Synopsis of study HBV-306 (101698)

Pharmaceutical entrepreneur:
GlaxoSmithKline GmbH & Co. KG
Prinzregentenplatz 9
81675 Munich
Germany

Personal identifiable data of investigators (name / full postal address) are not published in this report, as consent according to Section 4a of the German Federal Act on Data Protection is not available for any of the investigators.
The study summarized below may involve approved and non-approved uses, formulations or treatment regimens. The results reported for any single study may not reflect the overall results obtained during all studies involving the same product. Before prescribing any product mentioned in this Register, healthcare professionals should consult the prescribing information for the product approved in their country.

<table>
<thead>
<tr>
<th>Name of company:</th>
<th>GlaxoSmithKline Biologicals, Rixensart, Belgium.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of finished product:</td>
<td>Engerix™-B</td>
</tr>
<tr>
<td>Name of active substance:</td>
<td>Recombinant hepatitis B surface antigen</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study No.: 101698 (HBV-306 EXT:280 Month 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title of the study: A phase III, single-blinded, randomised, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals' thiomersal-free 2-dose Engerix™-B and 3-dose preservative-free Engerix™-B vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).</td>
</tr>
<tr>
<td>Note: Data pertaining to the long-term follow-up (LTFU) study for evaluation of anti-HBs antibody persistence at Months 30, 42, 54 and 66 after the first dose of primary vaccination are presented in this report.</td>
</tr>
<tr>
<td>Study centres: The study was conducted at four centres (two centres in Belgium and one centre each in Ukraine and Australia).</td>
</tr>
<tr>
<td>Study period: Primary Study Initiation Date: 10 September 2001 Primary Study Completion Date: 07 February 2003 Long-term Follow-up at M30 Initiation Date: 21 April 2004 Long-term Follow-up at M66 Completion Date: 10 January 2008</td>
</tr>
<tr>
<td>Objective: The objectives of the primary study are stated in the 103860/280 (HBV-280) study report. The objective of the LTFU study was:</td>
</tr>
<tr>
<td>• To evaluate anti-HBs antibody persistence at Months 30, 42, 54 and 66 after the first vaccine dose of primary vaccination.</td>
</tr>
<tr>
<td>Study design: The primary study was a self-contained, single-blind, randomised, multicentric, multicountry study with two parallel groups (Group 1 and Group 2). The two study groups in the primary study were:</td>
</tr>
<tr>
<td>• Group 1 received two doses of thiomersal-free Engerix-B vaccine at 0 and 6 months, with placebo at Month 1.</td>
</tr>
<tr>
<td>• Group 2 received three doses of preservative-free Engerix-B vaccine at 0, 1 and 6 months.</td>
</tr>
<tr>
<td>The LTFU study at Months 30, 42, 54 and 66 was a multicentric, multicountry study with the same two groups. At each visit, a blood sample was taken from all subjects and any serious adverse event (SAE) that had occurred since the last study visit and considered by the investigator to have a causal relationship to primary vaccination or related to lack of vaccine efficacy/ study participation was to be documented.</td>
</tr>
</tbody>
</table>

**Table 1: Subject attrition per group**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects enrolled in the primary study</td>
<td>384</td>
<td>258</td>
<td>126</td>
</tr>
<tr>
<td>Number of subjects included in the according-to-protocol (ATP) cohort for immunogenicity in the primary study</td>
<td>354</td>
<td>241</td>
<td>113</td>
</tr>
</tbody>
</table>
### Number of subjects

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Total</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>who returned for blood sampling at Month 30</td>
<td>267</td>
<td>179</td>
<td>88</td>
</tr>
<tr>
<td>included in the long-term (LT) ATP cohort for immunogenicity at Month 30</td>
<td>204</td>
<td>140</td>
<td>64</td>
</tr>
<tr>
<td>who returned for blood sampling at Month 42</td>
<td>258</td>
<td>174</td>
<td>84</td>
</tr>
<tr>
<td>included in the LT ATP cohort for immunogenicity at Month 42</td>
<td>246</td>
<td>166</td>
<td>80</td>
</tr>
<tr>
<td>who returned for blood sampling at Month 54</td>
<td>245</td>
<td>166</td>
<td>79</td>
</tr>
<tr>
<td>included in the LT ATP cohort for immunogenicity at Month 54</td>
<td>224</td>
<td>148</td>
<td>76</td>
</tr>
<tr>
<td>who returned for blood sampling at Month 66</td>
<td>234</td>
<td>158</td>
<td>76</td>
</tr>
<tr>
<td>included in the LT ATP cohort for immunogenicity at Month 66</td>
<td>202</td>
<td>132</td>
<td>70</td>
</tr>
</tbody>
</table>

#### Diagnosis and criteria for inclusion
At the time of initiation of the LTFU study, subjects and/or parents/guardians of subjects who had been enrolled in the primary study were contacted. Written informed consent was obtained from the subjects before they were enrolled in the LTFU study.

### Study vaccine, dose, mode of administration and lot no.:  
**Vaccination schedule/site:** Two doses of thiomersal-free Engerix-B administered as an intramuscular injection in the deltoid muscle of the non-dominant arm according to a 0, 6 month schedule in the primary study.  
**Vaccine composition/dose/lot number:** One dose of Engerix-B vaccine contained HBsAg and aluminium salt. Lot number: DENS001A4 (expiry date: 28 February 2003).

### Reference vaccine/Comparator, dose and mode of administration, lot no.:  
**Vaccination schedule/site:** Three doses of preservative-free Engerix-B administered as an intramuscular injection in the deltoid muscle of the non-dominant arm according to a 0, 1, 6 month schedule in the primary study.  
**Vaccine composition/dose/lot number:** One dose of Engerix-B vaccine contained HBsAg and aluminium salt. Lot number: ENG5010B2 (expiry date: 18 December 2003).

### Duration of study:  
Approximately 66 months for each subject.

### Criteria for evaluation:  
**Immunogenicity:** Anti-HBs antibody concentrations were measured 30, 42, 54 and 66 months after the first dose of the primary vaccination. Anti-HBs concentrations were measured using enzyme-linked immunoassay (EIA).

**Safety:** SAEs reported since the last follow-up study visit and considered to be related to the primary vaccination course, to lack of vaccine efficacy or to study procedures were to be documented.

### Statistical methods:  
**Demography:** 
- Demographic characteristics at Months 30, 42, 54 and 66 (age in years, gender, and race) were tabulated per group and overall. The mean age (plus range and standard deviation) of the subjects was calculated.

**Immunogenicity: Evaluation of antibody persistence:** LT anti-HBs antibody persistence 30, 42, 54 and 66 months after the first dose of the primary vaccination course was evaluated per group and overall on the LT ATP cohort for immunogenicity and additionally on the LT Total cohort using the following analyses:
- The seropositivity rates, percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml and geometric mean concentration (GMCs) with 95% confidence intervals (CI) at each time-point were tabulated for the two cohorts. GMC was calculated on seropositive subjects.
- The evolution of anti-HBs antibody GMCs over time was graphically presented for the LT ATP cohort for immunogenicity.
- The distribution of anti-HBs antibody concentrations were graphically presented using reverse cumulative curves (RCC) for the LT ATP cohort for immunogenicity.

**Safety:** The safety analysis was to be performed on the LT Total cohort. Any SAEs which the subject experienced since the last study visit and that were determined by the investigator to have a causal relationship to vaccination were to be described individually along with the nature of the SAEs and the outcome. Any SAE, related to lack of vaccine efficacy (hepatitis B infection) or study procedures during the LTFU study, was to be described in detail.

### Summary:  
**Demography (LT ATP cohort for immunogenicity):** At Month 66, the mean age of the subjects was 18.4 years. The percentage of females was 51.5%. The subject population was predominantly (99.5%) White/Caucasian.
Immunogenicity: Anti-HBs antibody persistence (LT ATP cohort for immunogenicity)

At Month 66:
- The anti-HBs seropositivity rate was 92.4% in Group 1 and 98.6% in Group 2.
- The percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml was 79.5% in Group 1 and 91.4% in Group 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>Timing</th>
<th>N</th>
<th>S+ ≥ 10 mIU/ml</th>
<th>GMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PI (M1)</td>
<td>240</td>
<td>45</td>
<td>18.8</td>
</tr>
<tr>
<td></td>
<td>PI (M2)</td>
<td>240</td>
<td>50</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>PI (M6)</td>
<td>239</td>
<td>94</td>
<td>39.3</td>
</tr>
<tr>
<td></td>
<td>PI (M7)</td>
<td>241</td>
<td>235</td>
<td>97.5</td>
</tr>
<tr>
<td></td>
<td>PI (M30)</td>
<td>140</td>
<td>128</td>
<td>91.4</td>
</tr>
<tr>
<td></td>
<td>PI (M42)</td>
<td>166</td>
<td>151</td>
<td>91.0</td>
</tr>
<tr>
<td></td>
<td>PI (M54)*</td>
<td>147</td>
<td>135</td>
<td>91.8</td>
</tr>
<tr>
<td></td>
<td>PI (M66)</td>
<td>132</td>
<td>122</td>
<td>92.4</td>
</tr>
</tbody>
</table>

Group 1 = subjects received 2 doses of thiomersal-free Engerix-B at Months 0, 6 in the primary study.
Group 2 = subjects received 3 doses of preservative-free Engerix-B at Months 0, 1 and 6 in the primary study.
S+ : Seropositivity was defined as anti-HBs antibody concentration ≥ 3.3 mIU/ml
GMC: geometric mean antibody concentration calculated on seropositive subjects
n (%): number (percentage) of subjects with concentration ≥ the specified cut-off.
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

PII (M66): Blood sampling after the second dose; 66 months after the first dose of primary vaccination course
PII (M30): Blood sampling after the third dose; 66 months after the first dose of primary vaccination course
*: From the primary study up to Month 42, anti-HBs antibody concentrations were tested with a commercial ELISA assay. From Month 54 onwards, anti-HBs antibody concentrations were tested with an in-house ELISA assay.

Safety:
Serious adverse events: None of the subjects reported SAEs causally related to the primary vaccination course, study procedures or lack of vaccine efficacy during the LTFU study.
Pregnancies: Since no vaccines were administered during the LTFU phase, no pregnancies were recorded.

Conclusions:
Sixty-six months after the primary vaccination of healthy adolescents (11-15 years) with either two doses of Engerix-B [Group 1] or three doses of Engerix-B [Group 2],
- The anti-HBs seropositivity rate was 92.4% in Group 1 and 98.6% in Group 2.
- The percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/ml was 79.5% of subjects in Group 1 and 91.4% of subjects in Group 2.
- None of the subjects reported any SAE causally related to vaccination, lack of vaccine efficacy or study procedures during the LTFU study.

Date of report: 07 July 2009
Appendix 1 to Synopsis for study
HBV-306 (101698)

Overview of Protocol Amendments

Excerpt from protocol including final amendment version 3
dated 08-Dec-2006
Amendments and Modifications to the Protocol

GlaxoSmithKline Biologicals.
Rue de l'Institut 89
1330 Rixensart, Belgium

Protocol Number: 103860/280 (HBV-280) dated 4 July 2001
Third Amendment Date: 8 December 2006

NOTE: THE CPMS No. FOR THE MAIN PROTOCOL AND THE eTRACK NOS. FOR THE LONG-TERM FOLLOW-UP STUDIES DIFFER

| eTRACK No. 101695 (HBV-303 EXT:280 Month 30) |
| eTRACK No. 101696 (HBV-304 EXT:280 Month 42) |
| eTRACK No. 101697 (HBV-305 EXT:280 Month 54) |
| eTRACK No. 101698 (HBV-306 EXT:280 Month 66) |

Protocol Title: A phase III, single-blinded, randomized, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals' thiomersal-free 2-dose Engerix-B and 3-dose preservative-free Engerix-B vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).

First amendment date: 9 August 2001
First modification date: 15 January 2002
Second amendment date: 2 February 2004

RATIONALE FOR CHANGES:

The protocol was previously amended (2 February 2004) to evaluate the persistence of humoral immune response at Months 30, 42, 54 and 66 after the first dose of primary vaccination. The amendment also stated that if a subject loses seroprotective concentrations for anti-HBs antibodies (i.e. concentrations < 10 mIU/ml) at the longterm blood sampling time point (i.e. Months 30, 42, 54 and 66), he/ she will be offered an additional vaccine dose 6-12 months after Month 66, where his/ her immune response to the additional vaccine will be evaluated.

The protocol is currently being amended to state that subjects who had anti-HBs antibody concentrations <10mIU/ml will not receive an additional vaccine dose as foreseen in this study (101698: HBV-306 EXT: 280 Month 66). All subjects in this study (irrespective of their seroprotective status) will be invited to participate in a separate hepatitis B vaccine challenge study, 108988 (HBV-314 BST: 280).

Study HBV-314 will be conducted in subjects primed in study HBV-280, after completion of the last follow-up (Month 66), and will evaluate immunological memory to hepatitis B in term of the ability to mount an anamnestic response to an additional vaccine dose of hepatitis B vaccine.

Thus, all study procedures related to additional vaccine dose in the second protocol amendment of study 103860 (HBV-280) dated 2 February 2004 are not applicable.

Also the address of an investigator and his study center is being updated in this amendment.
The following sections of the main protocol were amended:

Section 1: Rationale

The protocol is currently being amended to state that subjects who had antibody concentrations <10 mIU/ml will not receive an additional vaccine dose in this study, as all subjects in this study (irrespective of their seroprotective status), will be approached to participate in another study, 108988 (HBV-314 BST:280). Study HBV-314, will be conducted in subjects primed in study HBV-280, after completion of the last follow-up (Month 66), and will evaluate immunological memory to hepatitis B in terms of the ability to mount an anamnestic response to an additional vaccine dose of hepatitis B vaccine. Thus, all study procedures related to additional vaccine dose in the second protocol amendment of study 103860 (HBV-280) dated 2 February 2004 are not applicable.

Section 2: Objectives

Section 3: Objectives reached to participate in another study, 108988 (HBV-314 BST:280).

Seroprotective titres for anti-HBs antibodies (i.e. titres < 10 mIU/ml) at Months 30, 42, 54 and 66 and who received an additional vaccine dose (administered between 6 to 12 months after the Month 66 time point).

Section 5.3: Outline of study procedures

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

<table>
<thead>
<tr>
<th>Interval between visits</th>
<th>Size of interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0 to Month 30 (Visit 6)</td>
<td>30 months ± 2 months</td>
</tr>
<tr>
<td>Month 0 to Month 42 (Visit 7)</td>
<td>42 months ± 2 months</td>
</tr>
<tr>
<td>Month 0 to Month 54 (Visit 8)</td>
<td>54 months ± 2 months</td>
</tr>
<tr>
<td>Month 0 to Month 66 (Visit 9)</td>
<td>66 months ± 2 months</td>
</tr>
<tr>
<td>Month 66 to Additional vaccination (Visit 10)</td>
<td>6 to 12 months</td>
</tr>
<tr>
<td>Additional vaccination visit to blood sampling visit (Visit 11)</td>
<td>30 ± 7 days</td>
</tr>
</tbody>
</table>

Note: Month 0 = the first vaccine dose of the two-dose or three-dose primary vaccination

Additional vaccination (Visit 10) and blood sampling (Visit 11):

If a subject loses seroprotective titres for anti-HBs antibodies (i.e. titres < 10 mIU/ml) at the long-term blood sampling time point (i.e. Month 30, 42, 54 and 66), he/she will be offered an additional vaccine dose. The additional vaccine dose will be administered to the subject between 6 to 12 months after the long-term blood sampling visit at Month 66.
Visit at Month 66. etc between 6 to 12 months after the long-acting Engerix-B (20 µg).

The description of the procedures that will be performed prior to additional vaccination are as follows:

- Check contraindications to vaccination.
- Vaccination assessment of body temperature. If a subject has oral/axillary temperature ≥ 37.5 °C or rectal temperature ≥ 38 °C at the time scheduled for vaccination, the subject may be vaccinated at a later date, within the specified time window (see Section 5.3).
- Complete assessment of medical history and physical examination.

Concomitant medication (i.e. any immunosuppressants or other immune-modifying drugs or treatments, any vaccine other than the study vaccine and any antipyretics or antibiotics administered at any time during the period starting 30 days prior to the vaccine dose and ending one month (minimum 30 days) after the vaccine dose must be recorded in the CRF with trade name and/or generic name of the medication, medical indication, total daily dose, route of administration, start and end dates of treatment. Any other concomitant medication administered prophylactically in anticipation of reaction to the vaccination must also be recorded in the CRF with trade name and/or generic name of the medication, total daily dose, route of administration, start and end dates of treatment and coded as "Prophylactic."

- Treatment and coded as "Prophylactic.
- Investigator. Female subjects of childbearing age will be instructed by the investigator to take adequate contraceptive measures for 30 days prior to vaccination and up to two months after vaccination.

The vaccine will be administered as a deep intramuscular injection in the deltoid region of the non-dominant arm.

The vaccinees will be observed closely for at least 30 minutes after administration of additional vaccine dose, with appropriate medical treatment readily available in case of
a rare anaphylactic reaction following the administration of vaccine.

The subject and/or parent or guardian of the subject will be instructed to contact the investigator immediately should they (i.e. the subject) manifest any signs or symptoms they perceive as serious during the period extending from administration of the additional vaccine dose.

After the administration of the additional vaccine dose, there will be a follow-up for the occurrence of:

= solicited local/general symptoms during the 4-day (Day 0 to Day 3) follow-up period after vaccination.

= unsolicited symptoms (local/general) during the 30-day (Day 0 to Day 29) follow-up period after vaccination.

= SAEs during the follow-up period after vaccination (minimum 30 days).

One month after the additional vaccine dose is administered (i.e. at Visit 11), a blood sample of 7 ml will be taken from these subjects.

□ Recording of SAEs after additional vaccination:

The investigator will question the subject and/or parent or guardian of the subject and document:

= Any SAE which the subject may experience after additional vaccination.

= Any event related to a lack of vaccine efficacy (i.e. hepatitis B infection) will also be reported as SAEs.

Section 8.5.2 Reporting serious adverse events

The contact details for reporting serious adverse events (SAEs) has been updated to:

Study Contact for Reporting SAEs

GSK Biologicals Clinical Safety Physician

Tel: +32 2 656 8850

Fax: +32 2 656 51 16 or +32 2 656 80 09

Mobile phones for 7/7 day availability:

+32 477 404 713

Back-up mobile phone contact:
Section: 10.5.2.2 Analysis on subjects receiving the additional vaccine dose:

For subjects who will receive the additional vaccine dose between 6 to 12 months after Month 66 time point, the immunogenicity response will be evaluated as follows:

- Seropositivity rates, seroprotection rates and GMTs with 95% CI will be tabulated by group at pre-vaccination and post-vaccination time points for all cohorts. GMTs will be calculated for seropositive subjects.

- Be tabulated by group for the LT-ATP immunogenicity cohort.

Section: 10.5.3.2 Analysis on subjects receiving the additional vaccine dose

For subjects who will receive the additional vaccine dose between 6 to 12 months after Month 66 time point, safety and reactogenicity will be evaluated as follows:

- Individual solicited adverse event during the 4-day (Day 0 to Day 3) follow-up period after additional vaccination will be tabulated, in addition to the incidence of grade 3. symptoms and incidence of solicited general symptoms with causal relationship to vaccination.

- Relationship to vaccination with at least one report of an unsolicited symptom, classified by the Medical Dictionary for Regulatory Affairs (MedDRA), during the 30-day (Day 0 to Day 29) follow-up period after vaccination will be tabulated. The same tabulation will be performed for unsolicited symptoms considered by the investigator to have a causal relationship to vaccination.

- To have a causal relationship to vaccination, considered by the investigator will be described in detail.
Protocol Title: A phase III, single-blinded, randomized, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals’ thiomersal-free 2-dose Engerix-B and 3-dose preservative-free Engerix-B vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).

First amendment date: 9 August 2001

First modification date: 15 January 2002

RATIONALE FOR CHANGES:

The clinical study protocol 103860/280 (HBV-280) was designed to evaluate the immunogenicity of 3-dose primary vaccination course of preservative-free Engerix™-B administered at 0, 1, 6 months compared to a 2-dose vaccination course of thiomersal-free Engerix™-B administered at 0, 6 months.

Results from the primary study have shown the vaccine to be safe with a good immune response. Anti-HBs seroprotection rate was 96.7% in group receiving thiomersal-free Engerix™-B and 98.2% in group receiving preservative-free Engerix™-B, one month after the primary vaccination course i.e. at Month 7.

The protocol is currently being amended to evaluate the persistence of humoral immune response at Month 30, 42, 54 and 66 after the first dose of primary vaccination.

To evaluate the long-term antibody persistence, volunteers will be bled at Months 30, 42, 54 and 66 (intervals to be respected at ±2 weeks to evaluate the long-term antibody persistence, volunteers will be bled at Month 66 to determine their anti-HBs antibody titres.

If a subject loses seroprotective titres for anti-HBs antibodies (i.e. titres < 10 mIU/ml) at the long-term blood sampling time point (i.e. Month 30, 42, 54 and 66), he/she will be offered an additional vaccine dose of commercial Engerix™-B (to be administered between 6 to 12 months after Month 66 time point), in order to assess the immune memory after a primary three-dose schedule of preservative-free Engerix™-B or primary two-dose schedule of thiomersal-free Engerix™-B administered at 0, 6 months. A blood sample will be taken on the day of the additional vaccination and after one month to evaluate the immune response following this vaccination.

Note: The cleaning and analysis of data will be performed on immunogenicity data obtained after each long-term time point (i.e. Month 30, 42, 54 and 66). These results will be communicated to the investigator each year. All the data from Month 30 to Month 66 (including the data collected after additional vaccination) will be compiled and reported together in a report.
THE FOLLOWING SECTIONS OF THE MAIN PROTOCOL WERE AMENDED ON 2 February 2004:

Section 2: Objectives

Section 4.1: Number of subjects/ centres

Section 5.1.2: Informed consent

Section 5.3: Outline of study procedures

Section 5.5.2: Laboratory assays

Section 10.3: Study cohorts/ datasets to be evaluated

Section 10.5.1: Analysis of demographics

Section 10.5.2: Analysis of immunogenicity

Section 10.5.3: Analysis of reactogenicity
Protocol Title: A phase III, single-blinded, randomized, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals' thiomersal-free 2-dose Engerix-B and 3-dose preservative-free Engerix-B vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).

Rationale/background for changes:

The study protocol has been modified to include a new study centre located in the Ukraine. This centre has been added due to the decreased enrolment in the Belgian centres and to ensure that the necessary subjects are enrolled within study defined limits.

Please note that the pagination has increased by 1 page after page 5 due to the inclusion of a sign-off sheet for the additional centre.

The study design used at the Ukrainian study centre will be the same as that used in the Australian study centre which incorporated a screening visit.

Modified text in **bold** font was included in the following pages/sections:

**Page 1**: The modification date (and previous amendment date) has been entered.

**Page 2**: The complete address for the Medical monitor and study monitor at GSK Australia in the original protocol was not given, this has now been corrected. One investigator's fax number was written incorrectly and his complete address not stated, this has now been corrected.

**Pages 3, 4, 47 and Study personnel and study centres page**: A fax number has changed.

**Page 5**: A new investigator sign-off sheet has been added to include the new study centre located in the Ukraine.

**Page 16**: Footnote to diagram Centre 4 added.

**Pages 24 & 25: Section 5.3: Outline of study procedures.** To include Ukraine in with Centre 1 study design. Table 1 footer note adjusted to include Centre 4

**Pages 27 & 28: Section 5.4, Detailed description of study stages/visits.** To include Ukraine in with Centre 1 study design.

**Page 33: Section 5.5.2, Laboratory Assays.** To include screening assay for the Ukraine.

**Page 34: Section 5.5.3: Serology plan** changed to include screening for the Ukrainian Centre.

**Appendix F: Laboratory Assays.** To include screening assay for the Ukraine.

**Appendix H: Details of amendment 1 (August 9, 2001) have been added.**

**Study personnel and study centres page:**

The addresses for the Medical monitors and study monitors have been updated.

Details of the new Principal Investigator and Medical Centre in the Ukraine have been added.
Protocol Title: A phase III, single-blinded, randomized, multicentric study to compare the immunogenicity of GlaxoSmithKline Biologicals' thiomersal-free 2-dose Engerix™-B and 3-dose preservative-free Engerix™-B vaccines administered intramuscularly according to a 0, 6 month and 0, 1, 6 month schedule, respectively, and to evaluate safety and reactogenicity of each vaccine in healthy adolescent volunteers (11 to 15 years).

<table>
<thead>
<tr>
<th>Amendment 1 Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-August-2001</td>
</tr>
</tbody>
</table>

**Rationale/background for changes:**

**Page 3** In the original protocol one investigator’s e-mail address was written incorrectly and telephone and Fax numbers were incomplete.

**Page 4 and 15** In the primary objective the wrong units were used for Engerix™-B, the units should be in mcg (micrograms) not mg (milligrams)

**Page 34:** Due to logistic reasons the placebo provided will only consist of physiological saline.

The following items in *bold italics* were amended on August 9, 2001:

**Page 3:** The telephone numbers and e-mail address for one investigator have been changed.

**Page 4 and 15** Primary objective

To demonstrate non-inferiority of the immune response induced by (thiomersal-free) Engerix™-B HBsAg(*Amended August 9, 2001*) administered as a 2-dose vaccination schedule compared to (preservative-free) Engerix™-B (*Amended August 9, 2001*) administered as a 3-dose vaccination schedule, one month after the full vaccination course (month 7).

**Page 34:** Dosage and administration.

ii) Placebo, (administered at month 1 to the thiomersal-free hepatitis B vaccine group to maintain the study as a single-blinded study), containing per 1 ml dose **consisting of physiological saline.**

Aluminium salt 0.5 mg
Appendix 2 to Synopsis for study HBV-306 (101698)

List of study sites

- **Australia (click to hide all sites in Australia)**
  - GSK Investigational Site
    - Sydney, New South Wales; Completed;

- **Belgium (click to hide all sites in Belgium)**
  - GSK Investigational Site
    - Wilrijk, 2610; Completed;
  - GSK Investigational Site
    - Bruxelles, 1200; Completed;

- **Ukraine (click to hide all sites in Ukraine)**
  - GSK Investigational Site
    - Kyiv, 03038; Completed;