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<b>Study No.:</b> 100386 (HAB-158 Ext- 082) Y5/ 100387 (HAB-159 Ext- 082) Y6
<b>Title:</b> Phase III, open, randomised study, in two centres, to demonstrate the equivalence of the 0, 12 month schedule to the 0, 6 month schedule with respect to the immunogenicity and to evaluate the safety and reactogenicity of GlaxoSmithKline Biologicals' Twinrix™ Adult vaccine (720 EL. U. of hepatitis A antigen/ 20 µg of recombinant hepatitis B surface antigen) in healthy volunteers aged from 12 to 15 years inclusive.
<b>Rationale:</b> To evaluate the long-term antibody persistence of anti-HAV (antibodies against hepatitis A virus) and anti-HBs (antibodies against hepatitis B surface antigen) antibodies at Month 60 and Month 72 after the first vaccine dose of the primary vaccination course. The study was also designed to evaluate the immune memory in subjects seronegative for anti-HAV or anti-HBs antibodies at the long-term blood sampling time point (i.e. Month 60 or Month 72), via the assessment of the immune response to an additional dose of the appropriate vaccine.
<b>Phase:</b> III
<b>Study Period:</b> Month 60: 29 September 2003 to 17 December 2003 Month 72: 07 September 2004 to 14 December 2005
<b>Study Design:</b> The follow-up at Month 60 and Month 72 were open studies with only a blood sample being taken. If a subject was found to be seronegative for anti-HAV antibodies (anti-HAV antibody concentration <15 mIU/mL), or had anti-HBs antibody concentration <10 mIU/mL at Month 60 or Month 72 long-term time-points, he/she was offered an additional vaccine dose of the relevant vaccine approximately 12 months after the Month 72 long-term blood sampling visit.
<b>Centres:</b> Two study centres in Australia.
<b>Indication:</b> Immunisation against hepatitis A and hepatitis B diseases of healthy subjects between 12 and 15 years at the time of vaccination.
<b>Treatment:</b> The study groups were as follows: <ul style="list-style-type: none"> <li>• Group 1: subjects received the combined HAB vaccine according to 0, 6 months schedule in the primary study.</li> <li>• Group 2: subjects received the combined HAB vaccine according to 0, 12 months schedule in the primary study.</li> </ul> The additional vaccine dose was administered as a deep intramuscular injection in the deltoid region of the non-dominant arm between 6 to 12 months after the Month 72 time point. Note: As all subjects had anti-HAV antibody concentrations ≥15 mIU/mL at Year 5 (i.e. Month 60) and at Year 6 (i.e. Month 72), no additional HAV dose was administered after the Month 72 time point.
<b>Objectives:</b> The objectives of this long-term follow-up study were: <ul style="list-style-type: none"> <li>• To evaluate anti-HAV and anti-HBs antibody persistence at Year 5 (i.e. Month 60) and Year 6 (i.e. Month 72) after the first vaccine dose of two-dose primary vaccination.</li> <li>• To evaluate the immune memory (after a primary two-dose schedule of the combined HAB [hepatitis A and B] 720/20 vaccine) in subjects who became seronegative for anti-HAV antibodies or had anti-HBs antibody concentrations &lt;10 mIU/mL at the long-term blood sampling time point (i.e. Month 60 or Month 72) and who received the additional vaccine dose (administered between 6 to 12 months after the Month 72 time point).</li> </ul>
<b>Primary Outcome/Efficacy Variables:</b> At Year 5 & 6, i.e. at 60 and 72 months after the first vaccine dose of the two-dose primary vaccination: <ul style="list-style-type: none"> <li>• Seropositivity rates and geometric mean concentrations (GMCs) (calculated on seropositive subjects) for anti-HAV antibodies,</li> <li>• Seropositivity rates, percentage of subjects with antibody concentrations ≥10 mIU/mL and GMCs (calculated on seropositive subjects) for anti-HBs antibodies.</li> </ul> At Month 85, for the subjects who received an additional dose of hepatitis B vaccine at Month 84: <ul style="list-style-type: none"> <li>• Seropositivity rates, seroprotection rates and GMCs (calculated on seropositive subjects) for anti-HBs antibodies.</li> </ul>
<b>Secondary Outcome/Efficacy Variable(s):</b> <ul style="list-style-type: none"> <li>• Occurrence of solicited local and general symptoms within 4 days (Day 0-3) after the booster dose of hepatitis B vaccine.</li> <li>• Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0-30) after the booster dose of hepatitis B vaccine.</li> <li>• Occurrence of serious adverse events (SAEs) after the booster dose of hepatitis B vaccine.</li> </ul>
<b>Statistical Methods:</b> The analyses were performed on the Total Vaccinated Cohort.

- The Total Vaccinated Cohort (or Long-term Total Cohort) included all subjects vaccinated during the primary study, who returned to the follow-up study and for whom serology results were available for anti-HAV and/or anti-HBs antibodies.
- The ATP immunogenicity cohort (or Long-term ATP immunogenicity cohort) included all subjects from the Total vaccinated cohort who were included in the ATP cohort for immunogenicity in the primary study and who complied with the eligibility criteria as defined in the protocol.

*Analysis of immunogenicity*

The analyses were performed on the ATP cohort for immunogenicity and the Total Vaccinated Cohort. At each time point and for each group, GMCs were calculated for seropositive subjects with their 95 % confidence intervals (CIs). Seropositivity rates (HAV & HBV) and seroprotection rates (HBV) were calculated with their 95 % CIs per group for each time point. A subject with anti-HAV antibody concentration  $\geq 15$  mIU/mL was considered seropositive. A subject with anti-HBs antibody concentration  $\geq 3.3$  mIU/mL was considered seropositive and a subject with anti-HBs antibody concentration  $\geq 10$  mIU/mL was considered seroprotected.

*Analysis of safety*

The analyses were performed on the Total Vaccinated Cohort for subjects who received an additional dose of hepatitis B vaccine after Year 6 time point.

The percentage, with 95% CI, of subjects reporting any and Grade 3 individual solicited local symptoms during the 4-day (Day 0-3) follow-up period after the booster vaccination was tabulated. The percentage, with 95% CI, of subjects reporting any, Grade 3 and related individual solicited general symptoms during the 4-day (Day 0-3) follow-up period after the booster vaccination was tabulated. The percentage of subjects reporting unsolicited AEs, classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms during the 31-day (Day 0-30) follow-up period after booster vaccination was tabulated.

All SAEs occurring during the 30-day follow-up period after booster vaccination were to be tabulated per group according to MedDRA preferred terms.

**Study Population:** All subjects who were vaccinated in the primary study were eligible to be part of this study. Written informed consent was obtained from the subjects for all study procedures before the first blood-sampling visit at Month 60.

**For subjects included in the Year 5 (Month 60) persistence analysis**

<b>Number of subjects:</b>	<b>Group 1</b>	<b>Group 2</b>
<b>Demographics</b>	Group 1	Group 2
Planned, N	Not applicable	Not applicable
Randomised, N (Total Vaccinated Cohort)	67	81
N (Total Vaccinated Cohort)	67	81
Total Number Subjects Withdrawn, n (%)	Not applicable	Not applicable
Withdrawn due to AEs, n (%)	Not applicable	Not applicable
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	Not applicable	Not applicable
<b>Demographics</b>	<b>Group 1</b>	<b>Group 2</b>
Females: Males	23:44	37:44
Mean Age, years (SD)	18.8 (1.02)	18.6 (1.10)
White/ Caucasian, n (%)	64 (95.5)	77 (95.1)

**For subjects included in the Year 6 (Month 72) persistence analysis**

<b>Number of subjects:</b>	<b>Group 1</b>	<b>Group 2</b>
<b>Demographics</b>	Group 1	Group 2
Planned, N	Not applicable	Not applicable
Randomised, N (Total Vaccinated Cohort)	65	76
Completed, n (%)	65 (100)	76 (100)
Total Number Subjects Withdrawn, n (%)	Not applicable	Not applicable
Withdrawn due to AEs, n (%)	Not applicable	Not applicable
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	Not applicable	Not applicable
<b>Demographics</b>	<b>Group 1</b>	<b>Group 2</b>
N (Total Cohort)	65	76
Females: Males-	24:41	36:40
Mean Age, years (SD)	19.7 (1.05)	19.5 (1.08)
White/Caucasian, n (%)	61 (93.8)	71 (93.4)

**Primary Efficacy Results:**

Seropositivity rates and GMCs (calculated on seropositive subjects) for anti-HAV antibodies (ATP cohort for

immunogenicity).													
Group	Timing	N	S+		95% CI		GMC (mIU/mL)	95% CI					
			n	%	L.L.	U.L.		L.L.	U.L.				
1	PI(M1)	106	104	98.1	93.4	99.8	364.7	298.2	446.9				
	PI(M6)	105	100	95.2	89.2	98.4	140.4	120.1	164.1				
	PII(M7)	104	104	100	96.5	100	5991.7	5020.1	7151.4				
	PII (M7)*	104	104	100	96.5	100	8685.1	6889.9	10948.2				
	PII (M24)	89	89	100	95.9	100	743.5	588.7	938.9				
	PII (M36)	83	82	98.8	93.5	100	620.3	491.4	782.9				
	PII(M60)	54	53	98.1	90.1	100	536.3	414.7	693.6				
	PII(M72)**	46	46	100	92.3	100	529.0	391.6	714.7				
2	PI(M1)	102	101	99.0	94.7	100	293.9	241.3	358.1				
	PI(M12)	101	85	84.2	75.6	90.7	146.5	121.1	177.1				
	PII(M13)	101	100	99.0	94.6	100	8471.8	6970.6	10296.3				
	PII (M13)*	101	101	100	96.4	100	8910.4	6913.1	11484.6				
	PII (M24)	81	80	98.8	93.3	100	1704.7	1343.2	2163.5				
	PII (M36)	86	85	98.8	93.7	100	1273.6	1010.7	1604.8				
	PII(M60)	57	57	100	93.7	100	880.6	650.0	1193.0				
	PII(M72)**	42	42	100	91.6	100	932.6	655.9	1326.1				
* Blood samples at Month 7 in Group 1 and at Month 13 in Group 2 (i.e. the last blood sampling time point of the primary study) were re-tested with the new assay kits. Blood samples starting from Month 24 were tested using the new assay kits.													
** Primary endpoint.													
N: number of subjects with available results.													
PI (M1) etc.: 1 month after first vaccine dose, post vaccine Dose I, etc.													
S+ : seropositive for anti-HAV antibodies (antibody concentrations $\geq 33$ mIU/mL for the primary study time points and concentrations $\geq 15$ mIU/mL at months 24, 36, 60 & 72)													
n = number of subjects who were seropositive for anti-HAV antibodies													
95% CI: 95% confidence interval; LL = Lower Limit, UL = Upper Limit													
<b>Primary Efficacy Results:</b>													
Seropositivity rates, percentage of subjects with antibody concentrations $\geq 10$ mIU/mL and GMCs (calculated on seropositive subjects) for anti-HBs antibodies (ATP cohort for immunogenicity).													
Group	Timing	N	S+		95% CI		$\geq 10$ mIU/mL		95% CI		GMC (mIU/mL)	95% CI	
			n	%	LL	UL	n	%	LL	UL		LL	UL
1	PI(M1)	106	73	69.9	59.1	77.5	46	43.4	33.8	53.4	17.0	11.1	26.2
	PI(M6)	105	92	87.6	79.8	93.2	62	59.0	49.0	68.5	17.3	13.3	22.4
	PII(M7)	104	104	100	96.5	100	102	98.1	93.2	99.8	2791.4	1837.6	4240.3
	PII (M7)*	103	102	99.0	94.7	100	101	98.1	93.2	99.8	4705.8	3179.3	6965.3
	PII (M24)	89	83	93.3	85.9	97.5	81	91.0	83.1	96.0	248.2	168.0	366.7
	PII (M36)	83	74	89.2	80.4	94.9	68	81.9	72.0	89.5	149.3	99.6	223.8
	PII(M60)	54	52	96.3	87.3	99.5	44	81.5	68.6	90.7	81.5	49.6	134.0
	PII(M72)**	46	43	93.5	82.1	98.6	39	84.8	71.1	93.7	108.7	62.8	188.0
2	PI(M1)	102	64	62.7	52.6	72.1	35	34.3	25.2	44.4	15.0	9.5	23.8
	PI(M12)	101	79	78.2	68.9	85.8	51	50.5	40.4	60.6	16.1	11.6	22.3
	PII(M13)	101	100	99.0	94.6	100	98	97.0	91.6	99.4	4339.5	2793.0	6742.4
	PII(M13)*	101	99	98.0	93.0	99.8	98	97.0	91.6	99.4	6744.1	4486.4	10137.7
	PII (M24)	81	80	98.8	93.3	100	76	93.8	86.2	98.0	569.6	335.2	968.0
	PII (M36)	86	80	93.0	85.4	97.4	75	87.2	78.3	93.4	400.5	240.2	667.8
	PII(M60)	57	57	100	93.7	100	53	93.0	83.0	98.1	213.5	118.4	384.8
	PII(M72)**	42	42	100	91.6	100	39	92.9	80.5	98.5	231.9	111.5	482.2
* Blood samples at Month 7 in Group 1 and at Month 13 in Group 2 (i.e. the last blood sampling time point of the primary study) were re-tested with the new assay kits. Blood samples from Month 24 onwards were tested using the new assay kits.													
** Primary endpoint.													
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) etc.: 1 month after first vaccine dose, post vaccine Dose I, etc.  
 S+ : seropositive for anti-HBs antibodies (antibody concentrations  $\geq 1$  mIU/mL for the primary study time points and concentrations  $\geq 3.3$  mIU/mL at Months 24, 36, 60 & 72)

**Primary Efficacy Results:**

From the Total vaccinated cohort, 23 subjects had become seronegative for anti-HBs antibodies and were invited to receive an additional dose of hepatitis B vaccine; 14 subjects out of the 23 returned for the additional hepatitis B vaccination. Seropositivity rates, seroprotection rates and GMCs (calculated on seropositive subjects) for anti-HBs antibodies (Total Vaccinated Cohort - subjects who received an additional dose of hepatitis B vaccine)

Group	Timing	N	n	$\geq 3.3$ mIU/mL			$\geq 10$ mIU/mL				GMCs		
				%	95% CI		n	%	95% CI		mIU/mL	95% CI	
					LL	UL			LL	UL			
1	PII(M72)	5	3	60.0	14.7	94.7	0	0.0	0.0	52.2	5.7	2.3	14.2
	PII(M84)	6	4	66.7	22.3	95.7	0	0.0	0.0	45.9	6.0	2.8	12.5
	PIII(M85)	6	6	100	54.1	100	6	100	54.1	100	2574.0	1188.5	5574.4
2	PII(M72)	8	6	75.0	34.9	96.8	0	0.0	0.0	36.9	6.0	5.2	7.0
	PII(M84)	8	7	87.5	47.3	99.7	3	37.5	8.5	75.5	7.5	4.6	12.4
	PIII(M85)	8	8	100	63.1	100	8	100	63.1	100	692.9	156.4	3068.9

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  
 PII(M72): 72 months after first vaccine dose, post vaccine Dose II  
 PII(M84): prior to the booster vaccination  
 PIII(M85): post booster vaccination

**Solicited Symptoms:** Incidence of solicited local symptoms reported during the 4-day (Day 0-3) post-vaccination period after the booster dose (Total Vaccinated Cohort – all subjects from both groups who received an additional dose of hepatitis B vaccine)

Symptom	Type	Pooled groups (1 & 2)				
		N	n	%	95% CI	
					LL	UL
Pain	Any	14	7	50.0	23.0	77.0
	Grade 3	14	1	7.1	0.2	33.9
Redness (mm)	Any	14	3	21.4	4.7	50.8
	$\geq 50$ mm	14	0	0.0	0.0	23.2
Swelling (mm)	Any	14	3	21.4	4.7	50.8
	$\geq 50$ mm	14	0	0.0	0.0	23.2

N= number of subjects with a documented dose  
 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 regardless of grade.  
 Grade 3 pain =spontaneously painful, preventing normal activities

**Solicited Symptoms:** Incidence of solicited general symptoms reported during the 4-day (Day 0-3) post-vaccination period after the booster dose (Total Vaccinated Cohort – all subjects from both groups who received an additional dose of Hepatitis B vaccine)

Symptom	Type	Pooled groups (1 & 2)				
		N	n	%	95% CI	
					LL	UL
Fatigue	Any	14	4	28.6	8.4	58.1
	Grade 3	14	1	7.1	0.2	33.9
	Related	14	0	0.0	0.0	23.2
Fever (axillary temperature)	$\geq 37.5$ °C	14	1	7.1	0.2	33.9
	$> 38.5$	14	0	0.0	0.0	23.2
	Related	14	0	0.0	0.0	23.2
Gastrointestinal	Any	14	1	7.1	0.2	33.9

<b>Symptoms</b>	Grade 3	14	0	0.0	0.0	23.2
	Related	14	0	0.0	0.0	23.2
<b>Headache</b>	Any	14	2	14.3	1.8	42.8
	Grade 3	14	0	0.0	0.0	23.2
	Related	14	0	0.0	0.0	23.2

N= number of subjects with a documented dose  
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 regardless of grade and relationship to study vaccination.  
Grade 3: symptom that prevented normal activities  
Related: general symptoms considered by the investigator to have probable or suspected relationship to the study vaccine.

**Safety Results:** Number (%) of subjects with unsolicited AEs during the 31-day (Day 0-30) follow-up period after vaccination (Total Vaccinated Cohort - subjects who received an additional dose of hepatitis B vaccine)

<b>Most frequent AEs - On-Therapy (occurring within Day 0-30 following vaccination)</b>	<b>Pooled groups ( 1 &amp; 2) N = 14</b>
Subjects with any AE(s), n (%)	2 (14.3)
Arthralgia	1(7.0)
Joint stiffness	1(7.0)
Malaise	1 (7.0)
Cough	1 (7.0)
Pharyngolaryngeal pain	1 (7.0)
<b>SAEs - Following vaccination n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>Pooled groups ( 1 &amp; 2) N = 14</b>
Subjects with any SAE(s), n (%) [n Related]	0 (0.0) [0]
<b>Fatal SAEs</b>	<b>Pooled groups ( 1 &amp; 2) N = 14</b>
Subjects with fatal SAE(s), n (%) [related]	0 (0.0) [0]

**Conclusion:** At the Month 72 long-term time point (i.e. 6 years after the first dose of the primary vaccination), all subjects in both groups had anti-HAV antibodies concentrations  $\geq 15$  mIU/mL; 84.8% of subjects in Group 1 and 92.9% of subjects in Group 2 had anti-HBs antibody concentrations  $\geq 10$  mIU/mL.  
One month after receiving the additional dose of HBV vaccine, all subjects who had anti-HBs concentrations  $<10$  mIU/mL at the Month 72 long-term follow-up time point were found to have seroprotective anti-HBs antibody concentrations  $\geq 10$  mIU/mL.  
No SAEs were reported after the additional hepatitis B vaccine dose.

**Publications:**  
Burgess MA. et al. Comparative immunogenicity and safety of two dosing schedules of a combined hepatitis A and B vaccine in healthy adolescent volunteers: an open, randomised study.  
*Vaccine*. 2001, (19) 4835-4841

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