STN 103239/5019
GSK Thimerosal Free Hepatitis B vaccine
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Clinical Review
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Background: The original EngerixB formulation contained 50 µg/mL thimerosal. When it was decided to remove thimerosal from vaccines, especially childhood vaccines, GSK removed the thimerosal addition step [redacted] However, this resulted in a vaccine that contained a trace amount (<2 µg/mL) of thimerosal that remained from the addition of thimerosal at [redacted] manufacture which was not removed in the [redacted] process. The removal of thimerosal from the [redacted] necessitated other changes to the process.

The product of this new manufacturing process has now been used in three clinical trials designed to determine if the immunogenicity of the new product is non-inferior to the original EngerixB and the preservative free EngerixB and that the reactogenicity of the thimerosal free product is also similar to the original and the preservative free EngerixB. The three trials are as follows:

HBV-269: A phase II double-blind, randomized, controlled, multicenter study to evaluate the immunogenicity of GlaxoSmithKline Biologicals' preservative-free *EngerixB* and thimerosal free *EngerixB* vaccines compared to *EngerixB* and evaluate safety and reactogenicity of each vaccine when administered intramuscularly according to a 0, 1, 6 month schedule in healthy volunteers (18 to 50 years).

HBV-270: A phase III, double-blind, randomized, multicenter study to evaluate the safety and consistency of 3 consecutive lots of GlaxoSmithKline Biologicals' thimerosal-free *Engerix-B* vaccine containing 20 µg of HBsAg per 1 mL dose, when administered intramuscularly according to a 0, 1, 6 month schedule in healthy volunteers aged from 18 to 40 years.

HBV-277: A phase III, double-blind, randomized, comparative, multicenter study of the immunogenicity and safety of three doses of GlaxoSmithKline Biologicals' thimerosal-free hepatitis B vaccine (10 µg/0.5 mL) compared to the US-licensed GlaxoSmithKline Biologicals preservative-free hepatitis B vaccine (Engerix-B, 10 µg/0.5 mL) when administered intramuscularly on a 0, 1, 6-month schedule to healthy infants in their first two weeks of life

This BLA supplement requests licensure for the thimerosal free hepatitis B vaccine for both the adult and pediatric formulations and indications.

HBV-269

Title of the study: 103860/269 (HBV-269)

A phase II double-blind, randomized, controlled, multicenter study to evaluate the immunogenicity of GlaxoSmithKline Biologicals' preservative-free Engerix-*B* and thimerosal free *Engerix-B* vaccines compared to *Engerix*™*-B* and evaluate safety and reactogenicity of each vaccine when administered intramuscularly according to a 0, 1, 6 month schedule in healthy volunteers (18 to 50 years).

Objectives:

Primary:

To demonstrate non-inferiority of the immune response induced by preservative-free and thimerosal-free *Engerix-B* compared to *Engerix™-B* one month after the full vaccination course (Month 7).

Secondary:

- To evaluate the safety and reactogenicity of the HBV vaccines after each dose and overall, and per subject.
- To evaluate the immunogenicity at all time points.
- To evaluate the quality of the immune response elicited one month after the full vaccination course by using [redacted] in a subset of subjects.

Methodology:

Study design: Double-blinded, randomized, controlled, multicenter (4 centers) parallel study with three groups.

Population Group: Healthy adults aged 18 to 50 years.

- Preservative-free (PF) Group received preservative-free *Engerix-B,* 217 enrolled
- *Engerix™-B* (ENG-B) Group received *Engerix™-B* (thimerosal containing), 217 enrolled
- Thimerosal-free (TF) Group received thimerosal-free *Engerix-B*, 218 enrolled

There were 652 subjects enrolled of whom 621 completed the study (planned 618) and these were divided approximately 1:1:1 between the three arms. The study was conducted at eight sites in Europe. The subjects were limited to healthy 18 to 50 year olds without evidence of liver disease, viral hepatitis or HIV infections. Subjects were evaluated at 5 visits on months 0 (pre-vaccine, month 1 (post-vaccine 1), month 2 (post vaccine 2), month 6 (post vaccine 2) and month 7 (post vaccine 3). A follow-up visit was scheduled at month 12. A complete evaluation for AEs and immune responses were made at each of these visits as appropriate. The assays used to measure the immune responses are listed in table 5 below from the submission. These assays were performed at GSK in a validated lab. The assays are both standard and well validated.

Table 5 Laboratory assays

Marker	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
Anti-HBs	[redacted]		mIU/ml	3.3 mIU/ml	GSK Biologicals
Anti-HBc			+/–	-	GSK Biologicals
HbsAg			+/–	-	GSK Biologicals

+ /–: Only qualitative analysis of anti-HBc antibodies and HBsAg were done at pre-vaccination and were ranked + /– (positive or negative).

Reactogenicity was assessed by diary cards for the recording of both solicited and unsolicited AEs during the 4 days following vaccination. Any AE occurring during the

30 days after vaccination was recorded The solicited events are listed in Table 6 below from the submission.

Table 6 **Solicited local and general symptoms**

Solicited local adverse events	Solicited general adverse events
Pain at the injection site	Fever
Redness at the injection site	Headache
Swelling at the injection site	Fatigue
	Gastro-intestinal symptoms*

*Gastrointestinal symptoms include nausea, vomiting, diarrhoea and abdominal pain.

Intensity of AE symptoms was estimated on a scale from 0 to 3 as follows:

0: No adverse event

1: An adverse event which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2: An adverse event which was sufficiently discomforting to interfere with normal everyday activities.

3: An adverse event which prevented normal, everyday activities. (In adolescents/adults, such an adverse event would, for example, prevent attendance at work and would necessitate the administration of corrective therapy).

All serious AEs occurring during the period of the study were reported without regard to their causality by the investigator within 24 hours.

Causality of all AEs was assigned by the investigator with the exception that all injection site reactions were considered vaccine related.

The outcome of all AEs was determined and listed as either recovered, recovered with sequelae, still ongoing at the study conclusion, died or unknown.

Statistical Methods:

Primary endpoints:

Observed variables:

- Anti-HBs antibody titers in all subjects at Month 7

Derived variable:

- Anti-HBs seroprotection rate (defined as the proportion of subjects with anti-HBs antibody titers ≥ 10 mIU/mL) at Month 7

Secondary endpoints

Observed variables:

- At baseline and at Months 1, 2 and 6: anti-HBs antibody titers for all subjects.
- At baseline and at Month 7: [redacted] antibody titers in a random subset of 50 subjects/group.
- Occurrence, intensity and relationship to vaccination of solicited local and general signs and symptoms during the 4-day follow-up (i.e. the day of vaccination and the 3 subsequent days) after each vaccination and overall.

- Occurrence, intensity and relationship to vaccination of unsolicited local and general signs and symptoms within 30 days after each vaccination and overall.
- Occurrence, intensity and relationship to vaccination of serious adverse events during the study period, up to and including 30 days post-vaccination.

Derived variables:

- Seroprotection (SP) rates at baseline and at Months 1, 2 and 6 for all subjects.
- Seropositivity rates (percentage of subjects with anti-HBs antibody titers ≥ the assay cut-off of 3.3mIU/mL) at Months 0, 1, 2, 6 and 7, for all subjects.
- Geometric Mean Titers (GMT) calculated at baseline and at Months 1, 2, 6 and 7 for all subjects.
- [redacted] antibody Geometric Mean Titers (GMT) at baseline and at Month 7.

For anti-HBs antibodies, the assay cut-off was defined as 3.3mIU/mL. For [redacted] antibodies the assay cut-off was [redacted].

Sample size: It was calculated that at least 185 evaluable subjects would be needed in each arm in order to conclude non-inferiority with at least 90% global power assuming that the formulations were equally immunogenic. Assuming that up to 10% of the subjects would drop out during the study, 206 subjects were planned for each group. Two cohorts were defined; the total cohort and the According to Protocol cohort (see section 3.13.4). Two analyses were performed for both immunogenicity and reactogenicity. The primary analysis was on the ATP cohort and the other on the total cohort, as >5% of the enrolled subjects were eliminated from the ATP immunogenicity and reactogenicity analyses.

Immunogenicity:

GMTs were calculated in two ways; 1) using only the titers above the assay cutoff, and 2) using all the titers and arbitrarily assigning titers of half the cutoff value to those that fell below the cutoff. The main analysis was done using the titers that were above the cutoff.

Reactogenicity:

Two analyses were performed: the primary one on the ATP cohort. The other analysis was on the total cohort.

The incidence in terms of percentage (with exact 95% CI), of doses followed by each solicited local and general symptom, during the 4-day follow-up period after vaccination was calculated for each dose and overall and for each group, in addition to intensity and relationship. The percentage, with exact 95% C.I., of subjects reporting each individual solicited symptom during the 4-day follow-up period after at least one vaccination, was tabulated by group, in addition to intensity and relationship.

The number and percentage (based on the total number of documented doses), with exact 95% C.I., of doses followed by at least one report of an unsolicited adverse event and the number and percentage of subjects (with exact 95% C.I.) with at least one report of an unsolicited adverse event, classified by World Health Organization (WHO) Preferred Term and reported up to 30 days after vaccination was tabulated per group. The intensity and relationship to vaccination of unsolicited adverse events up to 30 days after vaccination was also analyzed.

There were a total of 31 subjects who dropped out of the study. The reasons for dropping out are listed in the following table (Table 9 from the app)

Table 9 Number of subjects enrolled, completed and dropped-out and the reasons for drop-out

	PF Group	ENG-B Group	TF Group	Total
Number of subjects enrolled	217	218	217	652
Number of subjects completed	207	207	207	621
Number of subjects dropped-out	10	11	10	31
Reasons for drop-out:				
Non-serious adverse event	0	2	2	4
PROTOCOL VIOLATION	0	1	1	2
Consent withdrawal (not due to an adverse event)	1	1	2	4
Migrated/moved from study area	1	1	1	3
Lost to follow-up (subjects with incomplete vaccination course)	6	4	1	11
LOST TO FOLLOW-UP (SUBJECTS WITH COMPLETE VACCINATION COURSE)	2	0	1	3
Others	0	2	2	4

The number of subjects enrolled and randomized into the study as well as the number excluded from ATP analysis for exclusion was comparable in the 3 groups. The demography of the three groups was comparable.

IMMUNOGENICITY ANALYSIS:

The table below (Table 13 from the application) presents the seropositivity and seroprotection rates and the GMTs for anti-HBs for the ATP immunogenicity cohort only with the GMTs calculated only on the seroconverters.

Table 13 **Seropositivity rate, seroprotection rate and GMTs (calculated in seroconverters only) for the ATP immunogenicity cohort**

Group	Timing	N	S+		95% C.I.		SP		95% C.I.		GMT	95% C.I.	
			n	%	L.L.	U.L.	n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.
PF	PI(M1)	183	24	13.1	8.6	18.9	13	7.1	3.8	11.8	19.2	11.0	33.5
	PII(M2)	183	142	77.6	70.9	83.4	114	62.3	54.8	69.3	36.5	28.7	46.6
	PII(M6)	181	167	92.3	87.4	95.7	153	84.5	78.4	89.5	104.7	83.1	131.9
	PIII(M7)	179	178	99.4	96.9	100	177	98.9	96.0	99.9	4955.5	3589.1	6842.3
ENG-B	PI(M1)	182	22	12.1	7.7	17.7	12	6.6	3.5	11.2	15.8	8.4	29.7
	PII(M2)	181	121	66.9	59.5	73.7	109	60.2	52.7	67.4	41.1	33.3	50.7
	PII(M6)	178	153	86.0	80.0	90.7	141	79.2	72.5	84.9	128.1	101.7	161.2
	PIII(M7)	178	172	96.6	92.8	98.8	168	94.4	89.9	97.3	4119.7	2961.7	5730.3
TF	PI(M1)	176	23	13.1	8.5	19.0	12	6.8	3.6	11.6	15.2	9.4	24.7
	PII(M2)	176	126	71.6	64.3	78.1	99	56.3	48.6	63.7	36.3	28.2	46.7
	PII(M6)	176	157	89.2	83.7	93.4	150	85.2	79.1	90.1	135.3	107.4	170.4
	PIII(M7)	175	171	97.7	94.3	99.4	169	96.6	92.7	98.7	5387.8	3940.8	7366.0

PF Group received *Engerix-B* (ENG3224A)
ENG-B Group received *Engerix™-B* (ENG3126E)
TF Group received thimerosal-free *Engerix-B* (DENS001A)
N: number of subjects tested
S+: Seropositivity for anti-HBs antibodies (*i.e.,* titers $\geq$ 3.3 mIU/mL)
SP: Seroprotection for anti-HBs antibodies (*i.e.,* titers $\geq$ 10 mIU/mL)
n/%: number/percentage of subjects who were seropositive/ seroprotected for anti-HBs antibodies
PI (M1), PII (M2), PII (M6),: post-vaccination blood samples obtained 1 month, 2 months and 6 months, respectively after the first dose
PIII (M7): post-vaccination blood samples obtained one month after the third dose
95% C.I.: 95% confidence interval; L.L.: Lower Limit; U.L.: Upper Limit
GMT: Geometric mean titers.

Supplement 5 below is a table with the GMT data calculated on the basis of the total subjects including the non-seroconverters. The GMT levels are lower by this method of calculation but they remain relatively similar between the three arms.

Supplement 5 **Anti-HBs GMTs (calculated on all subjects) one month after the last vaccine dose (i.e. Month 7) for ATP immunogenicity cohort**

Group	Timing	N	GMT (mIU/ml)	95% C.I.		MIN	MAX
				L.L.	U.L.		
PF	PRE	183	1.7	1.7	1.7	<3.3	<3.3
	PI(M1)	183	2.3	2.0	2.6	<3.3	442.3
	PII(M2)	183	18.3	14.0	23.8	<3.3	5730.0
	PII(M6)	181	75.9	58.1	99.3	<3.3	3257.0
	PIII(M7)	179	4738.7	3397.5	6609.4	<3.3	540200.0
ENG-B	PRE	182	1.7	1.7	1.7	<3.3	<3.3
	PI(M1)	182	2.2	1.9	2.5	<3.3	475.6
	PII(M2)	181	14.2	10.9	18.4	<3.3	1260.8
	PII(M6)	178	69.5	51.5	93.7	<3.3	1457.0
	PIII(M7)	178	3164.8	2161.2	4634.3	<3.3	134180.0
TF	PRE	176	1.7	1.7	1.7	<3.3	<3.3
	PI(M1)	176	2.2	1.9	2.5	<3.3	200.2
	PII(M2)	176	15.1	11.5	19.9	<3.3	3207.0
	PII(M6)	176	84.1	62.9	112.3	<3.3	3531.0
	PIII(M7)	175	4478.1	3139.7	6387.1	<3.3	511360.0

The table below is a simplified mixture of the two tables above so that easy comparisons of point estimates between the three groups can be seen.

		PF	**ENG-B**	**TF**
PD1	S+ (%)	13.1	12.1	13.1
M1	SP (%)	7.1	6.6	6.8
	GMT(S+ only)	19.2	15.8	15.2
	GMT (total)	2.3	1.9	1.7
PD2	S+ (%)	77.6	66.9	71.6
M2	SP (%)	62.3	60.2	56.3
	GMT(S+ only)	36.5	41.1	36.3
	GMT (total)	18.3	14.2	15.1
PD2	S+ (%)	92.3	86.0	89.2
M6	SP (%)	84.5	79.2	85.2
	GMT(S+ only)	104.7	128.1	135.3
	GMT (total)	75.9	69.5	84.1
PD3	S+ (%)	99.4	96.6	97.7
M7	SP (%)	98.9	94.4	96.6
	GMT(S+ only)	49955.5	4119.7	5387.8
	GMT (total)	4738.7	3164.8	4478.1

SAFETY AND REACTOGENICITY

All symptoms, solicited and non-solicited, local and general occurring during the 4 days following vaccination were recorded. The following table (table 16 from the application) summarizes these.

Table 16 **Incidence of symptoms (solicited/unsolicited) reported during the 4-day follow-up period for each vaccine dose and overall, according to per-dose and per-subject analyses (ATP reactogenicity cohort)**

Dose	Group	Any symptom					General symptoms					Local symptoms				
		N	n	%	95% C.I.		N	n	%	95% C.I.		N	n	%	95% C.I.	
					L.L.	U.L.				L.L.	U.L.				L.L.	U.L.
1	PF	208	155	74.5	68.0	80.3	208	93	44.7	37.8	51.7	207	118	57.0	50.0	63.8
	ENG-B	206	130	63.1	56.1	69.7	206	89	43.2	36.3	50.3	206	92	44.7	37.7	51.7
	TF	209	148	70.8	64.1	76.9	209	100	47.8	40.9	54.8	209	115	55.0	48.0	61.9
2	PF	209	129	61.7	54.8	68.3	209	63	30.1	24.0	36.9	209	104	49.8	42.8	56.7
	ENG-B	202	102	50.5	43.4	57.6	202	58	28.7	22.6	35.5	202	75	37.1	30.5	44.2
	TF	202	120	59.4	52.3	66.2	202	69	34.2	27.6	41.1	202	94	46.5	39.5	53.7
3	PF	201	128	63.7	56.6	70.3	201	67	33.3	26.9	40.3	200	111	55.5	48.3	62.5
	ENG-B	195	115	59.0	51.7	66.0	195	67	34.4	27.7	41.5	195	85	43.6	36.5	50.9
	TF	203	126	62.1	55.0	68.8	203	64	31.5	25.2	38.4	203	100	49.3	42.2	56.4
Overall/ dose	PF	618	412	66.7	62.8	70.4	618	223	36.1	32.3	40.0	616	333	54.1	50.0	58.0
	ENG-B	603	347	57.5	53.5	61.5	603	214	35.5	31.7	39.5	603	252	41.8	37.8	45.8
	TF	614	394	64.2	60.2	68.0	614	233	37.9	34.1	41.9	614	309	50.3	46.3	54.4
Overall/ subject	PF	209	184	88.0	82.9	92.1	209	134	64.1	57.2	70.6	209	158	75.6	69.2	81.3
	ENG-B	206	165	80.1	74.0	85.3	206	125	60.7	53.7	67.4	206	130	63.1	56.1	69.7
	TF	209	181	86.6	81.2	90.9	209	129	61.7	54.8	68.3	209	154	73.7	67.2	79.5

There were no significant differences in the number of general symptoms recorded between the three treatment arms either on a per dose basis or in the total number of symptoms recorded. Following each dose and in the totals there was a consistent pattern of the standard EngerixB being less locally reactogenic than the TF EngerixB which was slightly less reactogenic than the PF EngerixB. These differences did not hold for "grade 3" reactions. A total of 14 symptoms in the PF group, 19 in the EngerixB group and 11 in the TF group were reported as grade 3. Most local symptoms resolved within the 4 day reporting period.

Solicited symptoms including fatigue, gastrointestinal, headache and fever were similar in the 3 groups. However, the TF group was generally slightly higher than the other two groups.

General unsolicited symptoms during the 30 days post vaccination were also similar among the 3 groups with the TF group slightly lower than the PF group which was slightly lower than the Engerix group.

Serious Adverse Events: There were 14 serious AEs reported. None were thought by the sponsor nor by the FDA to be vaccine related.

Summary: This study demonstrated non-inferiority of the thimerosal free product in comparison to the preservative free and the thimerosal containing product for both immunogenicity and adverse events.

HBV-270

Title of the study: 103860/270 (HBV-270

A phase III, double-blind, randomized, multicenter study to evaluate the safety and consistency of 3 consecutive lots of GlaxoSmithKline Biologicals' thimerosal-free *Engerix-B* vaccine containing 20 μg of HBsAg per 1 mL dose, when administered

intramuscularly according to a 0, 1, 6 month schedule in healthy volunteers aged from 18 to 40 years.

Objectives:

Primary:

To demonstrate the lot-to-lot consistency of 3 consecutive lots of the thimerosal-free hepatitis B vaccine in terms of equivalence (anti-HBs seroprotection rates) one month after the full vaccination course (Month 7).

Secondary:

- To evaluate the lot-to-lot consistency in terms of pair-wise Geometric Mean Titers (GMT) ratio, one month after the full vaccination course (at Month 7).
- To evaluate the immunogenicity at all time points.
- To evaluate the safety and reactogenicity of the thimerosal-free hepatitis B vaccine after each dose and by subject.
- To evaluate the quality of the immune response elicited one month after the full vaccination course (at Month 7) by using [redacted] in a subset of subjects

Methodology:

Study design: Double-blind, randomized (1:1:1), multicenter (8 centers) study with 3 groups. Each group received a different lot of GlaxoSmithKline (GSK) Biologicals' Thimerosal-free *Engerix-B* vaccine. There were 230 subjects planned for each group for a total of 690. 667 completed the study, 656 ATP analysis of reactogenicity and 561 ATP analysis of immunogenicity.

Subject Population: Healthy male or female subjects between, and including, 18 and 40 years of age, who were seronegative for hepatitis B surface antigen (HBsAg), anti-HBc and anti-HBs antibodies at the time of first vaccination. The mean age of the total cohort was 23.3 years with a standard deviation of 5.41 years. The female/male ratio was about 1.9 (450/240). The subjects enrolled in this study were predominantly White (97.7%). Exclusion criteria were standard for HBV vaccines and included history of or recent exposure to hepatitis B, history of HB vaccine or non-response to HBV vaccine, liver disease, immunosuppression, pregnancy or plans for pregnancy in the near future.

The purpose of this study was to evaluate and compare three consecutive production lots of the thimerosal free Engerix B with regard to immunogenicity and safety. The primary endpoint was one month after the third dose or 7 months after the initial dose. At this time the subjects would be evaluated for seroconversion and seroprotection rates and anti-HBs titers. Evaluations were made one month after each of the three doses administered at 0, 1, 6 month schedule, but the primary endpoint was one month after dose three (month 7).

A total of 205 evaluable subjects were needed in each of the 3 groups to be able to demonstrate lot to lot consistency for seroprotection with an overall power of at least 80%. Of the 230 planned subjects in each group, drop outs were 7, 8 and 8 in groups 1, 2 and 3.

Group 1 received Thimerosal-free *Engerix-B* Lot DENS002A4 at 0, 1, 6 months
Group 2 received Thimerosal-free *Engerix-B* Lot DENS001A4 at 0, 1, 6 months
Group 3 received Thimerosal-free *Engerix-B* Lot DENS003A4 at 0, 1, 6 months

There were no significant differences in the three groups with respect to seroprotection rates, GMTs or AEs. The table below pulls out just the immune response data from the primary endpoint of month 7 (1 month post dose 3) At all the other time points, there were also no significant differences between the 3 groups.

Seroprotection (SP) rate (% of subjects with anti-HBs titers > 10mIU/mL) 1 month post dose 3. Table below was simplified from the application.

			95% CI			95% CI	
Group No.	**N**	**SC %**	**LL**	**UL**	**GMT mIU/mL**	**LL**	**UL**
1	182	99.5	97	100	7148.5	7148.5	9614.8
2	176	98.3	95.1	99.6	7209.3	7209.3	9421.0
3	191	98.4	96.3	99.9	6800.8	5129.4	9016.7

The table below from the application summarizes the adverse events in the 3 groups for all 3 injections on a per dose basis. Both solicited and unsolicited reactions were broken out and grade 3 reactions are also listed. The safety profile was equivalent in the 3 groups. None of the 11 serious AEs were considered to be causally associated with the vaccine. No study subject dropped out due to an adverse event.

Solicited/unsolicited symptoms:		Group 1			Group 2			Group 3		
		N	n	%	N	n	%	N	n	%
Any symptom		651	476	73.1	638	443	69.4	647	472	73.0
General symptoms		651	265	40.7	638	228	35.7	647	234	36.2
Local symptoms		650	411	63.2	637	387	60.8	645	411	63.7
		N = 650			N = 637			N = 645		
Solicited local symptoms		N	%		n	%		n	%	
Pain	Total	370	56.9		350	54.9		388	60.2	
	Grade "3"	10	1.5		17	2.7		17	2.6	
Redness	Total	108	16.6		107	16.8		120	18.6	
	Grade "3"	0	0.0		0	0.0		0	0.0	
Swelling	Total	51	7.8		57	8.9		64	9.9	
	Grade "3"	0	0.0		0	0.0		0	0.0	
Solicited general symptoms		N = 651			N = 638			N = 647		
Fatigue	Total	155	23.8		129	20.2		142	21.9	
	Grade "3"	5	0.8		3	0.5		6	0.9	
	Related	96	14.7		86	13.5		93	14.4	
	Grade "3" Related	3	0.5		1	0.2		3	0.5	
Gastro-Intestinal	Total	57	8.8		47	7.4		54	8.3	
	Grade "3"	3	0.5		2	0.3		6	0.9	
	Related	25	3.8		23	3.6		23	3.6	
	Grade "3" Related	2	0.3		2	0.3		4	0.6	

All other analyses of AEs failed to reveal significant differences between the three groups.

Summary: Three consecutive lots of thimerosal free Engerix B were compared in three groups of adult volunteers between the ages of 18 and 40. All three lots performed well for both immunogenicity and safety, The three lots were essentially equivalent in terms of the seroprotection rates induced, GMT levels and safety profiles. The 95% confidence intervals for the difference in percentage of seroprotected subjects between the three groups were well contained within the pre-defined limits for clinical equivalence [– 10%, + 10%]; thereby demonstrating consistency of the three lots of Thiomersal-free *Engerix-B* vaccine in terms of seroprotection rates achieved.

The consistency of the three vaccine lots was further supported by the results of an evaluation in terms of GMT ratios between Thiomersal-free *Engerix-B* groups (pair-wise comparison). Results indicate that ratio of GMTs between each pair-wise group was about 1, and their 95% CI were about [0.7, 1.6], thereby indicating that the consecutive lots elicited similar GMTs, one month after the full vaccination course.

HBV-277

Title of the study: 103860/277 (HBV-270)

A phase III, double-blind, randomized, comparative, multicenter study of the immunogenicity and safety of three doses of GlaxoSmithKline Biologicals' thimerosal-free hepatitis B vaccine (10 μg/0.5 mL) compared to the US-licensed GlaxoSmithKline Biologicals' preservative-free hepatitis B vaccine (Engerix-B, 10 μg/0.5 mL) when administered intramuscularly on a 0, 1, 6-month schedule to healthy infants in their first two weeks of life

Primary: To demonstrate that the immunogenicity of Engerix-B® thimerosal-free (TF) vaccine is not inferior to that of *Engerix-B* preservative-free (PF) vaccine, with respect to anti-hepatitis B surface antigen (anti-HBs) seroprotection rates one month after the third dose (Month 7).

Secondary:

- To assess the anti-HBs geometric mean concentrations (GMCs) one month after the second dose (Month 2) and one month after the third dose (Month 7) in both groups
- To assess the anti-HBs seroprotection rates one month after the second dose (Month 2) in both groups
- To assess the incidence and intensity of solicited local adverse events that occur during the four-day follow-up period (Days 0-3) after each vaccination
- To assess the incidence, intensity and causal relationship to vaccination of solicited general adverse events that occur during the four-day follow-up period (Days 0-3) after each vaccination
- To assess the nature, incidence and causal relationship to vaccination of unsolicited adverse events that occur during the 31-day follow-up period (Days 0-30) after each vaccination

- To assess the occurrence, nature and causal relationship to vaccination of serious adverse events (SAEs) that occur during the entire study period (through six months after the last dose of vaccine).
- Experimental design: double-blind, randomized (1:1 ratio), multicenter, comparative study with two groups:
  - *Engerix-B* preservative-free (planned: N = 294): three doses at Month 0 (dose 1), Month 1 (dose 2) and Month 6 (dose 3)
  - *Engerix-B* thimerosal-free (planned: N = 294): three doses at Month 0 (dose 1), Month 1 (dose 2) and Month 6 (dose 3)
- The third dose of *Engerix-B* (at Month 6) was co-administered with tetanus toxoid, diphtheria toxoid and acellular pertussis vaccine adsorbed, (Infanrix®), *haemophilus influenzae* type b vaccine (HibTITER® or ActHIB®) and 7-valent pneumococcal conjugate vaccine (*Prevnar*®).
- Blood samples were taken at Months 0, 2 and 7 for serological analysis.
- Study duration per subject was approximately seven months (active phase). A final extended safety follow-up phone contact took place six months after the last vaccination (extended follow-up phase).

This study in infants is the key to the vaccine as the thimerosal free product is intended primarily for this age group. This is a two arm study with an intention to enroll 294 subjects in each arm. The infants were to be vaccinated within the first 14 days after birth. They were bled at the time of the initial vaccination, the second dose (month 1) Month 2, month 6 at the time of the 3rd dose and at month 7. They were followed for AEs through month 12. The infants received all their recommended vaccinations on a typical schedule recommended by ACIP. Only at month 6 did they receive any other vaccines at the same time as they received EngerixB at which time they were given Infanrix, Hib and Prevnar. These were intended to be normal infants born after a full gestation period to HBsAg negative mothers and without other exposure to HBV.

The table below (Table 13 from the application) summarizes the basic immunogenicity data from the trial. The groups receiving the preservative free (PF) or the thimerosal free (TF) responded with nearly identical anti-HBs titers and seroprotection rates.

Table 13 Seropositivity and seroprotection rates and GMCs for anti-HBs antibodies (GMCs calculated on subjects with concentrations of at least 3.3 mIU/mL) (ATP cohort for immunogenicity)

Group	Timing	N	≥3.3 mIU/mL				≥10 mIU/mL				GMC		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
PF	Pre	208	76	36.5	30.0	43.5	65	31.3	25.0	38.0	113.9	71.7	180.8
	PII(M2)	219	151	68.9	62.4	75.0	131	59.8	53.0	66.4	38.4	31.8	46.4
	PIII(M7)	213	210	98.6	95.9	99.7	209	98.1	95.3	99.5	1294.4	1069.3	1566.8
TF	Pre	213	66	31.0	24.8	37.7	57	26.8	20.9	33.2	200.4	116.7	343.9
	PII(M2)	225	168	74.7	68.5	80.2	129	57.3	50.6	63.9	36.2	29.0	45.1
	PIII(M7)	227	222	97.8	94.9	99.3	220	96.9	93.7	98.8	1427.6	1146.4	1777.7

Table 14 below presents the difference in seroprotection rates for anti-HBs between the *Engerix-B* TF vaccine group and the *Engerix-B* PF group vaccine group one month after the last vaccine dose (Month 7) and the two-sided standardized asymptotic 90% CI for the difference (analysis of the primary endpoint) as well as the two-sided standardized asymptotic 95% CI for the difference (exploratory analysis).

Table 14 Difference between groups in anti-HBs seroprotection rate at PIII(M7) (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Difference (TF minus PF)		
						%	90 % CI	
							LL	UL
PF	213	98.1	TF	227	96.9	-1.21	-3.95	1.41
							95 % CI	
							LL	UL
PF	213	98.1	TF	227	96.9	-1.21	-4.59	2.02

This table shows that the primary endpoint of non-inferiority of the seroprotection rates at month 7 has been met at both the 2-sided 90% CI level and the 2-sided 95% CI level.

The table below (Table 15) shows the comparison in GMTs between the PF and TF groups as a ratio of GMT-TF/GMT-PF. The calculated ratio of 1.10 falls within the 95% CI of 0.82 and 1.48, thus meeting the pre-specified non-inferiority criteria for GMT comparisons.

Table 15 Ratio of anti-HBs GMCs between groups PIII(M7) (GMCs calculated on subjects with antibody concentrations of at least 3.3 mIU/mL) (ATP cohort for immunogenicity)

Antibody	TF		PF		GMC ratio		
	N	GMC	N	GMC	(TF / PF)	95% CI	
						LL	UL
Anti-HBs (mIU/mL)	222	1427.6	210	1294.4	1.10	0.82	1.48

Analyses done on the total vaccinated cohort resulted in a similar conclusion.

All adverse events occurring within one month following each dose of the vaccines were captured without regard to severity or to their relatedness to the vaccine. All serious AEs were reported throughout the term of the study and extending 180 days beyond the last dose of vaccine. Solicited AEs were reported by the parents during the 4 days following each vaccination. These included pain at the injection site, redness at the injection site, swelling at the injection site, fever, irritability/fussiness, drowsiness and loss of appetite. At the time of the third dose of vaccine, Infanrix, HibTITER or ActHIB and Prevnar were also administered and AEs directly related to those vaccines were also reported during the 4-day follow-up of the third vaccine dose. All AEs were graded for intensity on a scale of 0-3.

Data analysis was performed according to protocol on the ATP cohort and the secondary analysis on the Total cohort. In addition, they analyzed the Total vaccinated cohort, defined as all subjects who had received at least one dose of vaccine, for the purpose of evaluating unsolicited symptoms, SAEs, concomitant medications and vaccinations and for the analysis of combined solicited and unsolicited symptoms.

Table 18 below shows the total of solicited and unsolicited symptoms occurring within 4 days of vaccination for all doses on the Total vaccinated cohort.

Table 18 Incidence and nature of symptoms (solicited and unsolicited) reported during the four-day (Days 0-3) post-vaccination period following each dose and overall (Total vaccinated cohort)

	Group	Any symptom					General symptoms					Local symptoms				
		N	N	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Dose 1	PF	293	147	50.2	44.3	56.0	293	124	42.3	36.6	48.2	293	79	27.0	22.0	32.4
	TF	294	148	50.3	44.5	56.2	294	120	40.8	35.1	46.7	294	79	26.9	21.9	32.3
Dose 2	PF	283	174	61.5	55.5	67.2	283	163	57.6	51.6	63.4	283	69	24.4	19.5	29.8
	TF	281	182	64.8	58.9	70.3	281	166	59.1	53.1	64.9	281	82	29.2	23.9	34.9
Dose 3	PF	264	174	65.9	59.8	71.6	264	159	60.2	54.0	66.2	264	85	32.2	26.6	38.2
	TF	260	173	66.5	60.4	72.2	260	159	61.2	54.9	67.1	260	84	32.3	26.7	38.4
Overall/	PF	840	495	58.9	55.5	62.3	840	446	53.1	49.7	56.5	840	233	27.7	24.7	30.9
dose	TF	835	503	60.2	56.8	63.6	835	445	53.3	49.8	56.7	835	245	29.3	26.3	32.6
Overall/	PF	293	238	81.2	76.3	85.5	293	227	77.5	72.3	82.1	293	140	47.8	41.9	53.7
subject	TF	294	236	80.3	75.3	84.7	294	228	77.6	72.3	82.2	294	140	47.6	41.8	53.5

As can be seen in the table, there were no substantial differences between the PF and TF groups for any vaccine dose.

Table 19 below shows the solicited and unsolicited grade 3 symptoms for all vaccine doses in the Total vaccinated cohort. Again, there were no significant differences between the TF and PF groups for any vaccine dose though there were more reports of grade 3 symptoms in the TF group

Table 19 **Incidence and nature of Grade 3 symptoms (solicited and unsolicited) reported during the four-day (Days 0-3) post-vaccination period following each dose and overall (Total vaccinated cohort)**

	Group	Any symptom					General symptoms					Local symptoms*				
		N	N	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL				LL	UL
Dose 1	PF	293	10	3.4	1.6	6.2	293	7	2.4	1.0	4.9	293	3	1.0	0.2	3.0
	TF	294	7	2.4	1.0	4.8	294	5	1.7	0.6	3.9	294	2	0.7	0.1	2.4
Dose 2	PF	283	4	1.4	0.4	3.6	283	4	1.4	0.4	3.6	283	0	0.0	0.0	1.3
	TF	281	11	3.9	2.0	6.9	281	10	3.6	1.7	6.4	281	2	0.7	0.1	2.5
Dose 3	PF	264	10	3.8	1.8	6.9	264	4	1.5	0.4	3.8	264	5	1.9	0.6	4.4
	TF	260	13	5.0	2.7	8.4	260	10	3.8	1.9	7.0	260	5	1.9	0.6	4.4
Overall/ dose	PF	840	24	2.9	1.8	4.2	840	15	1.8	1.0	2.9	840	8	1.0	0.4	1.9
	TF	835	31	3.7	2.5	5.2	835	25	3.0	1.9	4.4	835	9	1.1	0.5	2.0
Overall/ subject	PF	293	20	6.8	4.2	10.3	293	13	4.4	2.4	7.5	293	8	2.7	1.2	5.3
	TF	294	27	9.2	6.1	13.1	294	22	7.5	4.7	11.1	294	7	2.4	1.0	4.8

Breaking out local from systemic symptoms also did not reveal significant differences between the vaccines. Of 55 SAEs reported during the active phase of the protocol and 12 reported during the 180 day extended safety follow-up, none were considered to be vaccine related.

Summary: The study in 587 infants to compare the safety and immunogenicity of the new thimerosal free EngerixB to the presently marketed vaccine with trace thimerosal termed preservative free has shown essentially no differences between the two formulations with regard to outcome. They both achieved similar seroprotection rates and GMTs one month after the third dose. Both had very similar safety profiles. Statistical analyses demonstrated that the primary endpoints of non-inferiority for immunogenicity at one month post dose 3 had been met.

Summary and critique of the clinical trials: In support of the change in formulation of EngerixB recombinant hepatitis B vaccine, the sponsor has completed 3 clinical trials. The first, HBV 269, was in 18-50 year olds and compared the new thimerosal free formulation with the presently marketed preservative free (trace thimerosal) and the original EngerixB containing thimerosal as a preservative. The second, HBV 270 compared 3 consecutive lots of TF EngerixB. The third trial, HBV 277, compared only preservative free with the thimerosal free formulation in infants born to non-HBsAg positive mothers. In trials 269 and 277, non-inferiority relative to currently licensed products was clearly established for both immunogenicity and safety. Detailed analyses of these trials based on the ATP cohort or the total vaccinated cohort did not reveal significant differences between the vaccines. In these two trials, 652 adults and 587 infants were enrolled. These studies included 217 adults and 294 infants who received the thimerosal free vaccine. In addition, 690 adults were enrolled in study 270 all of whom received the thimerosal free vaccine. A total of 1201 individuals were given the new vaccine formulation thought not all of these finished the entire protocol. There were no serious adverse events that were associated with the vaccine reported in any of these individuals. The non-serious AEs were essentially equivalent to those reported with the licensed products.