodies. Subjects with antibody concentrations ≥ 10 mIU/ml were considered seroprotected for anti-HBs antibodies. A different assay was used for the primary study and for the Months 36, 48 and 60 time points. Serum samples from the Month 7 time point (in the primary study) were re-tested using the new assays (Enzygnost from Behring for anti-HAV antibodies and AUSAB EIA from Abbot Laboratories for anti-HBs antibodies). |

| Statistical methods: Descriptive analyses were performed on the according-to-protocol (ATP) cohort and the intention-to-treat (ITT) cohort. Seropositivity rates, geometric mean concentrations (GMCs) with 95% confidence interval (CI) for anti-HAV and anti-HBs antibodies and seroprotection rates with 95% CI for anti-HBs antibodies were calculated. GMCs were calculated on seropositive subjects only. Reverse Cumulative Curves (RCC) were used to graphically present the distributions of anti-HAV and anti-HBs antibody concentrations at Month 48 and Month 60. |
| Note: Eighteen subjects who lost their protective level for hepatitis B (10 mIU/ml) at Month 36 received an additional dose of TWINRIX™ (720/20) at Month 44 (see HAB-123). To correct for these 18 subjects, a Last Observation Carried Forward (LOCF) approach was applied, extrapolating the Month 44 pre-additional dose results to Month 48 and Month 60. Three subjects with anti-HBs levels below 10 mIU/ml at Month 36 and just above 10 mIU/ml at Month 44 were assigned an arbitrary value of 5 mIU/ml. |

208127/100 and 208127/101 Synopsis page 2 of 4
**Name of company:** GlaxoSmithKline Biologicals, Rixensart, Belgium  
**Name of finished product:** Combined hepatitis A/hepatitis B vaccine  
**Name of active substances:** Inactivated hepatitis A antigen (Strain HM 175-RIT 4380) and recombinant Hepatitis B surface antigen (HBsAg)

### SUMMARY-Results:

**Immunogenicity Results:** Seropositivity rates and GMCs (GMCs calculated in seropositive subjects) of anti-HAV and anti-HBs antibodies and seroprotection rates of anti-HBs antibodies for the ATP immunogenicity cohort are as follows:

#### Anti-HAV antibodies

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+ 95% CI</th>
<th>GMC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>% L.L. U.L.</td>
<td>(mIU/ml) L.L. U.L.</td>
</tr>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>67</td>
<td>100.0 94.6 100.0</td>
<td>7360.2 5511.2 9829.5</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>59</td>
<td>100.0 93.9 100.0</td>
<td>710.2 533.7 945.2</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>55</td>
<td>100.0 93.5 100.0</td>
<td>494.5 379.4 644.5</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>54</td>
<td>100.0 93.4 100.0</td>
<td>443.2 341.9 574.5</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>55</td>
<td>100.0 93.5 100.0</td>
<td>14559.2 11312.4 18737.7</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>53</td>
<td>100.0 93.3 100.0</td>
<td>1023.4 781.9 1339.4</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>51</td>
<td>100.0 93.0 100.0</td>
<td>806.3 623.7 1042.3</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>50</td>
<td>100.0 92.9 100.0</td>
<td>716.0 541.8 946.2</td>
</tr>
</tbody>
</table>

#### Anti-HBs antibodies

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+ 95% CI</th>
<th>SP 95% CI</th>
<th>GMC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>% L.L. U.L.</td>
<td>n</td>
<td>% L.L. U.L.</td>
</tr>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>67</td>
<td>100.0 94.6 100.0</td>
<td>67</td>
<td>100.0 94.6 100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>59</td>
<td>91.5 81.3 97.2</td>
<td>50</td>
<td>84.7 73.0 92.8</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>51</td>
<td>92.7 82.4 98.0</td>
<td>47</td>
<td>85.5 73.3 93.5</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>50</td>
<td>90.7 79.7 96.9</td>
<td>46</td>
<td>85.2 72.9 93.4</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>55</td>
<td>100.0 93.5 100.0</td>
<td>55</td>
<td>100.0 93.5 100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>53</td>
<td>94.3 84.3 98.8</td>
<td>46</td>
<td>86.8 74.7 94.5</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>51</td>
<td>90.2 78.6 96.7</td>
<td>42</td>
<td>82.4 69.1 91.6</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>50</td>
<td>86.0 73.3 94.2</td>
<td>39</td>
<td>78.0 64.0 88.5</td>
</tr>
</tbody>
</table>

* Number of subjects included those who participated in the study HAB-123 (anti-HAV and anti-HBs antibody concentrations of these subjects were kept the same as that at the pre-additional dose time point in the HAB-123 study, approximately 44 months after last vaccine dose in HAB-075 study)

N: Number of subjects tested; n (%): Number (percentage) of subjects seropositive for anti-HAV antibodies or seroprotected for anti-HBs antibodies

S+: Seropositivity for anti-HAV antibodies (i.e. concentrations ≥ 15 mIU/ml) or anti-HBs antibodies (i.e. concentrations ≥ 3.3 mIU/ml); SP: Seroprotection for anti-HBs antibodies (i.e. concentrations ≥ 10 mIU/ml)

95% CI, L.L. and U.L.: 95% confidence intervals, lower and upper limits
In the long-term ATP immunogenicity cohort:

- All subjects in both groups were seropositive for anti-HAV antibodies up to Month 60.
- The decrease in anti-HAV antibody GMCs for the period from Month 36 to Month 48 was 30.4% (710.2 mIU/ml to 494.5 mIU/ml) for Group 1 and 21.2% (1023.4 mIU/ml to 806.3 mIU/ml) for Group 2 and for the period from Month 48 to Month 60 was 10.4% (494.5 mIU/ml to 443.2 mIU/ml) for Group 1 and 11.2% (806.3 mIU/ml to 716.0 mIU/ml) for Group 2.
- At Month 48, 85.5% of subjects in Group 1 and 82.4% of subjects in Group 2 had anti-HBs antibody levels > 10 mIU/ml. At Month 60, 85.2% of subjects in Group 1 and 78% of subjects in Group 2 had anti-HBs antibody levels > 10 mIU/ml.
- The decrease in anti-HBs antibody GMCs for the period from Month 36 to Month 48 was 19% (148.4 mIU/ml to 120.3 mIU/ml) for Group 1 and 19.3% (175.9 mIU/ml to 141.9 mIU/ml) for Group 2 and for the period from Month 48 to Month 60 was 23.5% (120.3 mIU/ml to 92.0 mIU/ml) for Group 1 and 8.2% (141.9 mIU/ml to 130.2 mIU/ml) for Group 2.

Retrospective follow-up for Serious Adverse Events (SAEs):

No SAEs were reported since the last study visit at Month 36 up to the long-term follow-up at Month 60. One subject reported SAE at Month 60 follow-up visit, which was determined by the investigator to be ‘not related’ to vaccination.

SUMMARY-Conclusions:

The long-term ATP analysis demonstrated that GSK Biologicals’ TWINRIX™ vaccine and high-dose combined hepatitis A/hepatitis B vaccine induced a satisfactory immune response in terms of anti-HAV and anti-HBs antibodies that persisted for at least 60 months after the first dose of the primary vaccination course (0, 6 month schedule) in a majority of healthy adolescents aged 11-18 years. This was evidenced by the fact that 60 months after the first dose of the primary vaccination course, all subjects were seropositive for anti-HAV antibodies. Following administration of GSK Biologicals’ high dose combined hepatitis A/hepatitis B vaccine, 86% of subjects were seropositive for anti-HBs antibodies and 78% had concentrations ≥ 10 mIU/ml at Month 60. Following administration of GSK Biologicals’ TWINRIX™ vaccine, 91% of subjects were seropositive for anti-HBs antibodies and 85% had concentrations ≥ 10 mIU/ml at Month 60.

Date of report: 7 December 2004 (Final)
CONTENTS: TEXT

1. INTRODUCTION

2. STUDY OBJECTIVES

3. METHODOLOGY
   3.1 STUDY DESIGN
   3.2 ETHICS
   3.3 STUDY VACCINE COMPOSITION
   3.4 STUDY PROCEDURES
      3.4.1 Intervals between study visits
      3.4.2 Laboratory assays and time points
   3.5 DATA QUALITY ASSURANCE
   3.6 STATISTICAL METHODS
      3.6.1 Study cohorts/data sets analysed
      3.6.2 Analysis of demographics
      3.6.3 Analysis of immunogenicity
      3.6.4 Analysis of safety
   3.7 CHANGES IN PLANNED ANALYSIS

4. STUDY POPULATION
   4.1 SUBJECT ELIGIBILITY AND ATTRITION FROM STUDY
      4.1.1 Eligibility for analysis
   4.2 DEMOGRAPHIC CHARACTERISTICS
      4.2.1 ATP immunogenicity cohort

5. ANALYSIS OF IMMUNOGENICITY
   5.1 DATA SETS ANALYSED
   5.2 ACCORDING-TO-PROTOCOL ANALYSIS
      5.2.1 Anti-HAV antibody persistence
      5.2.2 Anti-HBs antibody persistence
   5.3 ANALYSIS OF ITT COHORT

6. RETROSPECTIVE FOLLOW-UP FOR SERIOUS ADVERSE EVENTS

7. DISCUSSION

8. OVERALL CONCLUSIONS

9. REFERENCES

GLAXOSMITHKLINE BIOLOGICALS VACCINES CLINTRIAL ELIGIBILITY CODES
GLAXOSMITHKLINE BIOLOGICALS VACCINES NOTES TO APPENDIX TABLES
CONTENTS: REPORT TABLES AND FIGURES

TABLE 1 VACCINE COMPOSITION AND VACCINE LOTS................................................................. 13
TABLE 2 NUMBER OF SUBJECTS ENROLLED INTO THE PRIMARY STUDY AS WELL AS THE NUMBER
ELIMINATED FROM THE MONTH 48 AND MONTH 60 LONG-TERM ANALYSES......................... 19
TABLE 3 DEMOGRAPHICS (LONG-TERM ATP COHORT) .............................................................. 20
TABLE 4 SEROPOSITIVITY RATES AND GMCS (CALCULATED IN SEROPOSITIVE SUBJECTS ONLY) OF
ANTI-HAV ANTIBODIES (LONG-TERM ATP IMMUNOGENICITY COHORT).................................... 22
TABLE 5 SEROPOSITIVITY RATES, SEROPROTECTION RATES AND GMCS (CALCULATED ON
SEROPOSITIVE SUBJECTS ONLY) OF ANTI-HBS ANTIBODIES (LONG-TERM ATP
IMMUNOGENICITY COHORT) ................................................................................................... 24
TABLE 6 SAES REPORTED DURING THE LONG-TERM FOLLOW-UP AT MONTH 60................. 26

FIGURE 1 RCC OF ANTI-HAV ANTIBODY CONCENTRATIONS AT MONTH 48 (LONG-TERM ATP
IMMUNOGENICITY COHORT) ................................................................................................... 22
FIGURE 2 RCC OF ANTI-HAV ANTIBODY CONCENTRATIONS AT MONTH 60 (LONG-TERM ATP
IMMUNOGENICITY COHORT) ................................................................................................... 23
FIGURE 3 RCC OF ANTI-HBS ANTIBODY CONCENTRATIONS AT MONTH 48 (LONG-TERM ATP
IMMUNOGENICITY COHORT) ................................................................................................... 25
FIGURE 4 RCC OF ANTI-HBS ANTIBODY CONCENTRATIONS AT MONTH 60 (LONG-TERM ATP
IMMUNOGENICITY COHORT) ................................................................................................... 25

CONTENTS: SUPPLEMENTARY TABLE

SUPPLEMENTARY TABLE 1 DEMOGRAPHICS (LONG-TERM ITT COHORT) ............................... 29
SUPPLEMENTARY TABLE 2 DEMOGRAPHICS INCLUDING SUBJECTS FROM HAB-123 STUDY (LONG-
TERM ITT COHORT) ................................................................................................................ 30
SUPPLEMENTARY TABLE 3 DEMOGRAPHICS INCLUDING SUBJECTS FROM HAB-123 STUDY (LONG-
TERM ATP COHORT) ............................................................................................................. 30
SUPPLEMENTARY TABLE 4 SEROPOSITIVITY RATES AND GMCS (CALCULATED ON SEROPOSITIVE
SUBJECTS ONLY) OF ANTI-HAV ANTIBODIES (LONG-TERM ITT COHORT) ............................ 31
SUPPLEMENTARY TABLE 5 SEROPOSITIVITY RATES, SEROPROTECTION RATES AND GMCS
(CALCULATED ON SEROPOSITIVE SUBJECTS ONLY) OF ANTI-HBS ANTIBODIES (LONG-TERM ITT
COHORT) .................................................................................................................................. 32
APPENDICES

APPENDICES: INDIVIDUAL LISTINGS
I A ELIMINATION CODES
B DEMOGRAPHY
C DATES OF BIRTH – VACCINATION – SAMPLING-VISITS

III A IMMUNOGENICITY

APPENDICES: SERIOUS ADVERSE EVENTS
– CLINICAL NARRATIVES
– SERIOUS ADVERSE EVENTS TABLE

APPENDICES: STUDY INFORMATION
– AMENDMENT
– REPRESENTATIVE SUBJECT INFORMATION SHEET
– ONE PAGE CV FOR PRINCIPAL INVESTIGATOR
List of Abbreviations and Definitions of Terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HAV</td>
<td>Antibodies to hepatitis A virus</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Antibodies to hepatitis B surface antigen</td>
</tr>
<tr>
<td>ATP</td>
<td>According-to-protocol analysis</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>GMC</td>
<td>Geometric mean antibody concentration</td>
</tr>
<tr>
<td>GSK Biologicals</td>
<td>GlaxoSmithKline Biologicals</td>
</tr>
<tr>
<td>HAB</td>
<td>Hepatitis A / hepatitis B viruses</td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat analysis</td>
</tr>
<tr>
<td>IU</td>
<td>International Units</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>mcg</td>
<td>microgram</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</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>RIA</td>
<td>Radioimmunoassay</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Events</td>
</tr>
</tbody>
</table>
Glossary of Terms

According-to-protocol (ATP) cohort for long-term analysis of immunogenicity:
The long-term ATP immunogenicity cohort included all subjects in the ATP analysis of immunogenicity in the primary study who returned for blood sampling at the long-term time point (Month 48 or 60) except for the subjects who received elimination code(s) during the long-term follow-up up to that time point.

Intention-to-treat (ITT) cohort:
The ITT cohort included all subjects for whom assay results were available for anti-HAV and/or anti-HBs antibodies at that particular long-term time point (Month 48 or Month 60).

Serious Adverse Event:
A serious adverse event was any event which was fatal, life threatening *, disabling/incapacitating †, or resulted in hospitalization ‡, prolonged a hospital stay or was associated with congenital abnormality in offspring, cancer or overdose (either accidental or intentional). In addition any event which the investigator regarded as serious or which suggested any significant hazard, contraindication, side effect or precaution that may have been associated with the use of the vaccine was documented as a serious adverse event.

Seroprotection:
Anti-HBs antibody concentrations ≥ 10 mIU/ml.

Seropositive:
Anti-HBs antibody concentrations ≥ 3.3 mIU/ml or anti-HAV antibody concentrations ≥ 15 mIU/ml.

Subjects:
Term used throughout the report for the enrolled individuals in the study.
1. Introduction

This long-term follow-up study was done to evaluate the long-term anti-HAV and anti-HBs antibody persistence in subjects of the primary study 208127/075 (HAB-075), 48 and 60 months after the first dose of the primary vaccination course.

This report provides results up to and including the immunogenicity results at Month 60. Annex 1 report presented the immunogenicity results up to Month 36.

Please refer to the primary report of this study 208127/075 (HAB-075) or Annex 1 report 208127/099 (HAB-075) for sections not affected by the results of this long-term follow-up study (e.g. inclusion and exclusion criteria, investigator address, study centre and vaccination schedule/site). Reactogenicity results following the primary vaccination course are not presented in this annex report. Please refer the primary study report.

2. Study objectives

Objectives of the primary study can be found in the primary HAB-075 study report.

The objective of this long-term follow-up was to evaluate the long-term anti-HAV and anti-HBs antibody persistence through blood samples taken 48 and 60 months after the first of the two doses of primary vaccination course (0, 6 month schedule) with GlaxoSmithKline (GSK) Biologicals’ high-dose combined hepatitis A/ hepatitis B (HAB) vaccine or GSK Biologicals’ combined hepatitis A/ hepatitis B vaccine (TWINRIX™) in healthy volunteers aged 11 to 18 years (inclusive) at the time of primary vaccination.

3. Methodology

A protocol amendment dated 23 June 2000 required the collection of blood samples at 36, 48 and 60 months after the first of the two doses of primary vaccination course (0, 6 months). The amendment also required the documentation of any serious adverse events (SAE), which the subject might have experienced since the last study visit.

This annex report details the long-term results of the study up to and including Month 60.
3.1 Study design

The primary study was a comparative, double blind, randomized 1:1 study with two groups. The long-term follow-up at Months 48 and 60 was an open study with the same two groups.

At these time points, blood samplings were taken and data regarding Serious Adverse Events (SAEs) occurring since the last study visit (Month 36) up to Month 60 were to be documented retrospectively.

The blood sampling visits at Month 48 were conducted between 25 July 2001 and 28 October 2001.

The blood sampling visits at Month 60 were conducted between 5 July 2002 and 15 September 2002.

3.2 Ethics

The protocol amendment dated 23 June 2000 and the amended statement of informed consent were approved by the [Redacted] Australia on 21 July 2000.

Written informed consent was obtained from the parent/guardian and/or the subject, prior to entry into the long-term follow-up study at Month 36 (as required by local legislation).

3.3 Study vaccine composition

The two study vaccines used in the primary study were developed and manufactured by GlaxoSmithKline Biologicals.

The Quality Control Standards and Requirements for the study vaccines are described in separate release protocol and the required approvals were obtained. The vaccine release protocol was archived in the study file and is available upon request.

Group 1 received combined hepatitis A/hepatitis B vaccine (TWINRIX™) and Group 2 received high-dose combined hepatitis A/hepatitis B vaccine. The vaccines in both groups were given as intramuscular (IM) injections in the deltoid region according to a 0, 6 month schedule. Vaccine composition and the vaccine lots used in this study are given in Table 1.
3.4 Study procedures

At Month 48 (Visit 7) and Month 60 (Visit 8):

- **Before each bleeding:**
  The investigator asked each volunteer if he/she had received, since the last visit
  - a dose of hepatitis A or hepatitis B vaccine and/or
  - a dose of hepatitis A or hepatitis B immunoglobulins.
  If so, subjects were excluded from this extended long-term follow-up study.

- **Bleeding:**
  From each subject, 7 ml of whole venous blood was collected for testing anti-HAV and anti-HBs antibodies. Serum was stored at – 20°C until transported to GSK Biologicals for testing.

- **Recording of serious adverse events (SAEs):**
  Documentation of SAEs, which the subject might have experienced since the last study visit (i.e. Month 36; Visit 6).

3.4.1 Intervals between study visits

The interval between Month 0 and Month 48 was defined as 48 months ± 6 weeks and the interval between Month 0 and Month 60 was defined as 60 months ± 6 weeks. This interval was used to determine a subjects’ evaluability in the according-to-protocol (ATP) analyses.

3.4.2 Laboratory assays and time points

All laboratory assays were conducted in GSK Biologicals’ central laboratory.

In the primary study (up to Month 7), the serum concentrations of anti-HAV antibodies were measured by an ELISA inhibition assay kit (Enzymun from Boehringer) with an assay cut-off of 33 mIU/ml and anti-HBs antibodies were
measured by a Radioimmunoassay (RIA) kit (from Abbot Laboratories) with an assay cut-off of 1 mIU/ml. Due to the unavailability of these assays, different assays were used for testing blood samples at Months 36, 48 and 60.

At these long-term time points, the serum concentrations of anti-HAV and anti-HBs antibodies were measured using Enzyme Immunoassay. The assays used were Enzygnost from Behring for anti-HAV antibodies and AUSAB EIA from Abbot Laboratories for anti-HBs antibodies. The anti-HAV and anti-HBs antibody concentrations were expressed in milli-International Units per milliliter (mIU/ml).

GSK Biologicals has validated the new assays (used for long-term blood sampling time points) and shown that upon defining a cut-off of 15 mIU/ml for anti-HAV antibodies and 3.3 mIU/ml for anti-HBs antibodies, a good concordance with the old test kits in terms of seropositivity rates and seroprotection rates is obtained. In addition, the serum samples from the Month 7 time point (in the primary study) were re-tested using the new serological assays. Serology results for Months 7, 36, 48 and 60 time points have been presented in this annex report.

Subjects with antibody concentrations ≥ 15 mIU/ml were considered seropositive for anti-HAV antibodies. Subjects with antibody concentrations ≥ 3.3 mIU/ml were considered seropositive for anti-HBs antibodies. Subjects with antibody concentrations ≥ 10 mIU/ml were considered seroprotected for anti-HBs antibodies.

### 3.5 Data quality assurance

To ensure that study procedures conformed at the investigator site, the protocol amendment and safety reporting were reviewed with the investigator and his/her 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 the investigator site. All procedures were performed according to methodologies detailed in GlaxoSmithKline Standard Operating Procedures (SOPs).

### 3.6 Statistical methods

Only descriptive analysis was performed for immunology results at Month 48 and Month 60. Analyses were performed on two study cohorts: the according-to-protocol (ATP) cohort and the intention-to-treat cohort (ITT) cohort.
3.6.1 Study cohorts/data sets analysed

The long-term ATP immunogenicity cohort included all subjects in the ATP analysis of immunogenicity in the primary study who returned for blood sampling at the long-term time point (Month 48 or 60) except for the subjects who did not comply with the study procedures and time lines, had received additional doses of hepatitis A or B vaccines outside of the study or showed abnormal increase in concentrations since the last blood sample.

The ITT cohort included all subjects for whom assay results were available for anti-HAV and/or anti-HBs antibodies at that particular long-term time point (Month 48 or Month 60).

Note: Subjects in the primary study (HAB-075) who had previously shown seroprotection for anti-HBs antibodies but who had concentrations < 10 mIU/ml at Month 36 were offered an additional dose of GSK Biologicals’ TWINRIX™ (720/20) (See HAB-123 study report) given approximately 44 months after the primary vaccination. The immunology results of the pre-additional vaccination for these subjects were extrapolated to Month 48 and Month 60.

3.6.2 Analysis of demographics

The demographic data were tabulated for the long-term ITT cohort and long-term ATP cohort.

3.6.3 Analysis of immunogenicity

Descriptive analyses were performed on long-term ATP cohort and long-term ITT cohort.

Seropositivity (S+) rates and GMCs of anti-HAV antibodies and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies were calculated with 95% confidence interval (CI).

Seropositivity rate was defined as the percentage of subjects with concentrations ≥ 3.3 mIU/ml for anti-HBs antibodies or concentrations ≥ 15 mIU/ml for anti-HAV antibodies. Seroprotection rate for anti-HBs antibodies was defined as the percentage of subjects with concentrations ≥ 10 mIU/ml. Geometric Mean Concentration (GMC) of anti-HAV antibodies and anti-HBs antibodies were calculated by taking the anti-log of the mean of the log titre transformations. GMCs were calculated on seropositive subjects only.

Reverse Cumulative Curves (RCC) were used to graphically present the distributions of anti-HAV and anti-HBs antibody concentrations at Month 48 and Month 60.
3.6.4 Analysis of safety

SAEs occurring since the last study visit (Month 36) up to Month 60 were to be documented retrospectively.

3.7 Changes in Planned Analysis

- Eighteen subjects who lost their protective level for hepatitis B (10 mIU/ml) at Month 36 received an additional dose of TWINRIX™ (720/20) at Month 44 (see HAB-123). To correct for these 18 subjects, a Last Observation Carried Forward (LOCF) approach was applied, extrapolating the Month 44 pre-additional dose results to Month 48 and Month 60. Three subjects that had anti-HBs levels below 10 mIU/ml at Month 36 and just above 10 mIU/ml at Month 44 were assigned an arbitrary value of 5 mIU/ml.

4. Study Population

4.1 Subject eligibility and attrition from study

4.1.1 Eligibility for analysis

Elimination codes are defined on the first page of the Appendix Tables. See Appendix Table IA for individual subject data on elimination codes.

The elimination code for an abnormal increase in antibody concentrations was assigned only for the long-term follow-up. The definition of abnormal increase depended on the magnitude of the concentration reached at the first time point considered (reference time point). Abnormal increase in antibody concentrations was defined as a two-fold increase or more in antibody concentrations (when the antibody concentration at the reference time point was \( \geq 100 \) mIU/ml) or a four-fold increase or more in antibody concentrations (when the antibody concentration at the reference time point was < 100 mIU/ml). This code was assigned to give a more realistic evaluation of the long-term persistence of antibodies. Abnormal serological evolution could be due to an additional vaccine dose or gamma-globulin administered to the subject (outside the study) or natural exposure to wild-type virus during the follow-up phase.

The number of subjects enrolled and eliminated (with reasons for elimination) from the long-term ATP analyses at Month 48 and Month 60 is presented in Table 2.

A total of 150 subjects were enrolled in the primary study. Four years after the first dose of the primary vaccination (i.e. at Month 48), 141 subjects (69 subjects
in Group 1 and 72 subjects in Group 2) returned for the blood-sampling visit (94% compliance). Of these 141 subjects, 27 (8 subjects in Group 1 and 19 subjects in Group 2) had received elimination codes in the primary study (see primary study report for details regarding the reasons for their elimination) and 22 subjects (14 in Group 1 and 8 in Group 2) received elimination codes at the Month 48 long-term time point. The reason for their elimination were as follows:

- 
- 
- 
- 
- 
- 
- 

Thus, a total of 92 subjects (47 in Group 1 and 45 in Group 2) were included in the long-term ATP immunogenicity analysis at Month 48

Five years after the first dose of primary vaccination (i.e. at Month 60), 122 subjects (59 in Group 1 and 63 in Group 2) returned for the blood sampling visit (81.3% compliance). Of these 122 subjects, 23 (7 subjects in Group 1 and 16 subjects in Group 2) had received elimination codes in primary study (see primary study report for details regarding the reasons for their elimination) and 3 subjects received elimination codes in the Month 48 long-term follow-up. In addition, 6 subjects received elimination codes at the Month 60 long-term time point. The reason for elimination of these 6 subjects were as follows:

- 
- 
- 

Thus, a total of 90 subjects (46 in Group 1 and 44 in Group 2) were included in the long-term ATP immunogenicity cohort at Month 60.

Note: Eighteen subjects who lost their protective level for hepatitis B (10 mIU/ml) at Month 36 received an additional dose of TWINRIX™ (720/20) at
Month 44 (see HAB-123). To correct for these 18 subjects, a Last Observation Carried Forward (LOCF) approach was applied, extrapolating the Month 44 pre-additional dose results to Month 48 and Month 60. Three subjects (included only in the ITT cohort) with anti-HBs levels below 10 mIU/ml at Month 36 and just above 10 mIU/ml at Month 44 were assigned an arbitrary value of 5 mIU/ml. Hence the number of subjects for the ATP cohort tabulated in the immunogenicity table is different from that tabulated in the study attrition table.
Table 2 Number of subjects enrolled into the primary study as well as the number eliminated from the Month 48 and Month 60 long-term analyses

<table>
<thead>
<tr>
<th>Title</th>
<th>Total</th>
<th>Percent (%)</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects enrolled in primary study</td>
<td>150</td>
<td>100</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Number of subjects who completed the primary study</td>
<td>149</td>
<td>99.3</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>Number of subjects returned at Month 36</td>
<td>139</td>
<td>92.6</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>Number of subjects returned at Month 48 after adjustment with subjects from HAB-123</td>
<td>141</td>
<td>94.0</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Administration of vaccine(s) forbidden in the protocol (code 1040)</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Protocol violation (inclusion/exclusion criteria) (code 2010)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Initially seropositive or initially unknown antibody status (code 2020)</td>
<td>23</td>
<td></td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non compliance with blood sampling schedule (including wrong and unknown date) (code 2090)</td>
<td>17</td>
<td></td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Essential serological data missing (code 2100)</td>
<td>2</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Obvious incoherence or abnormality or error in data (code 2120)</td>
<td>3</td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Number of subjects in the long-term ATP cohort for immunogenicity at Month 48</td>
<td>92</td>
<td>61.3</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>Number of subjects returned at Month 60</td>
<td>122</td>
<td>81.3</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td>Administration of vaccine(s) forbidden in the protocol (code 1040)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Protocol violation (inclusion/exclusion criteria) (code 2010)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Initially seropositive or initially unknown antibody status (code 2020)</td>
<td>19</td>
<td></td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Essential serological data missing (code 2100)</td>
<td>4</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Obvious incoherence or abnormality or error in data (code 2120)</td>
<td>6</td>
<td></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Number of subjects in the ATP cohort for immunogenicity at Month 60</td>
<td>90</td>
<td>60.0</td>
<td>46</td>
<td>44</td>
</tr>
</tbody>
</table>

Individual subject data on elimination codes can be found in Appendix Table IA.

Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

Percent: Percentage of subjects in the considered ATP cohort relative to the ITT cohort.

Subjects may have one or more elimination code(s) assigned in which case the lowest code number is listed in the table. Codes are given based on a ranking order. The code numbers listed in the table are presented in order of ranking. Elimination codes are defined on the first page of the Appendix Tables.

4.2 Demographic characteristics

4.2.1 ATP immunogenicity cohort

The demographics of subjects who came back at Month 48 and Month 60 for the long-term ATP cohort are presented in Table 3.
• The mean age at Month 48 was 18.7 years with a standard deviation of 1.57 years and the male: female ratio was 1.09. The race of all subjects was White.

• The mean age at Month 60 was 19.7 years with a standard deviation of 1.57 years and the male: female ratio was 1.05.

Table 3 Demographics (long-term ATP cohort)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Group 1: TWINRIX™ (HAB116C4/M) in the primary study</th>
<th>Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean age (in years)</td>
</tr>
<tr>
<td>Month 48</td>
<td>1</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Month 60</td>
<td>1</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table 1B
Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study
N: Number of subjects with documented age and gender
SD: Standard deviation
Min, Max age: Minimum, maximum age in years

The demographics of the ITT cohort was similar to that of the long-term ATP cohort (see Supplementary Table 1).

Supplementary Table 2 presents the demographics (including subjects from HAB-123 study), for the long-term ITT cohort. Supplementary Table 3 presents the demographics (including subjects from HAB-123 study), for the long-term ATP cohort.
5. Analysis of immunogenicity

5.1 Data sets analysed

Immunogenicity analysis was performed on two cohorts: ITT cohort and ATP cohort. The long-term ATP cohort was regarded as the principal analysis for this report.

5.2 According-To-Protocol analysis

5.2.1 Anti-HAV antibody persistence:

Table 4 presents the seropositivity rates and GMCs of anti-HAV antibodies up to Month 60 for the long-term ATP immunogenicity cohort. Figure 1 and Figure 2 presents the reverse cumulative curve (RCC) of anti-HAV antibodies for the long-term ATP immunogenicity cohort at Month 48 and Month 60 respectively.

- At both time points i.e. 48 months and 60 months after the first dose of the primary vaccination, all subjects in both groups included in the long-term ATP immunogenicity analysis were seropositive for anti-HAV antibodies.

- The decrease in anti-HAV antibody GMCs from Month 36 to Month 48 was 30.4% (710.2 mIU/ml to 494.5 mIU/ml) for Group 1 and 21.2% (1023.4 mIU/ml to 806.3 mIU/ml) for Group 2.

- The decrease in anti-HAV antibody GMCs from Month 48 to Month 60 was 10.4% (494.5mIU/ml to 443.2 mIU/ml) for Group 1 and 11.2% (806.3 mIU/ml to 716.0 mIU/ml) for Group 2.
Table 4 Seropositivity rates and GMCs (calculated in seropositive subjects only) of anti-HAV antibodies (long-term ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI</th>
<th>GMC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>L.L.</td>
<td>U.L.</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>59</td>
<td>59</td>
<td>100.0</td>
<td>93.9</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>54</td>
<td>54</td>
<td>100.0</td>
<td>93.4</td>
<td>100.0</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>53</td>
<td>53</td>
<td>100.0</td>
<td>93.3</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>51</td>
<td>51</td>
<td>100.0</td>
<td>93.0</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>50</td>
<td>50</td>
<td>100.0</td>
<td>92.9</td>
<td>100.0</td>
</tr>
</tbody>
</table>

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

Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

* Number of subjects included those who participated in the study HAB-123 (the anti-HAV antibody concentrations of these subjects were kept the same as that at the pre-additional dose time point in the HAB-123 study, approximately 44 months after last vaccine dose in HAB-075 study)
N: Number of subjects tested
S+: Seropositivity for anti-HAV antibodies (i.e. concentrations ≥ 15 mIU/ml)
n (%): Number (percentage) of subjects seropositive for anti-HAV antibodies
95% L.L. and U.L.: 95% confidence intervals, lower and upper limits
PII(M7), etc.: Blood sampling after Dose 2; 7 months, etc. after the first dose of primary vaccination

Figure 1 RCC of anti-HAV antibody concentrations at Month 48 (long-term ATP immunogenicity cohort)

RCC of anti-HAV antibody concentrations at month 48 (ATP):

Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study
Figure 2 RCC of anti-HAV antibody concentrations at Month 60 (long-term ATP immunogenicity cohort)

RCC of anti-HAV antibody concentrations at month 60 (ATP):

- Group 1: TWINRIX™ (HAB116C4/M) in the primary study
- Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

5.2.2 Anti-HBs antibody persistence

Table 5 presents the seropositivity rates, seroprotection rates and GMCs of anti-HBs antibodies, up to Month 60, for the long-term ATP immunogenicity cohort. Figure 3 and Figure 4 present the RCC of anti-HBs antibody concentrations for the long-term ATP immunogenicity cohort at Month 48 and Month 60 respectively.

- At Month 48 (i.e. four years after the first dose of the primary vaccination), 85.5% of subjects in Group 1 and 82.4% of subjects in Group 2 included in the long-term ATP immunogenicity analysis had anti-HBs antibody concentrations above 10 mIU/ml.

- At Month 60 (i.e. five years after the first dose of the primary vaccination), 85.2% of subjects in Group 1 and 78.0% of subjects in Group 2 included in the long-term ATP immunogenicity analysis had anti-HBs antibody concentrations above 10 mIU/ml.

- The decrease in anti-HBs antibody GMCs from Month 36 to Month 48 was 19% (148.4 mIU/ml to 120.3 mIU/ml) for Group 1 and 19.3% (175.9 mIU/ml to 141.9 mIU/ml) for Group 2.
The decrease in anti-HBs antibody GMCs from Month 48 to Month 60 was 23.5% (120.3 mIU/ml to 92.0 mIU/ml) for Group 1 and 8.2% (141.9 mIU/ml to 130.2 mIU/ml) for Group 2.

Table 5 Seropositivity rates, seroprotection rates and GMCs (calculated on seropositive subjects only) of anti-HBs antibodies (long-term ATP immunogenicity cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI</th>
<th>SP</th>
<th>95% CI</th>
<th>GMC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
<td>100.0</td>
<td>3840.7</td>
<td>9529.1</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>59</td>
<td>54</td>
<td>91.5</td>
<td>81.3</td>
<td>97.2</td>
<td>148.4</td>
<td>233.6</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>55</td>
<td>51</td>
<td>92.7</td>
<td>82.4</td>
<td>98.0</td>
<td>120.3</td>
<td>197.1</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>54</td>
<td>50</td>
<td>90.7</td>
<td>79.7</td>
<td>96.9</td>
<td>92.0</td>
<td>147.3</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>55</td>
<td>55</td>
<td>100.0</td>
<td>93.5</td>
<td>100.0</td>
<td>4748.3</td>
<td>8009.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>53</td>
<td>50</td>
<td>94.3</td>
<td>84.3</td>
<td>98.8</td>
<td>175.9</td>
<td>298.2</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>51</td>
<td>46</td>
<td>90.2</td>
<td>87.6</td>
<td>96.7</td>
<td>141.9</td>
<td>253.3</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>50</td>
<td>43</td>
<td>86.0</td>
<td>73.3</td>
<td>94.2</td>
<td>130.2</td>
<td>237.1</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA
Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

* Number of subjects included those who participated in the study HAB-123 (the anti-HBs antibody concentrations of these subjects were kept the same as that at the pre-additional dose time point in the HAB-123 study, approximately 44 months after last vaccine dose in HAB-075 study)

N: Number of subjects tested
n (%): Number (percentage) of subjects seropositive or seroprotected for anti-HBs antibodies
S+: Seropositivity for anti-HBs antibodies (i.e. concentrations ≥ 3.3 mIU/ml)
SP: Seroprotection for anti-HBs antibodies (i.e. concentrations ≥ 10 mIU/ml)
95% L.L. and U.L.: 95% confidence intervals, lower and upper limits
PII(M7), etc.: Blood sampling after Dose 2; 7 months, etc. after the first dose of primary vaccination
Figure 3 RCC of anti-HBs antibody concentrations at Month 48 (long-term ATP immunogenicity cohort)

RCC of anti-HBs antibody concentrations at month 48 (ATP)

Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

Figure 4 RCC of anti-HBs antibody concentrations at Month 60 (long-term ATP immunogenicity cohort)

RCC of anti-HBs antibody concentrations at month 60 (ATP)

Group 1: TWINRIX™ (HAB116C4/M) in the primary study
Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study
5.3 Analysis of ITT cohort

The results of the long-term ITT cohort were consistent with those obtained from the long-term immunogenicity cohort.

Supplementary Table 4 presents the seropositivity rates and GMCs of anti-HAV antibodies up to Month 60, for the long-term ITT cohort.

Supplementary Table 5 presents the seropositivity rates, seroprotection rates and GMCs of anti-HBs antibodies up to Month 60, for the long-term ITT cohort.

6. Retrospective Follow-up for Serious Adverse Events

No SAEs were reported since the last study visit at Month 36 upto the long-term follow-up at Month 48. One subject reported SAE at Month 60 follow-up visit, which was determined by the investigator to be ‘not related’ to vaccination. Refer Table 6 for details.

Suspect adverse reaction report (SARR) and SAE table can be found in the Appendices for Serious Adverse Events.

Table 6 SAEs reported during the long-term follow-up at Month 60
7. Discussion

In this study amendment, subjects were followed up to Month 60 in order to assess their long-term anti-HAV and anti-HBs antibody persistence after having received according to a 2-dose schedule, either TWINRIX™ (720/20) or the high-dose combined hepatitis A/ hepatitis B vaccine (1440/40).

One month after primary vaccination, at Month 7, subjects responded well to vaccination illustrated by 100% seroconversion for anti-HAV and 100% seroprotection for anti-HBs. Five years after primary vaccination, all subjects remained seropositive for anti-HAV antibodies. The percentage of subjects with anti-HBs ≥ 10 mIU/ml was 85.2% and 78% in the TWINRIX™ and high-dose vaccine groups respectively. These results are in line with observations in other studies (1).

Note worthy to mention that subjects who responded to primary vaccination but had less than 10 mIU/ml of antibodies after 3 years were offered an additional dose and ALL had an anamnestic pattern of antibody response to the additional dose (see study HAB-123). This is secondary evidence of immune memory after the initial vaccine schedule and despite the fact circulating antibodies decreased, these subjects receiving a two-dose schedule of either TWINRIX™ or high dose combined hepatitis A/ hepatitis B vaccine were well primed.

The duration of protection has yet to be established and further studies on vaccine induced memory are needed in the future.

8. Overall Conclusions

The long-term ATP analysis demonstrated that GSK Biologicals’ TWINRIX™ vaccine and high-dose combined hepatitis A/ hepatitis B vaccine induced a satisfactory immune response in terms of anti-HAV and anti-HBs antibodies that persisted for at least 60 months after the first dose of the primary vaccination course (0, 6 month schedule) in a majority of healthy adolescents aged 11-18 years. This was evidenced by the fact that 60 months after the first dose of the primary vaccination course, all subjects were seropositive for anti-HAV antibodies. Following administration of GSK Biologicals’ high dose combined hepatitis A/ hepatitis B vaccine, 86% of subjects were seropositive for anti-HBs antibodies and 78% had concentrations ≥ 10 mIU/ml at Month 60. Following administration of GSK Biologicals’ TWINRIX™ vaccine, 91% of subjects were seropositive for anti-HBs antibodies and 85% had concentrations ≥ 10 mIU/ml at Month 60.
9. References

1 Study report HAB-084. An open, randomised study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham’s combined hepatitis A / hepatitis B vaccine Twinrix ™ (720 EL. U. of hepatitis A antigen / 20 mcg of recombinant hepatitis B surface antigen) administered following a 2 dose schedule (0, 6 months) to that of Twinrix ™ Junior (360 EL. U. of hepatitis A antigen / 10 mcg of recombinant hepatitis B surface antigen ) administered following a 3 dose schedule (0, 1, 6 months) in healthy volunteers aged 12-15 years.
### Supplementary Table 1 Demographics (long-termITT cohort)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Group</th>
<th>Gender</th>
<th>N</th>
<th>Mean age (in years)</th>
<th>SD</th>
<th>Min. age (in years)</th>
<th>Max. age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Female</td>
<td>33</td>
<td>19.0</td>
<td>1.41</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>33</td>
<td>18.6</td>
<td>1.64</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>66</td>
<td>18.8</td>
<td>1.53</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>37</td>
<td>18.8</td>
<td>1.56</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>34</td>
<td>18.6</td>
<td>1.45</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>71</td>
<td>18.7</td>
<td>1.50</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Female</td>
<td>70</td>
<td>18.9</td>
<td>1.49</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>67</td>
<td>18.6</td>
<td>1.54</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>137</td>
<td>18.8</td>
<td>1.51</td>
<td>15</td>
<td>21</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB

Group 1: TWINRIX™ (HAB116C4/M) in the primary study

Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

N: Number of subjects with documented age and gender

SD: Standard deviation

Min, Max age: Minimum, maximum age in years

Hence serology results for these subjects are missing.
### Supplementary Table 2 Demographics including subjects from HAB-123 study (long-term ITT cohort)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Group</th>
<th>Gender</th>
<th>N</th>
<th>Mean age (in years)</th>
<th>SD</th>
<th>Min. age (in years)</th>
<th>Max. age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 48</td>
<td>1</td>
<td>Female</td>
<td>44</td>
<td>19.1</td>
<td>1.43</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>40</td>
<td>18.8</td>
<td>1.61</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>84</td>
<td>18.9</td>
<td>1.51</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>37</td>
<td>18.8</td>
<td>1.56</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>34</td>
<td>18.6</td>
<td>1.45</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>71</td>
<td>18.7</td>
<td>1.50</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Month 60</td>
<td>1</td>
<td>Female</td>
<td>37</td>
<td>20.1</td>
<td>1.42</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>37</td>
<td>19.8</td>
<td>1.63</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>74</td>
<td>20.0</td>
<td>1.53</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>31</td>
<td>19.6</td>
<td>1.56</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>30</td>
<td>19.6</td>
<td>1.43</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>61</td>
<td>19.6</td>
<td>1.49</td>
<td>16</td>
<td>22</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB

- **Group 1:** TWINRIX™ (HAB116C4/M) in the primary study
- **Group 2:** High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study
- **N:** Number of subjects with documented age and gender
- **SD:** Standard deviation
- **Min, Max age:** Minimum, maximum age in years

**Note:** Subjects in the HAB-123 study from whom immunogenicity results were extrapolated, are included by assuming an increase in age of 4 and 16 months at Months 48 and 60 respectively.

### Supplementary Table 3 Demographics including subjects from HAB-123 study (long-term ATP cohort)

<table>
<thead>
<tr>
<th>Time point</th>
<th>Group</th>
<th>Gender</th>
<th>N</th>
<th>Mean age (in years)</th>
<th>SD</th>
<th>Min. age (in years)</th>
<th>Max. age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 48</td>
<td>1</td>
<td>Female</td>
<td>32</td>
<td>19.0</td>
<td>1.37</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>28</td>
<td>18.7</td>
<td>1.75</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>60</td>
<td>18.9</td>
<td>1.55</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>20</td>
<td>18.6</td>
<td>1.57</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>25</td>
<td>18.6</td>
<td>1.56</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>45</td>
<td>18.6</td>
<td>1.55</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Month 60</td>
<td>1</td>
<td>Female</td>
<td>32</td>
<td>19.9</td>
<td>1.40</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>27</td>
<td>19.8</td>
<td>1.77</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>59</td>
<td>19.9</td>
<td>1.56</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Female</td>
<td>20</td>
<td>19.6</td>
<td>1.57</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>24</td>
<td>19.5</td>
<td>1.53</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>44</td>
<td>19.5</td>
<td>1.53</td>
<td>17</td>
<td>22</td>
</tr>
</tbody>
</table>

Individual subject data on demographics can be found in Appendix table IB

- **Group 1:** TWINRIX™ (HAB116C4/M) in the primary study
- **Group 2:** High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study
- **N:** Number of subjects with documented age and gender
- **SD:** Standard deviation
- **Min, Max age:** Minimum, maximum age in years

**Note:** Subjects in the HAB-123 study from whom immunogenicity results were extrapolated, are included by assuming an increase in age of 4 and 16 months at Months 48 and 60 respectively.
### Supplementary Table 4 Seropositivity rates and GMCs (calculated on seropositive subjects only) of anti-HAV antibodies (long-term ITT cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>n</th>
<th>S+ 95% CI</th>
<th>GMC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>95% L.L.</td>
<td>95% U.L.</td>
</tr>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>67</td>
<td>67</td>
<td>100.0</td>
<td>94.6</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>66</td>
<td>66</td>
<td>100.0</td>
<td>94.6</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>65</td>
<td>65</td>
<td>100.0</td>
<td>94.5</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>72</td>
<td>72</td>
<td>100.0</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>71</td>
<td>71</td>
<td>100.0</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>PII(60)*</td>
<td>70</td>
<td>70</td>
<td>100.0</td>
<td>94.9</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1: TWINRIX™ (HAB116C4/M) in the primary study

Group 2: High-dose combined hepatitis A/hepatitis B vaccine (DHAB404A4) in the primary study

* Number of subjects included those who participated in the study HAB-123 (the anti-HAV antibody concentrations of these subjects were kept the same as that at the pre-additional dose time point in the HAB-123 study, approximately 44 months after last vaccine dose in HAB-075 study)

N: Number of subjects tested

S+: Seropositivity for anti-HAV antibodies (i.e. concentrations ≥ 15 mIU/ml)

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

95% L.L. and U.L.: 95% confidence intervals, lower and upper limits

PII(M7), etc.: Blood sampling after Dose 2; 7 months, etc. after the first dose of primary vaccination
### Supplementary Table 5

Seropositivity rates, seroprotection rates and GMCs (calculated on seropositive subjects only) of anti-HBs antibodies (long-term ITT cohort)

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+</th>
<th>95% CI</th>
<th>SP</th>
<th>95% CI</th>
<th>GMC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>L.L.</td>
<td>U.L.</td>
<td>n</td>
<td>%</td>
<td>L.L.</td>
</tr>
<tr>
<td>1</td>
<td>PII(7)</td>
<td>75</td>
<td>75</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
<td>95.2</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>67</td>
<td>61</td>
<td>91.0</td>
<td>81.5</td>
<td>96.6</td>
<td>74.3</td>
<td>92.6</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>66</td>
<td>61</td>
<td>92.4</td>
<td>83.2</td>
<td>97.5</td>
<td>75.7</td>
<td>93.6</td>
</tr>
<tr>
<td></td>
<td>PII(60)‡</td>
<td>65</td>
<td>59</td>
<td>90.8</td>
<td>81.0</td>
<td>96.5</td>
<td>73.5</td>
<td>92.4</td>
</tr>
<tr>
<td>2</td>
<td>PII(7)</td>
<td>73</td>
<td>73</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
<td>95.1</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>PII(36)</td>
<td>72</td>
<td>67</td>
<td>93.1</td>
<td>84.5</td>
<td>97.7</td>
<td>75.9</td>
<td>93.1</td>
</tr>
<tr>
<td></td>
<td>PII(48)*</td>
<td>71</td>
<td>63</td>
<td>88.7</td>
<td>79.0</td>
<td>95.0</td>
<td>70.7</td>
<td>89.9</td>
</tr>
<tr>
<td></td>
<td>PII(60)‡</td>
<td>70</td>
<td>59</td>
<td>84.3</td>
<td>73.6</td>
<td>91.9</td>
<td>64.0</td>
<td>85.2</td>
</tr>
</tbody>
</table>

Individual subject data can be found in Appendix table IIIA

Group 1: TWINRIX™ (HAB116C4/M) in the primary study

Group 2: High-dose combined hepatitis A/ hepatitis B vaccine (DHAB404A4) in the primary study

* Number of subjects included those who participated in the study HAB-123 (the anti-HBs antibody concentrations of these subjects were kept the same as that at the pre-additional dose time point in the HAB-123 study, approximately 44 months after last vaccine dose in HAB-075 study)

‡ At Month 60, three subjects (who participated in the HAB-123 study and excluded from the ATP analysis) with anti-HBs concentrations above 10 mIU/ml at Month 44 were given an arbitrary value of 5 mIU/ml assuming they lost seroprotection status at Month 60

N: Number of subjects tested

n (%): Number (percentage) of subjects seropositive or seroprotected for anti-HBs antibodies

S+: Seropositivity for anti-HBs antibodies (i.e. concentrations ≥ 3.3 mIU/ml)

SP: Seroprotection for anti-HBs antibodies (i.e. concentrations ≥ 10 mIU/ml)

95% L.L. and U.L.: 95% confidence intervals, lower and upper limits

PII(M7), etc.: Blood sampling after Dose 2; 7 months, etc. after the first dose of primary vaccination
### GLAXOSMITHKLINE BIOLOGICALS VACCINES
### CLINTRIAL ELIGIBILITY CODES

**Elimination from ATP safety (E) and ATP immunology analysis (I)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1010</td>
<td>Subject or vaccine number not allocated</td>
</tr>
<tr>
<td></td>
<td>Vaccine not administered at all</td>
</tr>
<tr>
<td></td>
<td>No subject allocated to the randomized number</td>
</tr>
<tr>
<td>1040</td>
<td>Administration of vaccine(s) forbidden in the protocol</td>
</tr>
</tbody>
</table>

**Elimination from ATP immunology analysis (I)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Protocol violation (inclusion/ exclusion criteria)</td>
</tr>
<tr>
<td></td>
<td>Demographics: Too young</td>
</tr>
<tr>
<td></td>
<td>Too old</td>
</tr>
<tr>
<td></td>
<td>Unknown age, gender</td>
</tr>
<tr>
<td></td>
<td>Gender not according to the protocol</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td>2020</td>
<td>Initially seropositive or initially unknown antibody status</td>
</tr>
<tr>
<td></td>
<td>Confirmed pre-vaccination abnormal value</td>
</tr>
<tr>
<td>2080</td>
<td>Non compliance with vaccination schedule (including wrong and unknown dates)</td>
</tr>
<tr>
<td>2090</td>
<td>Non compliance with blood sampling schedule (including wrong and unknown dates)</td>
</tr>
<tr>
<td>2100</td>
<td>Essential serological data missing</td>
</tr>
<tr>
<td></td>
<td>Blood sample lost</td>
</tr>
<tr>
<td></td>
<td>Blood sample unable to test (hemolysis, insufficient volume, ...)</td>
</tr>
<tr>
<td></td>
<td>Absence of parallelism</td>
</tr>
<tr>
<td>2120</td>
<td>Obvious incoherence or abnormality or error in data</td>
</tr>
<tr>
<td></td>
<td>Wrong labeling in BS</td>
</tr>
<tr>
<td></td>
<td>Abnormal serology evolution</td>
</tr>
</tbody>
</table>
GLAXOSMITHKLINE BIOLOGICALS VACCINES
NOTES TO APPENDIX TABLES

**Appendix table I A**
Sub. No. : subject number
Ctr : centre
Elig : eligibility
E : eliminated from analysis(es)
I : indicative of elimination for serological reason
F : female
M : male

**Appendix table I C**
Visit 7Month (48): post-vaccination blood samplings 7 months following dose 1, etc.
VAC ND : vaccination administration not documented
VIS ND : visit not documented
BS ND : blood sampling not documented

**Appendix table III A**
PII(M7) = Blood sampling at Month 7, one month post-vaccination dose 2
PII(M36) = Blood sampling at Month 36, 36 months post-vaccination dose 1
PII(M48) = Blood sampling at Month 48, 48 months post-vaccination dose 1
Appendices
Individual Listings
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.
Appendices
Serious Adverse Events
SAE Narratives
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.
SAE Table
Protocol
Amendment 1
SmithKline Beecham Biologicals
89, rue de l’Institut
1330 Rixensart, Belgium

Confidential

SmithKline Beecham Biologicals’ combined Hepatitis A/Hepatitis B vaccine.

Protocol Number: 208127/075 (HAB-075)

Protocol Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

FIRST AMENDMENT
CPMS No. 208127/099 (EXT HAB-075) – Month 36 Follow-up
CPMS No. 208127/100 (EXT HAB-075) – Month 48 Follow-up
CPMS No. 208127/101 (EXT HAB-075) – Month 60 Follow-up

Date: June 23, 2000

Protocol HAB-075 dated July 3, 1997

Coordinating Author: [Redacted]

BACKGROUND FOR CHANGES:
The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile. To follow-up the long term antibody persistence, it was decided to bleed the volunteers at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, and to determine their anti-HAV and anti-HBs antibody titres.

THE FOLLOWING SECTIONS WERE AMENDED ON JUNE 23, 2000:
Section 4.2: Enrolment strategy/plan
Section 7: Study Procedures
Section 10: Laboratory Assays
Section 11.3: Immunogenicity
Approved by:

<table>
<thead>
<tr>
<th>Position</th>
<th>Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Director, Clinical Development</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr.</td>
<td>dd-mm-yy</td>
</tr>
<tr>
<td>Principal Investigator</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dr.</td>
<td>dd-mm-yy</td>
</tr>
</tbody>
</table>
Study Vaccine: SmithKline Beecham Biologicals’ combined Hepatitis A/Hepatitis B vaccine.

CPMS Protocol No: 208127/075 (HAB-075)

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

FIRST AMENDMENT

CPMS NO. 208127/099 (EXT HAB-075) – MONTH 36 FOLLOW-UP
CPMS NO. 208127/100 (EXT HAB-075) – MONTH 48 FOLLOW-UP
CPMS NO. 208127/101 (EXT HAB-075) – MONTH 60 FOLLOW-UP
DATE: JUNE 23, 2000

Protocol HAB-075 dated July 3, 1997

1) RATIONALE

The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile.

Present Rationale:
Open follow-up study to evaluate the long term anti-HAV and anti-HBs antibody persistence in both groups (720/20 and 1440/40), at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, by drawing blood samples from all available subjects who received the primary vaccination schedule.

2) SECTIONS AMENDED

4.2 Enrolment strategy/plan

Signed informed consent (for this amendment) will be obtained from each subject before the blood sampling.
7 Study Procedures

The intervals to be respected for the long-term time points are as summarised below.

<table>
<thead>
<tr>
<th>Interval between visits</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0 – Month 36</td>
<td>36 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 48</td>
<td>48 months ± 6 weeks</td>
</tr>
<tr>
<td>Month 0 – Month 60</td>
<td>60 months ± 6 weeks</td>
</tr>
</tbody>
</table>

The intervals between visits are indicative and should be followed as closely as possible. These intervals may determine evaluation of the subjects.

**Detailed description of study stages/visits are as follows:** At month 36 (Visit 6), month 48 (Visit 7) and month 60 (Visit 8):

- **Before each bleeding:**
  The investigator will ask each volunteer if he/she has received, since the last visit
  - a dose of hepatitis A or hepatitis B vaccine and/or
  - a dose of hepatitis A or hepatitis B immunoglobulin.
  If so, subjects will be excluded from this extended long-term follow-up study.

- **Bleeding:**
  From each subject, 7 ml of whole venous blood will be collected for testing anti-HAV and anti-HBs antibodies. Serum will be stored at −20 °C until transported to SB Bio for testing.

- **Recording of serious adverse events (SAEs):**
  Documentation of any SAE, which the subject may have experienced since the last study visit.

10 Laboratory Assays

- The presence of anti-HAV antibodies will be determined using an ELISA (Boehringer Manheim Enzymun Kit® or equivalent assay) calibrated by the use of WHO international standard reference serum and expressed in milli-International Units per milliliter (mIU/ml). The assay cut-off is 33 mIU/ml.

- Anti-HBs antibodies will be tested by radio immunoassay (RIA) using the Test-Kit from AUSAB, Abbott Laboratories, North Chicago IL, USA, or equivalent assay. The anti-HBs titres will be expressed in milli-international units per milliliter (mIU/ml). The assay cut-off is 1 mIU/ml.
• Subjects with anti-HAV antibody titres ≥ 33 mIU/ml, will be considered to be seropositive for anti-HAV antibodies. Subjects with anti-HBs antibody titres ≥ 1 mIU/ml, will be considered to be seropositive for anti-HBs antibodies. Seroprotection rate for anti-HBs is defined as the percentage of subjects with anti-HBs antibody titres ≥ 10 mIU/ml.

• All serology assays will be performed in SmithKline Beecham Biologicals’ central laboratory or in a validated laboratory designated by SmithKline Beecham Biologicals.

11.3 Immunogenicity

The elimination code for an abnormal increase in antibody titres will be assigned for the long-term follow-up. The definition of abnormal increase will depend on the magnitude of the titre reached at the first time point considered (reference value). Abnormal increase in antibody titres is defined as a two-fold increase or more in antibody titres (when the antibody titre at the reference time point is ≥ 100 mIU/ml) or a four-fold increase or more in antibody titres (when the antibody titre at the reference time point is < 100 mIU/ml). This code will be assigned to give a more realistic evaluation of the long-term persistence of antibodies.

The immunogenicity analysis will be performed on two study cohorts: the according-to-protocol study cohort (study cohort eligible for the long-term ATP analysis of immunogenicity) and the total cohort (ITT).

The long-term ATP immunogenicity analysis will include all subjects who are in the ATP immunogenicity analysis in the main study report (except for the subjects who receive the elimination code for abnormal increase in anti-HAV and/or HBs antibody titres during the long-term follow-up). The ITT analysis will be on the total cohort, which will include all subjects for whom assay results are available for anti-HAV and/or anti-HBs antibodies at long term blood sampling time point (months 36, 48 or 60).

Seropositivity rates and GMTs with 95% confidence interval (CI) for anti-HAV and anti-HBs antibodies, seroprotection rates with 95% CI for anti-HBs antibodies will be calculated. Kinetics of anti-HAV and anti-HBs GMTs will be graphically represented.
SB

SmithKline Beecham Biologicals
SmithKline Beecham Pharmaceuticals
89, rue de l’Institut
1330 Rixensart, Belgium

CONFIDENTIAL

Study vaccines: SmithKline Beecham Biologicals’ high-dose combined hepatitis A / hepatitis B candidate vaccine

Protocol n°: 208127/075 (HAB-075)

Date of approval: July 3, 1997

Title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author: [Name]
Science Writer
Clinical Research & Development

SB Responsible Physician: Dr. [Name]
Project Manager

Principal Investigators: Dr. [Name], Dr. [Name]
Australia
SmithKline Beecham Biologicals
89, rue de l'Institut
1330 Rixensart, Belgium

**Study vaccine**
SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

**Protocol n°**
208127 / 075 (HAB-075)

**Date**
July 3, 1997

**Title:**
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

**Coordinating Author**
Science Writer

**Investigator:**
Dr.

**Study site address:**
Australia

**SB responsible physician**
Dr.

**Project Manager**

**Approvals**
SmithKline Beecham Biologicals
Dr.
Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator's Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date

Signature

(Day-month-year)
Study vaccine
SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°
208127 / 075 (HAB-075)

Date
July 3, 1997

Title :
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author
Science Writer

Investigator :
Dr.

Study site address:
Australia

SB responsible physician
Dr.

Project Manager

Approvals
SmithKline Beecham Biologicals
Dr.
Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator's Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date Signature
_______________________
(Day-month-year) Dr

SYNOPSIS OF PROTOCOL 208127/075 (HAB-075)
**Vaccine under study:** SmithKline Beecham Biologicals’ combined high-dose hepatitis A / hepatitis B vaccine

**Title:** A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

**Rationale for the study:** To determine which is the optimal dose of the high-dose HAB 2-dose vaccine, with respect to immunogenicity and reactogenicity & safety in this age category.

**Indication/Study population:** To protect healthy adolescents between the ages of 11 and 18 years against hepatitis A and B.

**Objectives of the study:**

- **Primary objective**

  To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine one month after the last dose (month 7).

- **Secondary objectives:**

  To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti-HBs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
  
  To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies; seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
  
  To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

**Study design:** Double blind, randomised study with two groups. Schedule: 0, 6 months.

**Number of subjects:** 150 enrolled (75 subjects per group)

**Endpoints:**

- Primary endpoints
  
  Titres for anti-HBs antibodies at month 7.
Secondary endpoints
At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP)*** for anti-HBs antibodies
At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample

**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.

***SP is defined as anti-HBs titre ≥10 mIU/ml

Solicited signs and symptoms during a three day follow-up period. Unsolicited signs and symptoms experienced within 30 days of vaccination.
TABLE OF CONTENTS

1. INTRODUCTION 3
   1.1 Title 3
   1.2 Background 3
   1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine 4

2. STUDY CENTRES 6

3. STUDY OBJECTIVES 6

4. STUDY POPULATION 7
   4.1 Number of subjects 7
   4.2 Enrollment strategy/plan 7
   4.3 Inclusion criteria 7
   4.4 Exclusion criteria 7

5. VACCINE AND VACCINE ADMINISTRATION 8

6. STUDY DESIGN 8
   6.1 Study design 8
   6.2 Randomisation 9
   6.3 Replacement of individual vaccine doses 10

7. STUDY PROCEDURES 10

8. CLINICAL SIGNS AND SYMPTOMS 14

9. ADVERSE EXPERIENCES 15
   9.1 Eliciting and Documenting Adverse Experiences 15
   9.2 Serious Adverse Experiences 16
      9.2.1 Reporting 16
      9.2.2 Definitions 17
   9.3 Treatment of adverse experiences 18
   9.4 Assessment of severity and outcome 19
   9.5 Assessment of Causality 19
   9.6 Following up of adverse experiences 20
   9.7 Pregnancy 20

10. LABORATORY ASSAYS 20

11. STATISTICAL ANALYSIS 20
   11.1 Sample size estimation 21
   11.2 Demographics 22
   11.3 Immunogenicity 22
   11.4 Reactogenicity 22
   11.5 Interim analyses 22

Approved: July 3, 1997
1. INTRODUCTION

1.1 Title

A double-blind study to compare the immunogenicity, safety and reactogenicity of two dose levels of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

1.2 Background

Hepatitis A
HAV is classified in the family Picornaviridae, genus Heparnavirus. Seven genotypes of the virus have been identified but only one serotype comprises all of these 1. Early researchers found that suspensions of fecal samples remained infectious after treatment with acids, ether, high temperatures and even after being frozen for more than a year. HAV can be inactivated by autoclaving, boiling, exposure to high levels of formalin and ultraviolet radiation. The serological marker for previous infection with HAV (anti-HAV) can be detected early in the course of the illness and usually remains detectable in slowly declining titres for years and confers immunity to repeat infection for a lifetime.

The most common route of HAV infection is simply through swallowing food or water contaminated with small amounts of infected fecal material. Most of the viral particles are shed in feces before any symptoms of infection appear so infected individuals may unwittingly pass on the disease to many others before they fall ill themselves.

The epidemiology of hepatitis A is highly influenced by personal and public hygiene. In areas of the world where there is inadequate or non-existent provision for sewage disposal, infection occurs early in life and is almost always subclinical 2. In developing countries, exposure, infection and subsequent immunity are virtually universal in childhood. In areas where the hepatitis A virus is not in wide circulation, the population is not immune and is therefore more vulnerable to infection occurring later in life 3. One of the most important factors for disease severity is the age of the patient. Childhood infections can be asymptomatic, while almost all adults suffer from the overt disease with symptoms ranging from mild flu-like symptoms to severe gastrointestinal symptoms, fever, prolonged jaundice and severe weight loss. Nearly two-thirds of adult patients with clinically apparent disease experience complete clinical recovery within two months. Fulminant hepatitis A can occur, although rarely, and is frequently fatal particularly in the older patient. Estimates of the risk of developing fulminant hepatitis A vary. One study estimates occurrence as less than 1% 4 and another estimates it at 6.9% 5. There appears to be a positive association between mortality and age, with the death rate from symptomatic disease increasing from 0.3% for all ages to 1.8% for those aged over 50 years 6. Chronic hepatitis A does not occur but a relapsing form of the disease has been
described \(^7\); relapse occurs 2-18 weeks after the primary infection and affects 3-20% of patients with acute hepatitis A infection - after a clinical phase and subsequent recovery, including normalisation of liver enzymes, a second clinical phase with an elevation of liver enzymes occurs, persisting for up to 40 weeks.

### Hepatitis B

HBV is classified in the family *Hepadnaviridae*, genus *Orthohepadnavirus*. Five genotypes of the virus have been identified but only one serotype comprises all of these. The outer coat of the virus or nucleocapsid is a complex structure containing several proteins including the surface antigen, HBsAg, which is recognised by the antibodies raised by the immune system to combat the virus: the anti-HBs antibody. Natural infection with hepatitis B virus leads to life-long detectable anti-HBs antibody in most individuals. Two other antibodies are also produced by the immune system - anti-HBc and anti-HBe which target the core and e antigens respectively. The presence of HBsAg indicates that the host has been infected and is contagious. Anti-HBc is the first antibody to appear after infection and remains present in the serum even after recovery from the illness and can be detected for years up to the lifetime of the patient.

Blood has long been recognised as a major vehicle for the transmission of hepatitis B virus. Four major modes of transmission are recognised: vertical (also known as perinatal), horizontal, parenteral/percutaneous and sexual. The age of infection is the primary correlate for route of infection. In areas of intermediate and high endemicity of the disease, infection occurs early in life through mother-child transmission and through close personal contact among children \(^8\). In areas of low HBV endemicity, infection occurs primarily in adult life and by the sexual route. Individual response to the infection varies greatly. The age at which infection is acquired affects whether the infection is self-limiting or results in the chronic carrier state. Although the acute infection is more severe in adults, infections in infants and pre-school age children carry much greater risks of chronic carriage thereby increasing the risk of primary hepatocellular carcinoma and cirrhosis later in life \(^9\). The precise mechanism by which carrier rates are influenced by age is unknown, but probably relates to the effect of age on the immune system's ability to eliminate a hepatitis B infection. The probability that an infant will become a chronic carrier if infected is about 90% in the first two years, about 50% at 3 years of age, and 6% to 10% from 6 years of age to adulthood \(^10\).

Up to one-third of individuals with laboratory evidence of infection, *i.e.*, serological markers, experience no symptoms, and so exhibit subclinical infection \(^11\). One-third of patients experience a mild flu-like illness without jaundice and another third develop full-blown jaundice with dark urine, extreme fatigue, anorexia and abdominal pain \(^12\). Individuals infected with hepatitis B may either proceed to full recovery or may become chronic carriers of virus. About 5% of the world’s population (around 350 million persons) are chronic carriers of hepatitis B \(^13\). About a quarter of these carriers will develop serious liver disease, including chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma \(^14\).

#### 1.3 Rationale for a high-dose combined hepatitis A and hepatitis B vaccine

There is currently no specific treatment for either of these infections. It has been recognised that vaccination is the only method of conferring long-term protection against clinical disease and/or infection. SB Biologicals has a licensed combined hepatitis A / hepatitis B (HAB) vaccine, Twinrix™, which facilitates the provision of
concurrent protection against the two diseases. The increased convenience provided by the use of combined vaccines will improve compliance with vaccination schedules. Studies performed with different lots of the combined vaccine have shown that the combination is safe and immunogenic. This vaccine is administered according to a three vaccination course (0, 1, 6-month schedule). Current studies performed by SB Biologicals are focusing on a high-dose HAB candidate vaccine consisting of a two dose vaccination course (0, 6-month schedule). This candidate high-dose HAB vaccine would offer added convenience and enhance the acceptance of immunisation by both the general public and the medical community. In order to achieve this shorter vaccination schedule the composition of the candidate high-dose HAB candidate vaccine has been modified. The antigen content has been doubled and the adjuvant content has been increased. SB Biologicals uses aluminium compounds, the only adjuvants used in routine human vaccines. These compounds are known to enhance the humoral immune response.

This study is undertaken to determine which is the optimal dose of the HAB 2-dose vaccine in adolescents (11-18 years of age) by comparing immunogenicity and reactogenicity & safety in this age category elicited by the vaccine containing 1440 EL.U of inactivated hepatitis A antigen and 40 µg of recombinant hepatitis B surface antigen to that of Twinrix™,(containing 720 EL.U of inactivated hepatitis A antigen and 20 µg of recombinant hepatitis B surface antigen), both administered according to a 0, 6-month schedule.

Please refer to the Investigator Brochure for a review of the pre-clinical and clinical studies of the combined hepatitis A / hepatitis B vaccine.
2. STUDY CENTRES

Principal Investigators: Dr. [name] Dr. [name]
Study site: [location]

Australia

3. STUDY OBJECTIVES

The objectives of the present study are:

a) Primary objective
To compare the geometric mean titres (GMT) of anti-HBs antibodies elicited by the 1440/40 HAB vaccine to that of Twinrix™, (720/20) vaccine one month after the last dose (month 7).

b) Secondary objectives
To compare the immunogenicity (seroconversion rates, seropositivity rates and GMTs for anti-HAV and anti-HBs antibodies and seroprotection rates for anti Hbs antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at months 1, 2, 6.
To compare the immunogenicity (seroconversion rates, seropositivity rates for anti-HAV and anti-HBs antibodies, seroprotection rates for anti-HBs antibodies and GMTs for anti-HAV antibodies) elicited by the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine at month 7.
To compare the safety and reactogenicity of the 1440/40 HAB vaccine to that of Twinrix™ (720/20) vaccine after each vaccine dose.

The endpoints of the present study are:

Primary endpoints
Titres for anti-HBs antibodies at month 7.

Secondary endpoints
At months 1, 2 and 6: seroconversion (SC)*, seropositivity (S+)** and titres for anti-HAV and anti-HBs antibodies, and seroprotection (SP) for anti-HBs antibodies
At month 7: SC and S+ for anti-HAV and anti-HBs antibodies, SP for anti-HBs antibodies, and titres for anti-HAV antibodies

*SC is defined as the evolution of antibody titres (anti-HBs and anti-HAV) ≥ the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample
**S+ is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) ≥ the lowest sensitivity limit of the serological assay.
***SP is defined as anti-HBs titre ≥10 mIU/ml

Approved: July 3, 1997
4. STUDY POPULATION

4.1 Number of subjects

The study population will be composed of adolescent volunteers arbitrarily defined as males and females between the ages of 11 and 18 years. In order to be included in the study, subjects will have completed their 11th birthday and will have not yet attained their 18th birthday at the time of the first vaccine dose. There will be 150 subjects enrolled (75 subjects/group).

4.2 Enrollment strategy/plan

The enrollment period, e.g. the period between the first and the last enrolled subject, is maximum 12 weeks. This will be followed up by monitoring.

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.

4.3 Inclusion criteria

- Age: from 11 to 18 years of age.
- Good physical condition as established by clinical examination and history taking at the time of entry.
- Sexually active female participants will avoid becoming pregnant during the study period and they will have been on a contraceptive program for at least 2 months before entry.
- Written informed consent will have been obtained from the parents/guardians of the subjects and/or from subjects themselves depending upon local regulations.

4.4 Exclusion criteria

- History of hepatitis.
- History of previous vaccination against hepatitis A or B.
- History of significant and persisting hematologic, hepatic, renal, cardiac or respiratory disease.
- Any acute disease at the moment of entry.
- Chronic alcohol consumption.
- Hepatomegaly, right upper quadrant abdominal pain or tenderness.

Approved: July 3, 1997
5. VACCINE AND VACCINE ADMINISTRATION

The vaccines employed in the present study will be:

**SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine**

- **SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine Twinrix™**
  - Hepatitis A (Strain HM 175 - RIT 4380) : at least 720 ELISA units
  - Hepatitis B (recombinant HBsAg) : 20 µg.
  - Aluminium salt : 0.45 mg.

- **SmithKline Beecham Biologicals’ combined hepatitis A - hepatitis B vaccine**
  - Hepatitis A (Strain HM 175 - RIT 4380) : at least 1440 ELISA units
  - Hepatitis B (recombinant HBsAg) : 40 µg.
  - Aluminium salt : 0.85 mg.

The Quality Control Standards and Requirements for the study vaccines are described in separate release protocols and the required approvals have been obtained.

The vaccines will be supplied as a single 1.0 ml monodose vials for intramuscular injection in the deltoid region.

The vaccine is to be injected intramuscularly in the deltoid muscle using a 25G 1” needle. Subjects will be closely observed for at least 15 minutes post-vaccination with resuscitation facilities readily available in case of any anaphylactic reaction.

**ALL VACCINES MUST BE STORED IN THE REFRIGERATOR (+2 to +8°C) AND MUST NOT BE FROZEN.** Storage temperature should be monitored at least once per week.

The investigator is further referred to the Investigator’s Brochure for further information regarding the combined hepatitis A and hepatitis B vaccine.

6. STUDY DESIGN

6.1 Study design

Approved: July 3, 1997
This will be a double-blind, randomised study. Subjects will be randomly allocated to one of two groups to receive one of the two dose levels of the combined hepatitis A / hepatitis B vaccine in the order in which they are enrolled into the study.

6.2 Randomisation

Each monodose vial will be coded according to a randomisation list prepared by the sponsor. The randomisation will be made using an algorithm of pseudo random numbers (given by RS/1 from BBN).

The vaccines, which will be packed and supplied by the sponsor, will be labelled with the subject number, the study number and the name of the sponsor. Each subject will be given only the vaccines carrying his/her number.

6.3 Breaking the Study Blind

A set of sealed envelopes, one for each subject number and containing the identity of the vaccine given to the subject will be stored at SmithKline Beecham (sponsor). In case of a serious adverse experience, the investigator needs to notify the sponsor immediately. The sponsor will then break the code and transmit the information to the investigator. The reason for breaking the code must be recorded by the sponsor on the corresponding envelope and by the investigator in the subject’s case report form (CRF) and the medical record.
6.4 Replacement of individual vaccine doses

In addition to the vials numbered from number 1 up to the planned number of subjects, 5% additional doses from the Twinrix™ (720/20) lot will be provided to replace broken or lost vials. Subjects who shall receive replacement vials will be eliminated from reactogenicity and serology analysis.

7. STUDY PROCEDURES

As the incidence of hepatitis A and hepatitis B is very low in Australia and in order to save an additional visit for the participants, blood sampling for screening and first vaccination will be performed on the same day. In addition, vaccination of seropositive subjects has proven to be safe and results in a boost in antibody titre.

IMPORTANT: An interval of 30 days ± 7 days is planned between:
- day 0 and month 1
- month 1 and month 2
- month 6 and month 7
An interval of 180 days ± 14 days between:
- day 0 and month 6.

The intervals indicated here will serve as a target and not as an absolute criteria for inclusion or exclusion from the study but should be followed as much as possible. However, if circumstances dictate other intervals, this will not necessarily lead to the exclusion of the subject(s) from analysis.

Details of the study procedures are as follows:

**DAY 0:**

**Screening of volunteers/Vaccine dose 1**

Visit 1

* Informed consent obtained from parents/guardians of subjects and/or from subjects themselves depending upon local regulations.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HBs, anti-HBc, anti-HAV antibody and HBsAg measurement in SmithKline Beecham Biologicals’ laboratory (SB Biologicals), storage (at -20°C).
* History taking and physical examination (including axillary body temperature). Include documentation of baseline symptomatology.
* Inclusion/exclusion criteria.
* Individual Case Report Forms will be filled in by the investigator.
* IM administration of the first vaccine dose (coded monodose vial) in the deltoid region
* Each vaccinee will be closely observed for 15 minutes following vaccination.
* Provision and explanation of diary card.

Approved: July 3, 1997
SmithKline Beecham Biologicals

SmithKline Beecham Biologicals’ combined hepatitis A/hepatitis B vaccine 208127/075 (HAB-075)

-11-

* Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

♦ DAYS 1 TO 3 AFTER VISIT 2

* In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs and symptoms on a diary card provided by the sponsor (see also section 8).

MONTH 1 : Follow-up visit
(30±7 days vs Day 0)
Visit 2
* Checking and collection of diary cards (completion of data concerning the local and/or general symptoms).
* Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 2 : Follow-up visit
(60±7 days vs Day 0)
Visit 3
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C.

MONTH 6 : Second vaccination
(180±14d. vs Day 0)
Visit 4
* Physical examination (if deemed necessary by the investigator).
* Documentation of baseline symptomatology.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C
* IM administration of the last dose (coded monodose vial) in the deltoid region
* Each vaccinee will be closely observed for 15 minutes after vaccination.
* Provision and explanation of diary card.
* Recording by the vaccinee or parent/guardian of axillary body temperature, local and general reactions 5-9 hours post injection on diary cards provided by the sponsor.

♦ DAYS 1 TO 3 AFTER VISIT 4

* In the morning, the vaccinee or parent/guardian will record axillary body temperature and general and/or local clinical signs and symptoms on a diary card provided by the sponsor (see also section 8).

Approved: July 3, 1997
MONTH 7: Closure of the study
(30 ± 7 d. vs Month 6)
Visit 5

* Checking and collection of diary cards
  (completion of data concerning the local and/or general symptoms).
* Documentation of any “other” (specify) adverse events which the vaccinee has experienced since the last visit.
* Collection of 10ml of whole venous blood to be centrifuged and separated for anti-HAV and anti-HBs antibody measurement in SB Biologicals - storage at -20°C

Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥ 10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.
Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titre ≥10 mIU/ml and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine.

Approved: July 3, 1997
8. CLINICAL SIGNS AND SYMPTOMS

After each vaccination, the subject will record on diary cards the local reactions and general symptoms, including axillary body temperature in the evening 5-9 hours post vaccination and thereafter every morning for 3 days.

The following signs and symptoms will be solicited:

**General symptoms:**
- Temperature*
- Headache*
- Fatigue*
- Gastrointestinal symptoms*
- Others (please specify)*

**Local reactions:**
(Injection site)
- Soreness*
- Redness **
- Swelling **
- Others (please specify)*

* Signs and symptoms will be scored as:

0 : No adverse experience.
1 : Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
2 : Adverse experience sufficiently discomforting to interfere with daily activities.
3 : Adverse experience which prevents normal everyday activities and necessitates medical advice. (In an adult, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.

(see also section 9.4)

**The size of redness and swelling will be obtained by measuring their largest diameter and scored at SmithKline Beecham Biologicals as follows:**

1 : 1 ≥30mm
2 : > 30 mm
3 : > 30 mm and persisting more than 24 hours.

°The temperature will be recorded only when it is 37.5°C or above and will be scored at SmithKline Beecham Biologicals as follows:

1 : 37.5°C-38.0°C
2 : >38.0°C-39.0°C
3 : >39.0°C

The vaccinees will be instructed to return the completed diary card with signs/symptoms on the next visit.

Approved: July 3, 1997
On that occasion, the forms completed by the vaccinee will be transcribed into the CRF by the clinical investigator after checking for completion and accuracy.

The relationship of any solicited or unsolicited symptom (those listed under “Others”) to the study vaccine will be assessed by the investigator and recorded in the CRF (see section 9.5).

**Medication**

Any concomitant medication administered during the period extending from 1 month prior until 1 month after each vaccination will be recorded in the medication section of the Case Report Form including: name, medical condition, code, start and end dates of treatment. Medications which do not need to be recorded include any homeopathic remedies, vitamins and contraceptives.

For antipyretics/analgesics, it should be specified whether they were given prophylactically or to treat an existing symptom (therapeutic use). If used prophylactically in anticipation of vaccines reaction, please code as "P" within the "medical indication" field of the Case Report Form.

**9. ADVERSE EXPERIENCES**

The recording of adverse experiences is an important aspect of study documentation. Detailed guidelines are set out hereafter.

**9.1 Eliciting and Documenting Adverse Experiences**

It is the responsibility of the investigator to document all adverse experiences which occur within 30 days after each dose administration of the study vaccine.

An adverse experience includes any noxious, pathologic or unintended change in anatomical, physiologic or metabolic function as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of the clinical trial whether associated with vaccine and whether or not considered vaccine related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses or vaccine or drug interaction, or (if applicable) the significant worsening of the disease under investigation that is not recorded elsewhere in the case report form under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study (if applicable), that do not represent a clinically significant exacerbation or worsening need not be considered adverse experiences. Discrete episodes of chronic conditions occurring during a study period should be reported as adverse experiences in order to assess changes in frequency or severity.

All adverse experiences which occur within thirty days after each dose either observed by the investigator or one of his clinical collaborators, or reported by the patient spontaneously or in response to a direct question, will be evaluated by the investigator and noted in the adverse experience section of the subject's case record form (CRF).

Ask the subject a non-leading question such as: "Do you feel different in any way since receiving the vaccine / within 30 days after receiving the vaccine".

Approved: July 3, 1997
The nature of each experience, time of onset after vaccine administration, duration, severity and relationship to vaccination should be established. Details of changes to the vaccination schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.

Symptomatology should be documented at baseline. It is important to collect baseline information in order to interpret data from subsequent assessments.

9.2 Serious Adverse Experiences

9.2.1 Reporting

Any serious adverse experiences which occur during the clinical trial or within 30 days of receiving the last dose of study vaccine, whether or not related to the study vaccine, must be reported by the investigator to the SB clinical trial monitor by telephone, telex or telefax, within 24 hours of his becoming aware of the occurrence.

This initial notification should include:
- Study protocol number + name of principal investigator
- Vaccine study number, initials, age, sex
- Date of onset of the experience and date of administration of the study vaccine(s)
- Relationship to the study vaccine (see section 9.5.)
All information should be sent promptly to the SmithKline Beecham monitors:

Dr. ________________________
Medical Director
SmithKline Beecham
Pharmaceuticals
300, Frankston Road
Dandenong
Victoria 3175 AUSTRALIA
Tel office: ____________________
Fax: ________________________

or

Dr. ________________________
Medical Director
SmithKline Beecham
Pharmaceuticals
300, Frankston Road
Dandenong
Victoria 3175 AUSTRALIA
Tel office: ____________________
Fax: ________________________

Dr. ________________________
Project Manager
SmithKline Beecham Biologicals
89, Rue de l'Institut
B-1330 Rixensart - Belgium
Tel office: ____________________
Fax: ________________________

or

Dr. ________________________
Project Manager
SmithKline Beecham Biologicals
89, Rue de l'Institut
B-1330 Rixensart - Belgium
Tel office: ____________________
Fax: ________________________

Investigators should not wait to collect additional information to fully document the event before notifying SmithKline Beecham of a serious adverse experience. The telephone report should be followed by a full written report to include copies of relevant hospital case records, autopsy reports and other documents where applicable. Moreover, instances of death, cancer or congenital abnormality if brought to the attention of the investigator AT ANY TIME after the cessation of study vaccine AND considered by the investigator to be probably associated to study vaccine or to have a reasonable possibility of an association to study vaccine, should be reported to the SmithKline Beecham Monitor.

9.2.2 Definitions

A serious adverse experience is defined as follows:

ANY experience that, in the investigator's opinion, suggests a significant hazard to the vaccinee and will always include any event that is:

1. Fatal
2. Life-threatening
3. Disabling or incapacitating
4. Results in hospitalisation or prolongation of hospitalisation

or is:

5. A congenital abnormality (in offspring)
6. A cancer

Approved: July 3, 1997
7. An overdose of the vaccine or an adverse experience associated with an overdose (either accidental or intentional)

In addition, any adverse experience which suggests a significant hazard, contraindication, side effect or precaution that may be associated with the use of the vaccine will be considered a serious adverse experience.

Life threatening - definition:

An adverse experience is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e. it does not include a reaction that if it had occurred in a more serious form might have caused death.

Disability/incapacitating - definition:

An adverse experience is incapacitating or the patient has suffered a temporary or permanent disability if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

Hospitalisation - definition:

In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. When in doubt as to whether 'hospitalisation' occurred or was necessary, the adverse experience should be considered serious.

9.3 Treatment of adverse experiences

Treatment of any adverse experience is at the sole discretion of the investigator and according to current Good Clinical Practice. The applied measures should be reported in the Case Report Form of the vaccinee.
9.4 Assessment of severity and outcome

Maximum intensity should be scored according to one of the following categories:

0: No adverse experience
1: Adverse experience which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
2: Adverse experience sufficiently discomforting to interfere with normal everyday activities
3: Adverse experience which prevents normal everyday activities and necessitates medical advice. (In adults, such an adverse experience would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

The outcome of adverse experiences should be indicated as follows:

1: Recovered
2: Recovered with sequelae
3: Ongoing
4: Died
5: Unknown

9.5 Assessment of Causality

Every effort should be made by the investigator to explain each general adverse experience and assess its relationship, if any, to study vaccine. Causality should be assessed using the following categories:

NR: Not related The adverse experience is definitely not related to the study vaccine.

UL: Unlikely There are other more likely causes and the study vaccine is not suspected as a cause.

SU: Suspected (reasonable possibility) A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.

PB: Probable There is probably a direct cause and effect relationship between the adverse experience and the study vaccine.

The degree of certainty with which an adverse experience is attributed to the study vaccine (or alternative causes, e.g. diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of:

a) Known toxico-pharmacology of the vaccine, in pre clinical and clinical experience.
b) Reaction of similar nature previously observed with this vaccine.

Approved: July 3, 1997
c) The experience having been reported in the literature for similar vaccines.

d) The experience being related by time to vaccine administration or reproduced on re-challenge.

9.6 Following up of adverse experiences

Investigators should follow-up patients with adverse experiences until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the patient's subsequent course must be submitted to the clinical trial monitor.

9.7 Pregnancy

Subjects who become pregnant during the study should discontinue the study immediately. Subjects should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant, either during the treatment phase of the study or within 30 days after the (last) vaccination. Whenever possible, a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to SmithKline Beecham after delivery.

10. LABORATORY ASSAYS

Blood samples obtained at the first visit (Day 0) will be tested at SmithKline Beecham Biologicals' laboratory for:
- Anti-HAV, anti-HBs and anti-HBc antibodies
- HBsAg

At each next visit serum will be collected for measurement of anti-HBs and anti-HAV antibodies in SmithKline Beecham Biologicals' laboratory. Radioimmunoassay technique (RIA technique) will be used to test the presence of HBsAg (AUSAB - Abbott) and anti-HBc (Corab-Abbott).

Antibody titres (anti-HAV and anti-HBs) will be expressed in mIU/ml, with reference to World Health Organisation (WHO) standard sera. Anti-HAV antibodies will be measured at day 0, months 1, 2, 6 and 7, using Enzymun (Boehringer Mannheim) kit. The cut-off level of this test is 33 mIU/ml. Measurements of anti-HBs antibodies at day 0, months 1, 2, 6 and 7 will be performed using a commercial radioimmunooassay kit (AUSAB-Abbott). The cut-off level of this test is 1 mIU/ml.

All serum samples should be kept at -20°C.

11. STATISTICAL ANALYSIS

Taking into consideration a 10 % dropout potential and the seroprevalence of hepatitis A (there is no screening and we will exclude the HAV positive subjects from the immunogenicity analysis) 150 subjects (75/group) will be enrolled to have at least 90 (45/group) evaluable subjects

Approved: July 3, 1997
11.1 Sample size estimation

Primary objective

A sample size of 45 evaluable subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HBs between groups if the difference exceed 50%. The calculation has been made with a type I error = 5% and a type II error of 20%. For these calculation, a variability of log titres of 0.7441 for anti-HBs has been used. The variability used came from data generated from a previous study with the combined hepatitis A and B vaccine20.

Secondary objectives

A sample size of 45 subjects per group will enable us to reject the null hypothesis of equivalence of GMTs of anti-HAV between groups if the difference exceed 50%. With a type error of 5% and variability of log titres of 0.1299 for anti-HAV, we will reach a power of 97.6%. The variability used came from data generated on a previous study with the combined hepatitis A and vaccine 21.

For reactogenicity analysis, with the sample size of 45 subjects, we will be allowed to detect differences mentioned in the table hereafter with a type error of 5% and a power of 80% and a reference rate of a symptom or combination of symptoms reported by 1,2,5,10,20 and 50% of subjects 22.

<table>
<thead>
<tr>
<th>Reference rate (in %)</th>
<th>Detectable difference (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>21.7</td>
</tr>
<tr>
<td>5</td>
<td>24.1</td>
</tr>
<tr>
<td>10</td>
<td>26.8</td>
</tr>
<tr>
<td>20</td>
<td>29.9</td>
</tr>
<tr>
<td>50</td>
<td>29.9</td>
</tr>
</tbody>
</table>

Approved: July 3, 1997
11.2 Demographics

The demographic characteristics (age, sex) of the study cohort will be tabulated. The mean age, plus the range and standard deviation, by sex of the enrolled subjects, will be calculated. Similar analysis will be performed for those subjects who are included in the different analysis of reactogenicity and immunogenicity. Mean ages of groups will be compared using a Student’s t test. Ratio of males to females will be compared using either a Chi-square test or a Fisher’s exact test.

11.3 Immunogenicity

Two analyses will be performed: a first one will include only subjects corresponding to criteria defined in the protocol and a second one, called "Intention-to-treat", will include all data available from all subjects.

Seropositivity rates, seroconversion rates and geometric mean titres (GMTs) for anti-HBs and anti-HAV antibodies and seroprotection rates for anti-HBs antibodies, with 95 % confidence intervals for each antigen, will be calculated for all time points for which blood samples are taken. Seropositivity is defined, at each time point, as antibody titres (anti-HAV and anti-HBs) \( \geq \) the lowest sensitivity limit of the serological assay. Seroconversion is defined as the evolution of antibody titres (anti-HBs and anti-HAV) \( \geq \) the lowest sensitivity limit of the serological assay in a subject who was seronegative in pre-vaccination blood-sample. Seroprotection is defined as anti-HBs titre \( \geq 10 \) mIU/ml.

The GMT will be calculated using the log-transformation of seropositive titres and taking the anti-log of the mean of these transformed values. GMTs will be compared using either a Student's t test or a Mann-Whitney test. Seroconversion rates will be compared between groups using a Chi-square test or Fisher’s exact test.

11.4 Reactogenicity

The incidence of any symptom reported, local, general and local and general symptoms after each injection and overall will be evaluated, in addition to the frequency, intensity, duration (\( \leq \) or \( >1 \) day) and relationship of each individual solicited symptoms. The incidence is calculated on the number of documented diary cards. Chi-square test or Fisher’s exact test will be used to compare the proportion of subjects reporting any symptoms, local symptoms, general symptoms, local and general symptoms between groups.

11.5 Interim analyses

An exploratory analysis will be performed at month 2 for immunogenicity and for reactogenicity.

Approved: July 3, 1997
12. REFERENCES

6 ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
11 MAYNARD JE. Hepatitis B: global importance and need for control. Vaccine. 1990; 8: S18-S20.
17 ANONYMOUS. Prevention of hepatitis A through active or passive immunization. MMWR. December 27, 1996; 45.
APPENDIX A: VACCINATION RELATED SEROLOGY

Serology

All of the serum samples will be tested in SmithKline Beecham Biologicals’ laboratory at the end of the study.

Anti-HBs antibodies will be tested using radio immunoassay (Ausab-Abbott). The anti-HBs titres will be expressed in international units (mIU/ml). The lowest sensitivity limit of this assay is 1 mIU/ml.

Anti-HAV antibodies will be tested by a commercially available test, Enzymun (Boehringer Mannheim). The lowest sensitivity limit of this assay is 33 mIU/ml.

Radio immunoassay (RIA technique) will be used to test the presence of HBsAg (Austria II - Abbott) and anti-HBc (Corab-Abbott) should it be necessary to validate screening results obtained in the investigator’s laboratory.
APPENDIX B: VACCINE SUPPLIES, PACKAGING AND ACCOUNTABILITY

1. Vaccine supplies

380 single monodose vials, including 5% dose replacement from Twinrix™ (720/20) will be provided. Subjects who fail to exhibit a satisfactory immune response following the two-dose vaccine course, as evidenced by anti-HBs titres ≥ 10 mIU/ML and/or seropositivity for anti-HAV, will be provided an additional dose of the appropriate commercial vaccine. It is at no time permitted to use the supplies for other purposes than those specified in the present protocol.

2. Vaccine packaging

Each vaccine dose will be labelled and placed in a plastic pack with 25 holes. A group label will be stuck on the top of each pack. The vials will be placed in numerical order from left to right starting from the lower left hand corner, as shown:

```
  21 0  0  0  0  0 25
  16 0  0  0  0  0 20
  11 0  0  0  0  0 15
   6 0  0  0  0  0 10
   1 0  0  0  0  0  5
```

Labeling

The vial label will contain the following details:

- Study number
- Investigator's name
- Subject number
- Study vaccine name
- Lot number
- Storage conditions
- Expiry date
- "For investigational use only"
- Mode of administration
- Dose number
- MFD SmithKline Beecham Biologicals, Belgium

The group label will be similar to the vial label. It will also include the pack number and total number of packs, e.g. 3/7 = 3rd pack of 7, containing vials numbered 51-75.

Storage

Approved: July 3, 1997
The vaccines should be stored at 2 to 8°C in a safe and locked place with no access for unauthorised personnel.

3. **Vaccine accountability**

   All vaccines need to be accounted for on the appropriate forms provided by the sponsor. At any time the figures on supplied, used and remaining vaccine should match.

   All remaining product will be collected by the sponsor for destruction after the study. Unused supplies will be collected by the sponsor on completion of the study.

4. **Other supplies provided by the sponsor**

   Additionally to the vaccines and the different documents, the investigator will receive the following supplies:

   - tubes with screw caps for serum specimens
   - labels for serum identification
   - racks for the tubes of serum

   No supplies should be used outside the scope of the protocol.
APPENDIX C: ETHICAL CONSIDERATIONS AND RESPECT OF LOCAL RULES AND REGULATIONS

1. Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki, enclosed with this protocol.

2. Ethics Review Committee

The study will have been approved by the appropriate Ethics Review Committee and documentation of this approval will be submitted to SmithKline Beecham Biologicals prior to the start of the study.

3. Informed consent

The investigators will inform the volunteers in a language which they clearly understand about the aims and the possible side effects of the research trial prior to enrollment; written consent will be obtained unless local law or customs preclude this. Under the circumstances, an oral witnessed consent will be obtained. Subjects have to be informed of the fact that their data will be stored in a coded fashion in an electronic database and may be subject to an internal or external audit. (See SOP SB Bio 06). Information should be given in both oral and written form.

4. Local rules and regulations

The study will be conducted in accordance with the local rules and regulations of the country and respecting the European Commission Directive 91/507/EEC issued July 19, 1991 and effective January 1, 1992 on Good Clinical Practice.

5. Insurance

All study participants are insured according to the SmithKline Beecham Insurance policy. The study participants (or their parents or guardians) may consult this contract at any time at the investigator site.

6. Withdrawals

Subjects are free to withdraw from the study for any reason at any time. A subject will be withdrawn from the study by the investigator in case of serious adverse experience or suspected health hazard. In all cases the reason of the withdrawal must be recorded in the Case Report Form by the investigator.

Attention should be paid to proper classification of reason for withdrawal. Subjects being withdrawn while presenting on adverse experience not related to the study and not responsible for withdrawal should not be included in the listing of subjects withdrawn for adverse experiences.

Approved: July 3, 1997
7. Current edition of declaration of Helsinki

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 fulfillment 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 etiology 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 recognized 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.

Approved: July 3, 1997
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 minimize 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.

Approved: July 3, 1997
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 judgment 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.

Approved: July 3, 1997
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 judgment 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 D: ETHICAL AND REGULATORY CONSIDERATIONS IN ACCORDANCE WITH GOOD CLINICAL PRACTICE FOR CLINICAL STUDIES

I. ETHICS REVIEW COMMITTEE (ERC) / INSTITUTIONAL REVIEW BOARD (IRB)

Ethics Committees must be constituted according to the local laws/customs of each participating country.

- This protocol will be submitted to an appropriate Committee or Board and their written unconditional approval obtained and submitted to the sponsor before commencement of the study.

- SB will supply relevant data for the investigator to submit to the hospital/university/independent ERC/IRB for the protocol's review and approval. Verification of the ERC/IRB's unconditional approval of the protocol and either written informed consent or oral consent with written information to be given to the subjects/patients will be transmitted to the SB Clinical Monitor prior to shipment of drug supplies and case record forms to the site. This approval must refer to the study by exact protocol title and number, identify the documents reviewed and state the date of review.

- The ERC must be informed by the investigator of all subsequent protocol amendments and of serious or unexpected adverse events occurring during the study which are likely to affect the safety of the subjects or the conduct of the trial. Approval for such changes must be transmitted in writing to the SB Clinical Monitor.

II. INFORMED CONSENT

Information should be given in both oral and written form.

Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

- WRITTEN INFORMED CONSENT

The consent form generated by the investigator with the assistance of SB, must be approved (along with the protocol) by the Ethics Review Committee and be acceptable to SB. Consent forms must be in a language fully comprehensible to the prospective subject. Where appropriate, informed consent shall be documented by the use of a written consent form approved by the Ethics Review Committee and signed by the subject or the subject's legally authorised representative.

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

Approved: July 3, 1997
Consent must be documented either by the subject's dated signature or by the signature of an independent witness who records the subject's assent. In either event 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 SB professional and regulatory compliance persons.

- WITNESSED ORAL CONSENT

In countries where written informed consent contravenes local law or custom, informed consent may be gained orally. Full and comprehensive information must be communicated to the potential subject (or his legal representative) in the presence of a witness. The witness will be an independent third party i.e. not a nominated co-investigator. The witness will sign the Informed Consent document (testifying that informed consent has been given orally) along with the investigator (or his/her nominated representative).

III. 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 to not divert essential subjects/patients 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.

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

- Preparing and maintaining adequate case histories designed to record observations and other data pertinent to the study.

IV. STUDY DRUGS

1) STORAGE OF STUDY DRUGS

Specify clearly the site where (e.g. pharmacy or safely locked place), and conditions under which the study drugs are to be stored, as it is essential that the sponsor can be certain that the drugs will retain their safety and potency for the duration of their assigned shelf life.

2) DRUG ACCOUNTABILITY

The investigator or pharmacist must sign that he/she has received the clinical supplies for the study. The statement should contain the assurance that investigational products are handled and stored safely and properly; that investigational products are only dispensed to study subjects/patients in accordance with the protocol; that any unused products (including placebo) will be returned to SB. 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 used and unused investigational drugs (including placebo) for the stated study have been returned.

Approved: July 3, 1997
3) ASSESSMENT OF COMPLIANCE

A record of the amount dispensed, taken (and returned for out-patient studies) for each patient/subject must be recorded in the CRF. The means of assessing compliance will be described.

V. SPONSOR'S TERMINATION OF TRIAL

SmithKline Beecham 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.

VI. Protocol Amendments

No modification to the study protocol will be allowed unless discussed in detail with the SmithKline Beecham Medical Monitor and filed as an amendment to this protocol.

Any modifications to the protocol will be adhered to by the study centre (or all participating centres) and will apply to all subjects/patients following approval by the Ethical Review Committee or Institutional Review Board.

VII. CASE REPORT FORMS (CRFs)

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 patient diary cards, if applicable), will be supplied by SB for recording all data. It is the responsibility of the investigator to ensure that CRFs (and patient diary cards) are legible and completely filled in.

Principal investigators or designated physicians under his/her supervision will sign the adverse experience page(s) as well as study conclusion page of the CRF to ensure that they have reviewed the data and that the data are complete and accurate. If sections of a CRF are to be brought into SB prior to study conclusion, a section conclusion signature is required.

An original case report form must be submitted for all patients who have given informed consent and who have undergone protocol specific procedures, whether or not the patient completed the study.

For each form on which information is entered, the patient's identification (2-3 alphabet letters representing initials or first letters of patient's name), allocation number and the date of the visit number and the date of the visit must be neatly hand-written with black ink ball-point 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 initialed, dated and justified by the authorised individual making the change if it is significant. Do not obliterate, write over, or erase the original entry when making a correction.

Approved: July 3, 1997
While completed CRFs will be reviewed by an SB professional monitor at the study site, errors detected by subsequent in-house CRF review may necessitate clarification or correction of errors. All changes will be documented and approved by the investigator.

When a patient completes a study, it is anticipated that all CRFs pages will be completed as soon as possible and that they can be submitted to SB at the time of the next monitoring visit. This also applies to forms for potential study participants who were not randomised to a treatment group.

Any questions or comments related to the CRF should be directed to the assigned Study Monitor.

VIII. 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 patient, during the study at appropriate intervals and after the last patient is completed.

These visits are for the purpose of verifying adherence to the protocol and the completeness and exactness of data entered on the Case Report Forms (CRF) and Drug Inventory Forms. The monitor will verify CRF entries by comparing them with the hospital/clinic/office records which will be made available for this purpose. The monitor will retrieve completed CRF sections at each visit. Adequate time and space for these visits should be made available by the investigator.

IX. ARCHIVING OF DATA

The investigator must retain patient records and case report forms as well as drug disposition records at a maximum period of time permitted by the hospital, institution or private practice. The subject identification codes should be kept at least 15 years in accordance with Good Clinical Practices. The investigator must have a “key” linking the patient’s trial identification number (i.e. treatment number) to the patient’s clinical file. If the investigator moves or retires, he/she should nominate someone in writing to be responsible for record keeping. Archived data may be held on a microfiche or electronic record, provided that a back-up exists and a hard copy can be obtained from it if required.

SmithKline Beecham agrees to retain a copy of the protocol, documentation, approvals and all other documents related to the trial, including certificates that satisfactory audit and inspection procedures have been carried out and to provide copies to the investigator should he/she wish another copy.

X. AUDITS

For the purpose of compliance with Good Clinical Practice and regulatory agency guidelines it may be necessary for SmithKline Beecham or a drug regulatory agency to conduct a site audit.

When an investigator signs the protocol, he agrees to allow drug regulatory agency and SB auditors to inspect his/her study records. Furthermore, if an investigator refuses an inspection, his data will not be accepted in support of a New Drug Registration and/or Application.

Approved: July 3, 1997
SB has a substantial investment in clinical trials. Having the highest quality data and studies are essential aspects of drug development. SB 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 SB sponsored studies are in accordance with 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 SB audits entail review of source documents supporting the adequacy and accuracy of CRFs, review of documentation required to be maintained, and checks on drug accountability. The SB audit therefore helps prepare an investigator for a possible regulatory agency inspection as well as assuring SB of the validity of the database across investigational sites.

The Inspector will be especially interested in the following items:

- Visits from the sponsor's representatives
- Ethical Review Committee approval
- Study vaccine accountability
- Study protocol and amendments
- Informed consent of the patients
- Medical records supportive of case report form data
- Reports to the ERC/IRB and the sponsor
- Record retention

SB will gladly help investigators prepare for an inspection.

APPENDIX E: CONFIDENTIALITY AND PUBLICATION

You agree that all information communicated to you by SmithKline Beecham Biologicals/Pharmaceuticals is the exclusive property of SmithKline Beecham Biologicals/Pharmaceuticals 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 by your or such person to any third party without the prior written consent of SmithKline Beecham Pharmaceuticals. You shall communicate the results of the work promptly to SmithKline Beecham Pharmaceuticals.

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 study monitor. SmithKline Beecham will undertake to comment on such documents within four weeks.

All rights and interests world-wide 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 trial 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.

Approved: July 3, 1997
APPENDIX F: HANDLING OF THE SERUM SAMPLES COLLECTED BY THE INVESTIGATOR

1. COLLECTION

The whole blood (by capillary or venous route) will be collected observing appropriate aseptic conditions.

It is recommended to use Vacutainer® tubes WITH integrated serum separator (e.g. Becton-Dickinson Vacutainer® SST or CorVac® Sherwood medical) to minimise hemolysis risks and to avoid blood cell contamination of the sera when transferring serum in standard tubes.

2. RECOMMENDED PROCEDURE FOR SERUM SEPARATION

These guideline’s aim is to insure a good quality of the serum by minimising hemolysis risks, blood cell contamination of the sera or serum adverse cell toxicity at testing.

◊ Vacutainer® tubes with integrated serum separator

- Invert gently the tube several times to allow close contact with clot activator

- Keep at room temperature (18 - 20°C) for minimum 30 minutes and maximum 2 hours. If necessary due to extenuating circumstances, the room temperature incubation period may be increased beyond 2 hours but shall never exceed 24 hours.

- Centrifuge at 1100 G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).

- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.

- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.

- Identify the standard tubes with the appropriate standard label - as described here below in point 3.

Approved: July 3, 1997
Vacutainer® tubes without separator

- PRELIMINARY NOTE: NEVER USE SILICONIZED TUBES (cell toxicity!)
- Keep at room temperature (18 - 20°C) for minimum 2 hours and ideally overnight.
- Centrifuge at 2000G for 10 minutes (The conversion G in rpm depends on your centrifuge head radius and must be calculated locally).
- Transfer aseptically the serum to appropriate standard tubes using a sterile disposable pipette. Act as gently as possible to avoid red cells contamination of the serum.
- DO NOT OVERFILL this tube (max. ¾ of the total volume) to allow room for expansion upon specimen freezing.
- Identify the standard tubes with the appropriate standard label - as described here below

3. LABELLING (see the diagram hereafter)

- Use the standard labels provided by SmithKline Beecham Biologicals.
- Attach the label on the tube, first by its written paper part and than turn around the tube with the plastic transparent part so that the clear plastic part will protect the text and codification.
- To be readable, the bar code must be vertical on the tube.
- Please, do not stick the label on caps.

Approved: July 3, 1997
4. **SORTING and STORAGE**

- Tubes should be placed in the SB racks in numerical order from left to right, starting from the lower left hand corner, beginning with the pre vaccination samples series, than with the post vaccination sample series.

  *When impossible as with new sealed bag/box (IATA regulation), samples should be sorted by numeric order per batch of 20 packed in plastic bags, all those plastic bags packed together in the sealed box.*

- The tubes of serum will be stored at temperature between -20°C and -70°C in a vertical position until sent to SmithKline Beecham Biologicals.
APPENDIX G: INSTRUCTIONS FOR SHIPMENT OF SAMPLES

- Serum samples should always be sent by air unless otherwise requested by the sponsor and must be made on Mondays, Tuesdays and Wednesdays preferably.

- Serum samples should be placed in a container complying with IATA requirements with dry ice (-20°C). The completed standard serum listing form should always accompany the shipment. The Air Way Bill form should mention ‘-20°C storage’.

- ‘A “proforma” invoice, stating a value for customs purposes only should be prepared and attached to the parcel, the mention : store at -20°C should be added on this document.

- ‘Details of the shipment, including airway bill number, flight number, flight departure and arrival times should be sent by fax, two days before the shipment to: SmithKline Beecham Biologicals.

- Shipment and fax to be addressed to: SmithKline Beecham Biologicals
  Attn. Dr. [Redacted]
  Clinical Immunology
  R&D Department / Building 44
  Rue de l’institut, 89
  B - 1330 Rixensart - Belgium
  Telephone: [Redacted]
  Fax: [Redacted]

c/o MSAS Nedlloyd
Brussels National Airport
Zaventem - Belgium

- The box should be clearly identified by using stickers provided by SBBio mentioning the shipment address as well as with red stickers ‘STORE AT -20°C’
APPENDIX H: DESCRIPTION OF SERA LABELS

<table>
<thead>
<tr>
<th>Pre</th>
<th>Study day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post vacc 1</td>
<td>Study month 1</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 2</td>
</tr>
<tr>
<td>Post vacc 1</td>
<td>Study month 6</td>
</tr>
<tr>
<td>Post vacc 2</td>
<td>Study month 7</td>
</tr>
</tbody>
</table>

Approved: July 3, 1997
Protocol Agreement
AGREEMENT

SmithKline Beecham Biologicals
89, rue de l'Institut
1330 Rixensart, Belgium

Study vaccine
SmithKline Beecham Biologicals' high-dose combined Hepatitis A / Hepatitis B vaccine

Protocol n°
208127 / 075 [HAB-075]

Date
July 3, 1997

Title:
A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 ELU of hepatitis A antigen/40 µg of hepatitis B surface antigen to that of Twinrix® (containing 720 ELU of hepatitis A antigen/20 µg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Coordinating Author

Investigator:
Study site address:
Australia

SB responsible physician

Approvals
SmithKline Beecham Biologicals
Director
Clinical Development

I, the undersigned, have reviewed this protocol, including Appendices and I will conduct the study as described and will adhere to the Ethical and Regulatory Considerations delineated herein. I have read and understood the contents of the Investigator’s Brochure and I was informed on the principles and requirements of the Good Clinical Practices.

Date
25.8.97
(Day-month-year)

Dr.
NOTE TO FILE

From: [Redacted]

Subject: Study 208127/075 (HAB-075)

Date: 15 May 2001

RE: Protocol (03/07/97) signature pages

Dr. [Redacted] signature page is missing:
as Dr. [Redacted] is not working in the trial centre, it has been agreed that Dr. [Redacted] would be the only person to sign the study agreements. (see mail attached)

Internal approval signature page missing:
not present in study file, reason unknown.

Names

CSM

Date

15 May 2001

Signature
Dear Jacqueline,

Thank you very much for sending me the SB Bio Protocol Agreements for study HAB-075. However, Dr [redacted] is listed as the only Principle investigator and in fact she and Dr [redacted] are co-investigators.

[redacted] is no longer working at the centre or running the trial so [redacted] will be the one signing the Agreement, therefore it is important that her name be included.

Could you please send me the amended Agreement and I will send these copies back unless I hear otherwise from you. Thanks again.

Kind regards, [redacted]
SmithKline Beecham Biologicals
89, rue de l'Institut
1330 Rixensart, Belgium

Confidential

SmithKline Beecham Biologicals' combined Hepatitis A/Hepatitis B vaccine.

Protocol Number: 208127/075 (HAB-075)

**Protocol Title:** A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

**FIRST AMENDMENT**
CPMS NO. 208127/099 (EXT HAB-075) – MONTH 36 FOLLOW-UP
CPMS NO. 208127/100 (EXT HAB-075) – MONTH 48 FOLLOW-UP
CPMS NO. 208127/101 (EXT HAB-075) – MONTH 60 FOLLOW-UP
**DATE:** JUNE 23, 2000

Protocol HAB-075 dated July 3, 1997

**Coordinating Author:**

**BACKGROUND FOR CHANGES:**
The protocol was designed to determine the optimal dose of the combined hepatitis A/hepatitis B vaccine (720/20 or 1440/40), when administered according to a 2-dose schedule, in healthy adolescents (11-18 years). The optimal dose was determined with respect to immunogenicity, reactogenicity and safety profile. To follow-up the long term antibody persistence, it was decided to bleed the volunteers at months 36, 48 and 60 (intervals to be respected at ± 6 weeks) after the first vaccine dose of the primary vaccination course, and to determine their anti-HAV and anti-HBs antibody titres.

**THE FOLLOWING SECTIONS WERE AMENDED ON JUNE 23, 2000:**
Section 4.2: Enrolment strategy/plan
Section 7: Study Procedures
Section 10: Laboratory Assays
Section 11.3: Immunogenicity
Representative SIS/IC Amendment 1
SMITHKLINE BEECHAM BIOLOGICALS

ADDENDUM TO SUBJECT/PATIENT INFORMATION SHEET AND INFORMED CONSENT FOR THE STUDY 208127/075 (HAB-075)

Study title: A double-blind study to compare the immunogenicity, safety and reactogenicity of SmithKline Beecham Biologicals’ high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of Twinrix™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6-month schedule in healthy adolescents (11-18 years of age).

Investigator: Dr. [Name Redacted], Australia

Sponsor: SmithKline Beecham Biologicals

CPMS Protocol no.: 208127/099 (EXT HAB-075) – Month 36 follow-up
208127/100 (EXT HAB-075) – Month 48 follow-up
208127/101 (EXT HAB-075) – Month 60 follow-up

Date of approval:

Prepared by: [Name Redacted]

This document should be presented to the subject and parents/guardians of the subject in full; no page(s) or section(s) should be omitted. The document contents should be explained verbally to the participant and the parents/guardians of the participant.
Introduction

The main objective of this document is to provide the potential study participants and parents/guardians of the participants with the information necessary to help them in deciding to participate in the long-term follow-up of the HAB-075 study. The document provides a full but simple understanding of the scientific reasons, the likely effects and benefits of this long-term follow-up of the HAB-075 study. This document also informs subjects and parents/guardians of subjects about their rights, benefits, risks and responsibilities in participating in this follow-up trial.

Hepatitis A and B are diseases caused by viruses that infect the liver. The symptoms of both infections may be quite similar - characterised by fever, ill-feeling, loss of appetite, abdominal discomfort, jaundice and liver damage. Both diseases are transmitted by person-to-person contact.

There are no effective therapies against hepatitis A or hepatitis B. Vaccination, resulting in protection against both the diseases, is the best method of reducing the incidence of infection. SmithKline Beecham Biologicals has developed vaccines against both hepatitis A (Havrix™) and hepatitis B (Engerix™-B) which have shown to be protective and are available on the world market. SmithKline Beecham Biologicals has also developed a combination hepatitis A / hepatitis B vaccine (Twinrix™) which is also available on the market. This combination is known to provide simultaneous protection against both diseases.

You have / your son/daughter/ward has already received a course of SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine in the original HAB-075 study. In this long-term follow-up study, the long-term protection against hepatitis A and hepatitis B achieved by this combined hepatitis A/hepatitis B vaccine is being determined.
Approval

This addendum to subject information sheet has been reviewed and accepted by an independent ethics review committee/Institutional review board.

Study Participation

All volunteers in this long-term follow-up study-extension have received SmithKline Beecham Biologicals’ combined high dose hepatitis A/hepatitis B vaccine (1440/40) or Twinrix™ (720/20) vaccine (given according to 0, 6 months schedule), in HAB-075 study. This long-term follow-up study is designed to assess the immune response 36, 48 and 60 months after the first dose of the primary vaccination course.

Your/your son’s/daughter’s/ward’s participation in this follow-up period will require 3 visits (one visit per year) to the investigator. At each visit, 7 ml (approximately 3 ½ tablespoons) of blood will be collected to determine antibody titres.

Risks associated with the study

You/your son/daughter/ward may experience momentary mild discomfort during the blood collection. The amount to be taken will not cause any symptoms or anaemia.

Benefits of the study

The principal benefit of you/your son/daughter/ward participating in this long-term follow-up study, is the evaluation of your/your son’s/daughter’s/ward’s long-term protection against hepatitis A and hepatitis B.

Voluntary participation

Your/your son’s/daughter’s/ward’s participation is voluntary. Refusal to take part or continue with this long-term follow-up study will involve no penalty or loss of benefits or attention to which you/your son/daughter/ward is otherwise entitled to
receive from your healthcare provider. You are entitled to receive a signed copy of this form.

**Alternative measures of prevention**

Not applicable.

**Confidentiality and data access**

This section ensures that you/your son/daughter/ward benefits from the protection and the rights granted by the European Union Data Protection Directive and other national laws on the protection of your son’s/daughter’s/ward’s personal data.

You understand and consent to the following:

I. Your/your son’s/daughter’s/ward’s data, including data relating to your/your son’s/daughter’s/ward’s health, will be recorded and processed for the purpose of 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/your son’s/daughter’s/ward’s data may also be processed for product registration and for notification to organisations monitoring the safety and effectiveness of medicines. Your/your son’s/daughter’s/ward’s data may also be processed in order to add to scientific knowledge;

II. Your/your son’s/daughter’s/ward’s participation in the study will be treated as confidential. You/your son/daughter/ward will not be referred to by name in any report on the study and your/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical data or study samples (e.g. 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 access your/your son’s/daughter’s/ward’s personal data and 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/your son’s/daughter’s/ward’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/your son’s/daughter’s/ward’s medical records may be accessed by representatives of SB Bio or regulatory bodies for medicines.

**Right to ask questions and/or withdraw from the long-term study follow-up**

You may ask questions about the study. Although your continuous support is appreciated, you have the right to withdraw yourself/your son/daughter/ward from this long-term study-extension at any time and you/your son/daughter/ward will be under no further obligation for blood samplings.

If you have any questions, please contact:

**Name of investigator:**
Dr.

**Address of investigator:**
[Redacted]

**Telephone number of investigator:**
Australia
Compensation

If you become/your son/daughter/ward 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 you have/your son/daughter/ward has experienced a research-related illness or injury, please contact:

Name of investigator:  
Address of investigator:  
Telephone number of investigator:  

Informed Consent for the long-term follow-up
(adolescents/minors)

The 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 study.

Participant’s Name: ________________________________
(First Name, Family Name)

Participant’s signature (where applicable): ________________________________

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: __________________________________________

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 consent form.

Name: __________________________________________

Signature: __________________________________________

Designation: __________________________________________

Date: _______________ Time: _______________

(DD-MM-YY)
Informed Consent for the long-term follow-up (adults)

The aims and procedures of the study have been clearly explained to me and I have read the preceding information sheet and understood the information provided. I agree to be enrolled in the study. I understand that I have the right to decline to enter the study and to withdraw from it at any time for any reasons, without consequence to my present or future health care and attention, which I receive from my healthcare provider. I have been made aware of my right to access and request correction of my personal data. I acknowledge that I have received a copy of this form for future reference.

I, ______________________________, (subject’s first name and family name)

hereby freely give my consent to take part in this [clinical/vaccine] study.

Participant’s signature: ______________________________

Participant’s main address: ______________________________

Participant’s phone number: ______________________________

Date: ____________________ Time: ____________________

(DD-MM-YY)

Witness: ______________________________
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 consent form.

Name: ________________________________________________

Signature: ______________________________________________

Designation: ______________________________________________

Date: ___________________ Time: ___________________

(DD-MM-YY)
Investigator CV
This section contained Principal Investigator’s Curriculum Vitae and has been excluded to protect Principal Investigator privacy.
GlaxoSmithKline Biologicals
Clinical Research and Development
Clinical Study Report Approval form

Report number: 208127/100 and 208127/101 (Ext-HAB-075) Annex-2

Study title: A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 EL.U of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of TWINRIX™ (containing 720 EL.U of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6 month schedule in healthy adolescents (11-18 years of age).

Report date: 7 December 2004

Report prepared by:

Scientific Writer

Report reviewed by:

Biometrician

Central Study Coordinator

Pascale Vandoolaeghe

Regulatory

Signature/ Date
| **GlaxoSmithKline Biologicals**  
| **Clinical Research and Development**  
| **Clinical Study Report Approval form**  

**Report number:** 208127/100 and 208127/101 (Ext-HAB-075) Annex-2  
**Study title:** A double-blind study to compare the immunogenicity, safety and reactogenicity of GlaxoSmithKline Biologicals' high-dose combined hepatitis A/B (HAB) vaccine containing 1440 ELU of hepatitis A antigen/40 mcg of hepatitis B surface antigen to that of TWINRIX™ (containing 720 ELU of hepatitis A antigen/20 mcg of hepatitis B surface antigen), both administered following a 0, 6 month schedule in healthy adolescents (11-18 years of age).  

**Report date:** 7 December 2004  

**Report accepted by:** Archana S  
Clinical Project Manager, Hepatitis  

**Report approved by:** Bernard Hoet  
Director, Clinical R & D, Hepatitis and Travelers vaccines  

| 15/12/04 |