The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 104387 (HBV-308)

Title: A phase IV, single-blinded, randomized, single centre study to demonstrate the non-inferiority of immunogenicity elicited by GSK Biologicals' hepatitis B vaccine, Engerix™-B in multidose presentation to that elicited by Engerix™-B in monodose presentation when administered according to 0, 1, 6 months schedule in healthy adults aged ≥ 18 years.

Rationale: To evaluate the immunogenicity and safety of the currently licensed multidose Hepatitis B vaccine (HBV) (containing 2-phenoxyethanol as preservative) when compared to the currently licensed monodose HBV (without preservative) formulation.

Phase: IV

Study Period: 24 March 2005 to 12 December 2005

Study Design: Single-blinded, randomized (1:1) study with two parallel groups.

Centres: Single centre in Belgium.

Indication: Vaccination against Hepatitis B virus in healthy adults aged ≥ 18 years at the time of first vaccination.

Treatment: The study groups were as follows:

- Multidose group received the multidose presentation of HBV at 0, 1, and 6 months.
- Monodose group received the monodose presentation of HBV at 0, 1, and 6 months.

The vaccines were administered as a deep intramuscular injection in the deltoid region of the non-dominant arm.

Objectives:

- To demonstrate non-inferiority of multidose HBV to monodose HBV, in terms of anti-HBs antibodies (antibodies against hepatitis B surface antigen); seroprotection rate elicited one month after complete vaccination course (i.e. at Month 7).

Primary Outcome/Efficacy Variable:

Immunogenicity:

One month after the 3rd vaccine dose (Month 7):

- Anti-HBs antibody concentrations ≥ 10 mIU/mL (seroprotection rate).

Secondary Outcome/Efficacy Variable(s):

Immunogenicity:

One month after the 1st vaccine dose (Month 1), 1 month (Month 2) and 5 months (Month 6) after the 2nd vaccine dose and 1 month after the 3rd vaccine dose (Month 7):

- Anti-HBs antibody concentrations ≥ 10 mIU/mL (seroprotection rate).
- Anti-HBs antibody concentrations ≥ 3.3 mIU/mL (seropositivity rates).
- Geometric mean concentrations (GMCs) calculated on seropositive subjects.

Safety:

- Occurrence and intensity of solicited local symptoms during the 4-day follow-up period (Day 0–3) after vaccination.
- Occurrence, intensity and relationship of solicited general symptoms during the 4-day follow-up period (Day 0–3) after vaccination.
- Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) during the 31-day follow-up period (Day 0–30) after vaccination.
- Occurrence and relationship to vaccination of serious adverse events (SAEs) reported during the study period.

Statistical Methods:

The analyses were performed on the According-To-Protocol (ATP) Cohort for Immunogenicity and the Total Vaccinated Cohort.

- The Total Vaccinated Cohort included all vaccinated subjects for whom data were available.
- The ATP Cohort for Immunogenicity included all evaluable subjects who had received at least one dose of study vaccine/comparator according to their random assignment, who had not received a vaccine not specified or forbidden in the protocol, for whom assay results were available for anti-HBs antibodies at Month 7, and who were seronegative for Hepatitis B surface antigen (HBsAg), antibodies against Hepatitis B core antigen (anti-HBc) and anti-HBs antibodies prior to administration of first vaccination dose.

Analysis of immunogenicity:

The analysis was performed on the ATP Cohort for Immunogenicity.

For both groups, at each time point when a serological result was available, GMCs with 95% confidence intervals (CIs)

and seropositivity/seroprotection rates with exact 95% CIs were calculated.
The asymptotic standardized 95% CI on the difference in seroprotection rate at Month 7 (Multidose group minus Monodose group) was computed. If the lower limit of the CI was ≥ −10% (non-inferiority limit), non-inferiority of Multidose group with respect to Monodose group was to be concluded.

Analysis of safety:
The analysis was performed on the Total Vaccinated Cohort.
The percentage of subjects reporting any and Grade 3 solicited local and general symptoms during the 4-day (Day 0–3) follow-up period after each vaccination was tabulated with exact 95% CI. In addition, the percentage of subjects with each solicited general symptom, considered to be causally related to vaccination was tabulated with exact 95% CI.
The percentage of subjects with at least one report of unsolicited adverse event (AE) classified according to the Medical Dictionary for Regulatory Activities (MedDRA) terms during the 31-day (Day 0–30) follow-up period after each vaccination was tabulated. The percentage of subjects with Grade 3 unsolicited AEs and unsolicited AEs with a causal relationship to vaccination was tabulated. Serious adverse events (SAEs) during the study were tabulated according to the MedDRA preferred term.

Study Population: Healthy male and female adults aged ≥ 18 years, free of obvious health problems as established by medical history and clinical examination before entering the study were included. If female, the subject was of non-childbearing potential (either sterilized or post-menopausal) or if of childbearing potential, were abstinent or were using adequate contraceptive precautions. Subjects with previous vaccination against Hepatitis B or history of Hepatitis B infection or known exposure to Hepatitis B within 6 weeks prior to vaccination were excluded.

Number of Subjects:	**Multidose group**	**Monodose group**
Planned, N	140	140
Randomised, N (Total vaccinated cohort)	140	140
Completed, n (%)	139 (99.3)	136 (97.1)
Total Number Subjects Withdrawn, n (%)	1 (0.7)	4 (2.9)
Withdrawn due to Adverse Events n (%)	0 (0.0)	1 (0.7)
Withdrawn due to Lack of Efficacy n (%)	Not applicable	
Withdrawn for other reasons n (%)	1 (0.7)	3 (2.1)
Demographics	**Multidose group**	**Monodose group**
N (Total vaccinated cohort)	140	140
Females: Males	89:51	75:65
Mean Age, years (SD)	37.8 (14.94)	37.8 (14.76)
White/Caucasian, n (%)	140 (100)	137 (97.9)

Primary Efficacy Results:
Difference between groups in terms of anti-HBs seroprotection rate one month after the last vaccine dose (Month 7) (ATP cohort for immunogenicity)

						Difference in seroprotection rate			
						Difference	**%**	**95% CI**	
Group 1	**N**	**%**	**Group 2**	**N**	**%**			**LL**	**UL**
Multidose	130	92.3	Monodose	122	91.8	Multidose – Monodose	0.50	-6.48*	7.69

* Non-inferiority of Multidose group with respect to Monodose group can be concluded as the 95% CI of the LL is ≥ −10%
N = number of subjects with available results
% = percentage of subjects with anti-HBs antibody concentration ≥ 10 mIU/mL
95% CI = 95% Standardised asymptotic confidence interval; LL = lower limit, UL = upper limit

Secondary Outcome Variable(s):
Seropositivity, seroprotection rates and GMCs calculated for all subjects for anti-HBs antibodies (ATP cohort for immunogenicity)

Group	**Timing**	**N**	**Seropositivity (≥ 3.3 mIU/mL)**				**Seroprotection (≥ 10 mIU/mL)**				**GMC (mIU/mL)**		
			n	**%**	**95% CI**		**n**	**%**	**95% CI**		**mIU/mL**	**95% CI**	
					LL	**UL**			**LL**	**UL**		**LL**	**UL**
Multidose	PI(M1)	130	8	6.2	2.7	11.8	7	5.4	2.2	10.8	21.0	10.2	43.2
	PII(M2)	130	64	49.2	40.4	58.1	49	37.7	29.3	46.6	27.8	19.6	39.4
	PII(M6)	130	102	78.5	70.4	85.2	87	66.9	58.1	74.9	55.2	41.8	72.9
	PIII(M7)	130	122	93.8	88.2	97.3	120	92.3*	86.3	96.2	1788.7	1189.8	2689.3

Monodose	PI(M1)	122	14	11.5	6.4	18.5	9	7.4	3.4	13.5	25.9	10.3	65.1
	PII(M2)	120	58	48.3	39.1	57.6	46	38.3	29.6	47.6	31.9	22.5	45.3
	PII(M6)	122	95	77.9	69.5	84.9	83	68.0	59.0	76.2	61.3	45.9	81.9
	PIII(M7)	122	114	93.4	87.5	97.1	112	91.8*	85.4	96.0	1989.3	1308.0	3025.4

* Primary outcome/efficacy variable
N = number of subjects with available results
n (%) = number (percentage) of subjects with the specified antibody concentrations
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PI(M1) = Post Dose 1 (Month 1); PII(M2) = Post Dose 2 (Month 2)
PII(M6) = Post Dose 2 (Month 6); PIII(M7) = Post Dose 3 (Month 7)

Secondary Outcome Variable(s):
Incidence of solicited local symptoms during the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort)

Symptom	**Type**	**Multidose group**					**Monodose group**				
		N	**n**	**%**	**95% CI**		**N**	**n**	**%**	**95% CI**	
					LL	**UL**				**LL**	**UL**
Dose 1											
Pain	Any	140	58	41.4	33.2	50.1	139	55	39.6	31.4	48.2
	Grade 3	140	0	0.0	0.0	2.6	139	1	0.7	0.0	3.9
Redness	Any	140	10	7.1	3.5	12.7	139	12	8.6	4.5	14.6
	≥ 50 mm	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6
Swelling	Any	140	3	2.1	0.4	6.1	139	6	4.3	1.6	9.2
	≥ 50 mm	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6
Dose 2											
Pain	Any	140	49	35.0	27.1	43.5	137	41	29.9	22.4	38.3
	Grade 3	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
Redness	Any	140	10	7.1	3.5	12.7	137	9	6.6	3.0	12.1
	≥ 50 mm	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
Swelling	Any	140	4	2.9	0.8	7.2	137	2	1.5	0.2	5.2
	≥ 50 mm	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
Dose 3											
Pain	Any	140	45	32.1	24.5	40.6	137	53	38.7	30.5	47.4
	Grade 3	140	0	0.0	0.0	2.6	137	2	1.5	0.2	5.2
Redness	Any	140	13	9.3	5.0	15.4	137	12	8.8	4.6	14.8
	≥ 50 mm	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
Swelling	Any	140	7	5.0	2.0	10.0	137	6	4.4	1.6	9.3
	≥ 50 mm	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
Across Doses											
Pain	Any	140	80	57.1	48.5	65.5	139	80	57.6	48.9	65.9
	Grade 3	140	0	0.0	0.0	2.6	139	3	2.2	0.4	6.2
Redness	Any	140	23	16.4	10.7	23.6	139	22	15.8	10.2	23.0
	≥ 50 mm	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6
Swelling	Any	140	10	7.1	3.5	12.7	139	12	8.6	4.5	14.6
	≥ 50 mm	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6

N = number of subjects with a symptom sheet returned
n (%) = number (percentage) of subjects reporting the symptom at least once
95%CI = exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = incidence of a particular symptom irrespective of intensity grade
Grade 3 pain: pain that prevented normal activity

Secondary Outcome Variable(s):
Incidence of solicited general symptoms during the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort)

Symptom	Type	Multidose group					Monodose group				
		N	n	%	95% CI		N	n	%	95% CI	
					LL	UL				LL	UL
Dose 1											
Fatigue	Any	140	30	21.4	14.9	29.2	139	25	18.0	12.0	25.4
	Grade 3	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6
	Related	140	22	15.7	10.1	22.8	139	18	12.9	7.9	19.7
Fever (Axillary)	≥ 37.5°C	140	4	2.9	0.8	7.2	139	1	0.7	0.0	3.9
	> 39.0°C	140	0	0.0	0.0	2.6	139	0	0.0	0.0	2.6
	Related	140	4	2.9	0.8	7.2	139	1	0.7	0.0	3.9
Gastrointestinal	Any	140	10	7.1	3.5	12.7	139	11	7.9	4.0	13.7
	Grade 3	140	0	0.0	0.0	2.6	139	1	0.7	0.0	3.9
	Related	140	10	7.1	3.5	12.7	139	10	7.2	3.5	12.8
Headache	Any	140	25	17.9	11.9	25.2	139	21	15.1	9.6	22.2
	Grade 3	140	1	0.7	0.0	3.9	139	0	0.0	0.0	2.6
	Related	140	16	11.4	6.7	17.9	139	17	12.2	7.3	18.9
Dose 2											
Fatigue	Any	140	17	12.1	7.2	18.7	137	15	10.9	6.3	17.4
	Grade 3	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
	Related	140	13	9.3	5.0	15.4	137	8	5.8	2.6	11.2
Fever (Axillary)	≥ 37.5°C	140	2	1.4	0.2	5.1	137	1	0.7	0.0	4.0
	> 39.0°C	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
	Related	140	1	0.7	0.0	3.9	137	1	0.7	0.0	4.0
Gastrointestinal	Any	140	8	5.7	2.5	10.9	137	8	5.8	2.6	11.2
	Grade 3	140	0	0.0	0.0	2.6	137	2	1.5	0.2	5.2
	Related	140	5	3.6	1.2	8.1	137	5	3.6	1.2	8.3
Headache	Any	140	8	5.7	2.5	10.9	137	20	14.6	9.2	21.6
	Grade 3	140	0	0.0	0.0	2.6	137	2	1.5	0.2	5.2
	Related	140	4	2.9	0.8	7.2	137	11	8.0	4.1	13.9
Dose 3											
Fatigue	Any	140	19	13.6	8.4	20.4	137	20	14.6	9.2	21.6
	Grade 3	140	1	0.7	0.0	3.9	137	0	0.0	0.0	2.7
	Related	140	14	10.0	5.6	16.2	137	12	8.8	4.6	14.8
Fever (Axillary)	≥ 37.5°C	140	1	0.7	0.0	3.9	137	3	2.2	0.5	6.3
	> 39.0°C	140	0	0.0	0.0	2.6	137	1	0.7	0.0	4.0
	Related	140	1	0.7	0.0	3.9	137	1	0.7	0.0	4.0
Gastrointestinal	Any	140	13	9.3	5.0	15.4	137	8	5.8	2.6	11.2
	Grade 3	140	0	0.0	0.0	2.6	137	0	0.0	0.0	2.7
	Related	140	12	8.6	4.5	14.5	137	6	4.4	1.6	9.3
Headache	Any	140	21	15.0	9.5	22.0	137	21	15.3	9.7	22.5
	Grade 3	140	2	1.4	0.2	5.1	137	1	0.7	0.0	4.0
	Related	140	16	11.4	6.7	17.9	137	17	12.4	7.4	19.1
Across Doses											
Fatigue	Any	140	45	32.1	24.5	40.6	139	42	30.2	22.7	38.6
	Grade 3	140	1	0.7	0.0	3.9	139	0	0.0	0.0	2.6
	Related	140	37	26.4	19.3	34.5	139	28	20.1	13.8	27.8
Fever (Axillary)	≥ 37.5°C	140	6	4.3	1.6	9.1	139	5	3.6	1.2	8.2
	> 39.0°C	140	0	0.0	0.0	2.6	139	1	0.7	0.0	3.9
	Related	140	6	4.3	1.6	9.1	139	3	2.2	0.4	6.2
Gastrointestinal	Any	140	25	17.9	11.9	25.2	139	21	15.1	9.6	22.2
	Grade 3	140	0	0.0	0.0	2.6	139	3	2.2	0.4	6.2
	Related	140	22	15.7	10.1	22.8	139	18	12.9	7.9	19.7
Headache	Any	140	42	30.0	22.6	38.3	139	40	28.8	21.4	37.1
	Grade 3	140	3	2.1	0.4	6.1	139	2	1.4	0.2	5.1
	Related	140	31	22.1	15.6	29.9	139	36	25.9	18.8	34.0

N = number of subjects with a symptom sheet returned n (%) = number (percentage) of subjects reporting the symptom at least once 95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit Any = incidence of a particular symptom irrespective of intensity grade and relation to study vaccination Grade 3 symptoms = symptoms that prevented normal activity Related = any symptom that was causally related to vaccination		
Safety Results: Number (%) of subjects with unsolicited AEs (Total Vaccinated Cohort)		
Most frequent AEs - On-Therapy (occurring within day 0-30 following vaccination)	**Multidose group N = 140**	**Monodose group N = 140**
Subjects with any AE(s), n (%)	80 (57.1)	87 (62.1)
Subjects with severe AE(s), n (%)	13 (9.3)	13 (9.3)
Subjects with related AE(s), n (%)	20 (14.3)	18 (12.9)
Headache	28 (20.0)	22 (15.7)
Nasopharyngitis	17 (12.1)	18 (12.9)
Back pain	8 (5.7)	6 (4.3)
Injection site reaction	6 (4.3)	7 (5.0)
Dysmenorrhoea	4 (2.9)	6 (4.3)
Pharyngolaryngeal pain	6 (4.3)	4 (2.9)
Insomnia	4 (2.9)	5 (3.6)
Injection site haematoma	5 (3.6)	3 (2.1)
Diarrhoea	4 (2.9)	3 (2.1)
Rhinitis	4 (2.9)	3 (2.1)
Abdominal pain	2 (1.4)	4 (2.9)
Influenza like illness	5 (3.6)	1 (0.7)
Neck pain	5 (3.6)	1 (0.7)
Nausea	0 (0.0)	5 (3.6)
Laryngitis	4 (2.9)	0 (0.0)
Migraine	1 (0.7)	3 (2.1)
Cough	0 (0.0)	3 (2.1)
Ear pain	0 (0.0)	3 (2.1)
Toothache	0 (0.0)	3 (2.1)
Safety Results: Number (%) of subjects with SAEs (Total Vaccinated Cohort)		
SAE, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	**Multidose group N = 140**	**Monodose group N = 140**
Subjects with any SAE(s), n (%) [n related]	4 (2.9) [0]	5 (3.6) [0]
Bile duct stone	0 (0.0) [0]	1 (0.7) [0]
Breast cancer	0 (0.0) [0]	1 (0.7) [0]
Cholelithiasis	1 (0.7) [0]	0 (0.0) [0]
Convulsion	0 (0.0) [0]	1 (0.7) [0]
Nephrolithiasis	0 (0.0) [0]	1 (0.7) [0]
Pneumonia	1 (0.7) [0]	0 (0.0) [0]
Pneumonia primary atypical	0 (0.0) [0]	1 (0.7) [0]
Rib fracture	1 (0.7) [0]	0 (0.0) [0]
Upper limb fracture	1 (0.7) [0]	0 (0.0) [0]
Fatal SAEs	**Multidose group N = 140**	**Monodose group N = 140**
Subjects with fatal SAE(s), n (%) [related]	0 (0.0) [0]	0 (0.0) [0]

Conclusions: One month after the third vaccine dose (i.e. at Month 7), the percentage of subjects with anti-HBs antibody concentrations ≥ 10 mIU/mL (seroprotection rate) was 92.3% and 91.8% in Multidose and Monodose groups, respectively. Pain at injection site was the most frequently reported solicited local symptom, reported by 57.1% of subjects in the Multidose group and 57.6% of subjects in the Monodose group across doses.
Fatigue was the most frequently reported solicited general symptom across doses, reported by 32.1% of subjects in the Multidose group and 30.2% in Monodose group. At least one unsolicited adverse event was reported by 57.1% of subjects in the Multidose group and 62.1% of subjects in the Monodose group during the 31-day follow-up period after vaccination. Nine subjects (4 subjects in the Multidose group and 5 subjects in the Monodose group) reported non-related SAEs during the study period. No fatal SAEs were reported during the study period.

Date updated: 13-February-2015