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Committee for Medicinal Products for Human Use (CHMP)

Twinrix Paediatric

(Hepatitis A virus (inactivated) / hepatitis B surface antigen)

Procedure No. EMEA/H/C/000129/P45/042

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

I. INTRODUCTION

On 9th December 2008 the MAH submitted four completed paediatric studies relevant to Ambirix and Twinrix Paediatric in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview was provided for each study.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Ambirix or Twinrix Paediatric and that there is no consequential regulatory action.

The assessor agrees that the MAH has fulfilled Article 45 for the two vaccines as a result of this submission and that there are no implications for the prescribing information.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies

Ambirix is the exact same product as Twinrix Adult and therefore contains twice as much inactivated HAV (720 EL.U/ml compared to 360 EL.U/ml) and rHBsAg (20 μg rHBsAg compared to 10 μg) as Twinrix Paediatric.

Both products may be used to immunise children aged from 1-15 years against hepatitis A and B but offer the alternative of two doses of Ambirix administered at least 6 months apart versus a standard three-dose regimen of Twinrix Paediatric administered at 0, 1 and 6 months.

The advantage of the Twinrix Paediatric three-dose regimen is that a higher degree of protection (especially against hepatitis B) can be expected between months 1 and 6 compared to that between months 0 and 6-12 of a two-dose Ambirix regimen. Therefore the choice between products depends on how quickly it is desired to elicit a high level of immunity to both viruses. If there is no hurry then prescribers, parents and children may prefer the 2-dose Ambirix due to the lesser number of injections.

Due to the overlapping nature of these products and their relevance to the paediatric population the Rapporteur has chosen to include the four studies in a single assessment report.

II.2 Non-clinical aspects

Not applicable.

II.3 Clinical aspects

1. Introduction

The MAH submitted reports for:

Ambirix: **Studies HAB-051, -052 and -053**
Twinrix Paediatric **Study HAB-164 Ext 038 Year 10**

2. Clinical studies

HAB-051

The study was conducted in Taiwan in 1997-1998 and the study report is dated October 29th 1998.

- Objectives

Primary Objective
To compare the immunogenicity of Ambirix administered alone with that of Havrix and Engerix B (both adult dose versions) when given concomitantly into opposite arms.
Secondary Objective
To evaluate the reactogenicity after each dose of Ambirix compared to co-administration of Havrix and Engerix B.

- Study design

This was an open, randomised study in which 64 subjects were to receive Ambirix or Havrix + Engerix B with dosing at Month 0 and Month 6. Blood samples were obtained on the day of screening and at months 1, 6, and 7 for assay of anti-HAV and anti-HBsAg antibodies.

Approximately six hours post vaccination and in the morning for three subsequent days parents were to record general (systemic) and local injection site signs and symptoms, including axillary body temperature.

- Study population /Sample size

Subjects were to be between 1 and 11 years old and seronegative for anti-HAV and anti-HBs at screening.

The sample size calculation was based on the primary serological end-points but was not fixed by a statistical method. The number selected was considered sufficient to draw valid clinical conclusions. Results of similar studies showed that seroconversion rates after Havrix and seroprotection rates after Engerix-B were both 95 %. With 50 completed and evaluable subjects by group, a power of 80 % and an alpha level of 5 % using the Bonferroni correction for multiple testing, a 25 % difference between the two groups could be detected for either the anti-HAV seroconversion rate or the anti-HBs seroprotection rate.

- Treatments

Group 1 received Ambirix and Group 2 received full strength Havrix + Engerix B. Single lots were used.

- Outcomes/endpoints

- Seroconversion rates for hepatitis A and seroprotection rates for hepatitis B
- GMTs at month 7
- Nature and incidence of the reactions after each dose administration.

- Statistical Methods

Two analyses were performed: ATP and ITT.

Seropositivity was defined as the appearance of antibodies ≥ 1 mIU/ml for anti-HBs and ≥33mIU/ml for anti-HAV. Seroprotection against HBV was defined as anti-HBs ≥ 10 mIU/ml. The seroconversion and seroprotection rates were compared using Fisher's exact test. The corresponding GMTs were compared by the ANOVA one-way test or by a nonparametric test (Kruskal-Wallis test).

➢ **Results**

- Recruitment/ Number analysed

Two of the 64 volunteers enrolled were eliminated from the analysis of reactogenicity as one of the study vaccine doses was not administered. One subject was eliminated from the immunogenicity analysis as no blood sampling was done at month 7. Hence, 61 completed the study up to month 7.

- Baseline data

Group	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D (years)
1	Female	13	8.0	5	11	1.63
	Male	19	7.5	2	11	2.39
	Total	32	7.7	2	11	2.10
2	Female	12	7.3	1	11	3.08
	Male	20	6.9	2	11	2.43
	Total	32	7.0	1	11	2.65
Total	Female	25	7.6	1	11	2.41
	Male	39	7.2	2	11	2.39
	Total	64	7.4	1	11	2.39

Notes: Group 1 received HAB lot DHAB401A2
Group 2 received Havrix lot VHA525A2/M and Engerix-B lot DHBP4302

- Immunogenicity

Hepatitis A

All subjects seroconverted after a single dose of vaccine except for one in the Ambirix group. All subjects were seropositive at Month 7 with comparable GMTs between vaccine groups. The increases in anti-HAV GMTs from month 1 to month 7 were 88.7% and 91.8%.

Group	Timing	N	S +		CI 95%	GMT	CI 95%
			n	%			
1	PI(M1)	30	29	96.7	82.8 - 99.9	325	240 - 440
	PI (M6)	30	29	96.7	82.8 - 99.9	119	93 - 152
	PII (M7)	30	30	100.0	88.4 - 100.0	2865	1964 - 4179
2	PI(M1)	31	31	100.0	88.8 - 100.0	252	185 - 343
	PI(M6)	31	31	100.0	88.8 - 100.0	140	106 - 184
	PII(M7)	31	31	100.0	88.8 - 100.0	3062	2145 - 4372

Notes: Group 1 received HAB lot DHAB401A2
Group 2 received Havrix lot VHA525A2/M and Engerix-B lot DHBP4302
PI(M1), etc. = post vaccination blood sampling one month following dose 1, etc.
N = number of subjects tested
S+ = seropositive to anti-HAV antibody titres (anti-HAV titre ≥ 33mIU/ml).
n = number of subjects who had anti-HAV seropositive antibody titres.
95% CI, L.L. and U.L. = 95% confidence intervals

Statistics:
Seropositvity: No statistically significant difference between groups at any time point.
PI (M1) : p =0.49, PI (M 6) : p =0.49 (Fisher's exact test)
GMTs (mIU/ml): No statistically significant difference between groups at any time point.
PI (M1) : p = 0.11 (Kruskal-Wallis test), PI (M6): p= 0.38, PII (M7) : p =0.79 (One-way ANOVA)

Hepatitis B

One month after the first dose > 90% had already seroconverted and about 80% were seroprotected. At month 7, all subjects were seropositive, all except one was seroprotected and the GMTs were comparable.

G	Timing	N	S+		C I 95%		SP		C I 95%	GMT	C I 95%
			n	%	L.L.	U. L.	n	%			
1	PI(M1)	30	28	93.3	77.9	99.2	24	80.0	61.4 - 92.3	135	51 - 359
	PI(M6)	30	29	96.7	82.8	99.9	23	76.7	57.7 - 90.1	39	19 - 80
	PII(M7)	30	30	100.0	88.4	100.0	30	100.0	88.4 -	1243	716 - 2159
2	PI(M1)	31	28	90.3	74.2	98.0	25	80.6	62.5 - 92.5	236	104 - 535
	PI(M6)	31	30	96.8	83.3	99.9	24	77.4	58.9 - 90.4	40	20 - 81
	PII(M7)	31	31	100.0	88.8	100.0	30	96.8	83.3 - 99.9	1379	712 - 2669

Notes: Group 1 received HAB lot DHAB401A2
Group 2 received Havrix lot VHA525A2/M and Engerix-B lot DHBP4302
PI m1, etc. = post vaccination blood sampling one month following dose 1, etc..
N = number of subjects tested;
S+= seropositive anti-HBs antibody titres (anti-HBs titre ≥ assay cut-off of 1 mlU/ml)
SP= seroprotective anti-HBS antibody titres (anti-HBs titre ≥10 mlU/ml)
n = number of subjects who had anti-HBs seropositive/ seroprotective antibody titres
CI 95% L.L, U.L = 95% confidence interval

Statistics:
Seropositivity : No statistically significant difference between groups at any time point.
PI (M1) : p =1.00, PI (M6) : p =1.00 (Fisher's exact test)
Seroprotection: No statistically significant difference between groups at any time point.
PI (M1) : p = 1.00, PI (M6) : p = 1.00, PII (M7) : p= 1.00 (Fisher's exact test)
GMTs : No statistically significant difference between groups at any time point.
PI (M1) : p =0.37, PI (M6): p = 0.97, PII (M7) : p=0.81 (One-way ANOVA)

The results for the total population immunogenicity analysis were consistent with those for the ATP cohort.

- Safety

Overall, solicited or unsolicited signs and symptoms within the 4-day follow-up periods were reported following 24.2% of doses of Ambirix and 66.1% of doses in the HAV+HBV group. Local symptoms predominated. The rates of solicited symptoms can be summarised as follows:

Dose	Group	N	Symptoms		General		Local					
							HAB		Havrix		Engerix-B	
			n	%	n	%	n	%	n	%	n	%
1	1	31	4	12.9	1	3.2	3	9.7	-	-	-	-
	2	31	19	61.3	5	16.1	-	-	14	45.2	12	38.7
2	1	31	11	35.5	4	12.9	8	25.8	-	-	-	-
	2	31	22	71.0	3	9.7	-	-	19	61.3	20	64.5
Overall	1	62	15	24.2	5	8.1	11	17.7	-	-	-	-
	2	62	41	66.1	8	12.9	-	-	33	53.2	32	51.6

Notes: Group 1 received HAB lot DHAB401A2
Group 2 received Havrix lot VHA525A2/M and Engerix-B lot DHBP4302
This table includes both solicited and unsolicited symptoms reported on symptom sheets.

All solicited local signs and symptoms were assumed to be related to vaccination. After all doses, redness at the injection site was the most frequently reported solicited local symptom. One local injection site symptom was grade 3. All solicited local symptoms resolved within the 4-day follow-up period.

		After dose 1						After dose 2					
Symptom	Incidence and intensity	Group 1 N=31		Group 2 N=31				Group 1 N=31		Group 2 N=31			
				Havrix		Engerix-B				Havrix		Engerix-B	
		n	%	n	%	n	%	n	%	n	%	n	%
Redness	Total	0	0.0	6	19.4	2	6.5	8	25.8	18	58.1	18	58.1
	grade "3"*	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Soreness	Total	2	6.5	10	32.3	11	35.5	0	0.0	7	22.6	7	22.6
	grade "3"*	0	0.0	0	0.0	1	3.2	0	0.0	0	0.0	0	0.0
Swelling	Total	1	3.2	4	12.9	2	6.5	4	12.9	12	38.7	12	38.7
	grade "3"*	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Following dose 1 and dose 2, the concomitant HAV+HBV group had a higher incidence of local symptoms.

After all doses							
Symptom	Incidence and intensity	Group 1 N=62		Group 2 N=62			
				Havrix		Engerix-B	
		n	%	n	%	n	%
Redness	Total	8	12.9	24	38.7	20	32.3
	grade "3"*	0	0.0	0	0.0	0	0.0
Soreness	Total	2	3.2	17	27.4	18	29.0
	grade "3"	0	0.0	0	0.0	1	1.6
Swelling	Total	5	8.1	16	25.8	14	22.6
	grade "3"*	0	0.0	0	0.0	0	0.0

Headache was the most frequently reported solicited general symptom. All general solicited signs and symptoms except two cases of fatigue were considered to be unrelated to the vaccines. None was of grade 3 and most lasted less than one day.

		After dose 1				After dose 2			
Symptom	Incidence and intensity	Group 1 N=31		Group 2 N=31		Group 1 N=31		Group 2 N=31	
		n	%	n	%				
Fatigue	Total	0	0.0	2	6.5	3	9.7	3	4.8
	R/PR	0	0.0	0	0.0	2	6.5	0	0.0
Fever	Total	0	0.0	1	3.2	0	0.0	2	3.2
	R/PR	0	0.0	0	0.0	0	0.0	0	0.0
Headache	Total	1	3.2	5	16.1	3	9.7	7	11.3
	R/PR	0	0.0	0	0.0	0	0.0	0	0.0
Malaise	Total	0	0.0	1	3.2	0	0.0	1	1.6
	R/PR	0	0.0	0	0.0	0	0.0	0	0.0
Nausea	Total	0	0.0	1	3.2	1	3.2	1	1.6
	R/PR	0	0.0	0	0.0	0	0.0	0	0.0
Vomiting	Total	0	0.0	1	3.2	0	0.0	1	1.6
	R/PR	0	0.0	0	0.0	0	0.0	0	0.0

One subject reported 3 unsolicited symptoms within 30 days of the first dose. All the three symptoms were grade 1 and were considered to be unrelated to vaccination.

No serious adverse event was reported in the study and no subject received concomitant medication.

HAB-052

This study was also conducted in Taiwan but from 1996-1998 at a different site and in adolescents aged from 10-19 years that were seronegative for anti-HAV and anti-HBs at screening. The study report is dated November 9th 1998.

The study design was essentially the same as that for HAB-051 described above.

- **Results**

- Recruitment/ Number analysed

Of the 103 enrolled four subjects were eliminated from the analysis of reactogenicity as a study vaccine dose was not administered. Three subjects were eliminated from the analysis of immunogenicity. Thus, 99 completed the study up to month 7 and 96 were assessed for immune responses.

- Baseline data

G	Sex	N	Mean age (years)	Min age (years)	Max age (years)	S.D (years)
1	Female	24	14.2	10	19	2.90
	Male	27	14.0	10	17	2.53
	Total	51	14.1	10	19	2.68
2	Female	19	12.1	10	18	1.79
	Male	33	12.5	10	19	2.43
	Total	52	12.4	10	19	2.21
Total	Female	43	13.3	10	19	2.66
	Male	60	13.2	10	19	2.56
	Total	103	13.2	10	19	2.59

Notes: Group 1 received: HAB lot HABP706A2
Group 2 received Havrix lot DVHAP7205A2 and Engerix-B lot DHBP43D2.

- Immunogenicity

Hepatitis A response

At month 1 all except one subject in each group had already seroconverted. All subjects were seropositive at month 7 at which time the anti-HAV GMT in the Ambirix group was more than twice that in the concomitant HAV + HBV group and the 95% CI did not overlap. The increase in anti-HAV GMTs from month 1 to month 7 was 89.8 % for the Ambirix group and 87.2% for Group 2.

Group	Timing	N	S+		CI 95%	GMT	CI 95%
			n	%			
1	PI(m1)	49	48	98.0	89.1-99.9	379	277-519
combined	PI (m2)	49	47	95.9	86.0-99.5	210	162-273
HAB vaccine	PI(m6)	49	42	85.7	72.8-94.1	122	92-160
	PII(m7)	49	49	100.0	92.7-100.0	3701	2959-4630
2	PI(m1)	47	46	97.9	88.7-99.9	219	168-287
concomitant	PI (m2)	47	43	91.5	79.6-97.6	136	109-168
HAV + HBV	PI(m6)	47	40	85.1	71.7-93.8	74	60-92
	PII(m7)	47	47	100.0	92.5-100.0	1705	1343-2165

Notes: Group 1 received: HAB lot HABP706A2
Group 2 received Havrix lot DVHAP7205A2 and Engerix-B lot DHBP43D2.

Hepatitis B response

At month 1, 61.2% in the Ambirix group and 70.2% in the concomitant HAV + HBV group had seroconverted and about half the vaccinees in each group were seroprotected. At month 6, seropositivity had increased in both groups to 79.6% and 72.3% while seroprotection rates were 51.0% and 42.6%. At month 7 the seroprotection rate in the Ambirix group was 91.8% compared to 95.7% in the concomitant HAV + HBV group, yet the GMT was approximately 2 times higher in the Ambirix group. The increase in GMTs from month 1 to month 7 was 96.4% in the Ambirix group and 95.0% in the concomitant HAV + HBV group.

Group	Timing	N	S+		CI 95%	SP		CI 95%	GMT	CI 95%
			n	%		n	%			
1	PI(m1)	49	30	61.2	46.2-74.8	25	51.0	36.3-65.6	55	24 -127
combined	PI(m2)	49	36	73.5	58.9-85.1	20	40.8	27.0-55.8	19	9-42
HAB	PI(m6)	49	39	79.6	65.7-89.8	25	51.0	36.3-65.6	17	8-33
vaccine	PII(m7)	49	46	93.9	83.1-98.7	45	91.8	80.4 -97.7	1524	844-2752
2	PI(m1)	47	33	70.2	55.1-82.7	23	48.9	34.1-63.9	36	17-78
concomitant	PI(m2)	47	33	70.2	55.1-82.7	20	42.6	28.3-57.8	23	12-43
HAV	PI(m6)	47	34	72.3	57.4-84.4	20	42.6	28.3-57.8	15	8-28
+ HBV	PII(m7)	47	45	95.7	85.5-99.5	45	95.7	85.5-99.5	720	356-1457

Notes : Group 1 received: HAB lot HABP706A2
Group 2 received Havrix lot DVHAP7205A2 and Engerix-B lot DHBP43D2.

The results of the total population immunogenicity analysis were consistent with those obtained from the analysis performed according to protocol.

- Safety

Solicited or unsolicited signs and symptoms occurring within the 4-day follow-up period after vaccination were reported following 22.0% of Ambirix doses and 33.7% of doses in the concomitant HAV+HBV vaccine group. Most symptoms were local in both vaccine groups.

Dose	Group	N	Symptoms		General		Local					
							HAB		Havrix		Engerix-B	
			n	%	n	%	n	%	n	%	n	%
1	1	50	10	20.0	4	8.0	8	16.0	-	-	-	-
	2	49	14	28.6	3	6.1	-	-	4	8.2	11	22.4
2	1	50	12	24.0	4	8.0	9	18.0	-	-	-	-
	2	49	19	38.8	4	8.2	-	-	4	8.2	16	32.7
Overall	1	100	22	22.0	8	8.0	17	17.0	-	-	-	-
	2	98	33	33.7	7	7.1	-	-	8	8.2	27	27.6

After dose 1 and dose 2, the concomitant HAV+HBV vaccine group had a higher incidence of local symptoms. After all doses, soreness at the injection site was the most frequently reported solicited local symptom (17% of Ambirix doses, 8.2% of Havrix and 27.6% of Engerix doses). One subject had a local injection site symptom of soreness that was of grade 3, which occurred at both the Havrix and Engerix sites following the first dose.

		After dose 1						After dose 2					
Symptom	Incidence and intensity	Group 1 N=50		Group 2 N=49				Grou N=50		Group 2 N=49			
				Havri		Engerix-B				Havri		Engerix-B	
		n	%	n	%	n	%	n	%	n	%	n	%
Redness	Total	1	2.0	0	0.	0	0.0	0	0.	0	0.	0	0.0
	grade "3"*	0	0.0	0	0.	0	0.0	0	0.	0	0.	0	0.0
Soreness	Total	8	16	4	8.	1	22.4	9	18	4	8.	16	32.7
	grade	0	0.0	0	0.	0	0.0	0	0.	1	2.	1	2.0
Swelling	Total	1	2.0	0	0.	0	0.0	0	0.	0	0.	0	0.0
	grade "3"*	0	0.0	0	0.	0	0.0	0	0.	0	0.	0	0.0

Headache and fatigue were the most frequently reported solicited general symptoms. The investigator considered these general symptoms to be related or possibly related to the candidate vaccine in all cases reported. There were no incidences of malaise, nausea or vomiting following any of the doses.

After dose 2, one subject from group 2 reported fatigue that was scored as grade 3 and considered as related or possibly related to vaccination.

The duration of most solicited symptoms was one to two days and all resolved within the four day follow-up period.

No unsolicited symptoms were reported in this study during the 30-day follow-up period. No SAEs were reported and no subjects from either group were reported to have received concomitant medications.

		After dose 1				After dose 2			
Symptom	**Incidence and intensity**	**Group 1 N=50**		**Group 2 N=49**		**Group 1 N=50**		**Group 2 N=49**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fatigue	Total	3	6.0	3	6.1	2	4.0	4	8.2
	R/PR	3	6.0	3	6.1	2	4.0	4	8.2
	grade "3"	0	0.0	0	0.0	0	0.0	1	2.0
	grade "3" R/PR	0	0.0	0	0.0	0	0.0	1	2.0
Fever (axillary	Total	1	2.0	0	0.0	1	2.0	0	0.0
temperature	R/PR	1	2.0	0	0.0	1	2.0	0	0.0
> 37.5°C)	grade "3"	0	0.0	0	0.0	0	0.0	0	0.0
	grade "3" R/PR	0	0.0	0	0.0	0	0.0	0	0.0
Headache	Total	4	8.0	1	2.0	3	6.0	1	2.0
	R/PR	4	8.0	1	2.0	3	6.0	1	2.0
	grade "3"	0	0.0	0	0.0	0	0.0	0	0.0
	grade "3" R/PR	0	0.0	0	0.0	0	0.0	0	0.0

HAB-053

Study 053 was conducted in 1997-1998 at four centres – two in Brazil, one in Mexico and one in Argentina. The study report is dated December 1999 but with an amendment made in June 2000 to correct the injection sites (right and left arms for Havrix and Engerix injections had been interposed) and to add that centres 1 and 2 (in Brazil) had been audited.

This study was essentially of the same design as 051 and 052 described above. However, 2:1 randomisation was used for Ambirix versus Havrix + Engerix and the study intended to enrol subjects from 5-18 years (the actual enrolment was from 4-20 years). Also, the final blood draw was at 6 weeks after the second dose rather than at Month 7 (although the tables still refer to Month 7).

All laboratory assays at the preliminary visit were done at the investigators' laboratories. RIA was used to test for HBsAg (Austria II – Abbott) and anti-HBc (Corab-Abbott). Anti-HAV was tested by Enzymun (Boerhinger Mannheim) and anti-HBs using the RIA of Ausab-Abbott. ALT and AST were measured with a Merck kit or a Beckman Instruments analyzer.

Samples obtained at the post-vaccination visits were assayed in the MAH's laboratories using a Boerhinger Mannheim commercial kit for anti-HAV and the Ausab-Abbott kit for anti-HBs.

- **Results**

- Recruitment/ Number analysed

Of the 248 subjects that received at least one dose of assigned vaccine 19 failed to complete the study due to drop-out. Subject disposition was as shown below.

Center No.	Location	Group 1 Combined high dose Hepatitis A and B (N=168)	Group 2 High dose Havrix and Engerix-B (N=80)
1 & 2	Brazil	60	29
3	Mexico	49	24
4	Argentina	59	27

	Total	Percent	Group 1	Group 2
Number of subjects planned	270 *		180	90
↓				
Subject or vaccine number not allocated (code 1010)	24		14	10
↓				
Number of subjects enrolled	248	100.0	168	80
↓				
Number of subjects included in the ATP analysis of reactogenicity	248	100.0	168	80
↓				
Essential serological data missing (code 2100)	6		3	3
↓				
Number of subjects included in the ATP analysis of immunogenicity	242	97.6	165	77

As shown below, the majority of subjects received both doses.

Number of doses received	Group 1 (N = 168)	Group 2 (N = 80)	Total (N = 248)
2 doses *	160	76	236
1 dose **	8	4	12

Individual subject data in Appendix Table I B
Group 1 received combined high dose hepatitis A/hepatitis B vaccine lot DHAB401A2
Group 2 received concomitant administration of high dose Havrix lot VHA525A2/M and high dose Engerix lot DHBP43D2, in opposite arms (Havrix: *right*, Engerix: *left*) (***Amended June 29, 2000***)
* Number of subjects who received 2 doses
** Number of subjects who received *only* 1 dose

- Baseline data

The mean age was 11 years. The male-female ratio was 1.12:1. The majority of the subjects enrolled in the study were white (there were a few Hispanic and Black).

Group	Sex	N	Mean age (in years)	S.D (in years)	Min. age (in years)	Max. age (in years)
1	Female	80	10.6	3.93	5	18
	Male	88	11.5	4.07	5	20
	Total	168	11.1	4.02	5	20
2	Female	37	11.1	4.02	4	18
	Male	43	10.8	4.16	4	18
	Total	80	10.9	4.07	4	18
All	Female	117	10.7	3.95	4	18
	Male	131	11.3	4.10	4	20
	Total	248	11.0	4.03	4	20

- Immunogenicity

Hepatitis A response

After the second doses of assigned vaccines all subjects in group 1 and all except one in group 2 were seropositive. The anti-HAV GMT for group 1 was significantly higher than that for group 2 (the 95% CI do not overlap). The results were comparable in all countries.

The second table below shows that in the age group of 4-11 years all subjects were seropositive after the second doses and the difference in GMTs was even more marked.

The third table shows the results for those aged 12-20 years, which were similar to the overall results.

Table 15: Geometric mean titres (GMT) of anti-HAV antibody titres (in seroconverters) and seropositivity rates (Subjects included in the ATP immunogenicity analysis)

Group	Timing	N	S+		CI 95%		GMT	CI 95%		Min.	Max.
			n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.	titre	Titre
1	PI(m1)	159	154	96.9	92.8	99.0	501.8	402.1	626.1	35	76160
	PI(m2)	161	158	98.1	94.7	99.6	283.8	227.6	354.0	39	91823
	PI(m6)	157	146	93.0	87.8	96.5	185.0	147.4	232.2	33	94575
	PII(m7)	155	155	100.0	97.6	100.0	6634.6	5526.0	7965.6	46	203921
2	PI(m1)	73	71	97.3	90.5	99.7	342.4	244.2	480.0	48	34881
	PI(m2)	77	73	94.8	87.2	98.6	187.9	132.3	266.9	42	32130
	PI(m6)	74	68	91.9	83.2	97.0	132.9	90.1	196.2	34	31196
	PII(m7)	73	72	98.6	92.6	100.0	2727.6	2098.9	3544.6	147	36531

*Table 16: Geometric mean titres (GMT) of anti-HAV antibody titres (in seroconverters) and seropositivity rates, **in the age group of 4-11 years** (Subjects included in the ATP immunogenicity analysis)*

Group	Timing	N	S+		CI 95%		GMT	CI 95%		Min.	Max.
			n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.	Titre	Titre
1	PI(m1)	92	90	97.8	92.4	99.7	540.7	418.6	698.5	42	76160
	PI(m2)	92	91	98.9	94.1	100.0	285.3	226.1	360.2	47	91823
	PI(m6)	91	87	95.6	89.1	98.8	181.5	143.0	230.3	33	94575
	PII(m7)	91	91	100.0	96.0	100.0	8627.3	6995.5	10639.7	107	203921
2	PI(m1)	43	42	97.7	87.7	99.9	364.7	230.9	576.2	48	34881
	PI(m2)	44	41	93.2	81.3	98.6	200.9	119.5	337.7	42	32130
	PI(m6)	42	39	92.9	80.5	98.5	128.4	76.8	214.9	34	31196
	PII(m7)	42	42	100.0	91.6	100.0	2941.1	2039.9	4240.5	147	35867

*Table 17: Geometric mean titres (GMT) of anti-HAV antibody titres (in seroconverters) and seropositivity rates, **in the age group of 12-20 years** (Subjects included in the ATP immunogenicity analysis)*

Group	Timing	N	S+		CI 95%		GMT	CI 95%		Min.	Max.
			n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.	Titre	Titre
1	PI(m1)	67	64	95.5	87.5	99.1	451.7	302.8	674.0	35	66180
	PI(m2)	69	67	97.1	89.9	99.6	281.8	184.8	429.8	39	85710
	PI(m6)	66	59	89.4	79.4	95.6	190.2	121.4	298.2	39	72615
	PII(m7)	64	64	100.0	94.4	100.0	4567.1	3344.4	6236.8	46	76993
2	PI(m1)	30	29	96.7	82.8	99.9	312.5	184.3	529.8	60	20290
	PI(m2)	33	32	97.0	84.2	99.9	172.5	107.2	277.6	44	27841
	PI(m6)	32	29	90.6	75.0	98.0	139.2	74.0	262.0	34	27753
	PII(m7)	31	30	96.8	83.3	99.9	2454.5	1666.7	3614.7	420	36531

Hepatitis B response

At 2 months after the first dose > 80% had seroconverted and around half were seroprotected. After the second assigned doses all subjects had seroconverted and almost all were seroprotected. The GMT was higher in group 1 but the 95% CI overlapped for the entire study population results. The results were comparable in all countries.

Table 18: Geometric mean titres (GMT) in seroconverters, seropositivity rates and seroprotection rates of anti-HBs antibodies (Subjects included in the ATP immunogenicity analysis)

Group	Timing	N	S+		CI 95%		SP		CI 95%		GMT	CI 95%	
			n	%	L.L.	U.L.	n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.
1	PI(m1)	158	126	79.7	72.6	85.7	69	43.7	35.8	51.8	16.0	11.0	23.5
	PI(m2)	160	142	88.8	82.8	93.2	89	55.6	47.6	63.5	18.2	13.1	25.1
	PI(m6)	157	143	91.1	85.5	95.0	106	67.5	59.6	74.8	32.3	23.8	43.8
	PII(m7)	155	155	100.0	97.6	100.0	153	98.7	95.4	99.8	3362.1	2456.9	4600.9
2	PI(m1)	73	52	71.2	59.4	81.2	21	28.8	18.8	40.6	12.7	6.4	25.5
	PI(m2)	76	63	82.9	72.5	90.6	37	48.7	37.0	60.4	21.7	11.7	40.3
	PI(m6)	74	69	93.2	84.9	97.8	51	68.9	57.1	79.2	26.4	17.3	40.1
	PII(m7)	73	73	100.0	95.1	100.0	70	95.9	88.5	99.1	1723.9	1002.2	2965.4

The results in the age group 4-11 years were comparable to those for the entire study population although a slightly higher proportion was seroprotected after only one dose of assigned vaccine.

*Table 19: Geometric mean titres (GMT) of anti-HBs antibody titres (in seroconverters), seropositivity rates and seroprotection rates, **in the age group of 4-11 years** (Subjects included in the ATP immunogenicity analysis)*

Group	Timing	N	S+		CI 95%		SP		CI 95%		GMT	CI 95%	
			n	%	L.L.	U.L.	n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.
1	PI(m1)	91	74	81.3	71.8	88.7	46	50.5	39.9	61.2	17.1	11.3	25.9
	PI(m2)	91	84	92.3	84.8	96.9	63	69.2	58.7	78.5	23.7	17.0	33.0
	PI(m6)	91	88	96.7	90.7	99.3	74	81.3	71.8	88.7	43.9	31.5	61.2
	PII(m7)	91	91	100.0	96.0	100.0	90	98.9	94.0	100.0	5577.7	3897.9	7981.4
2	PI(m1)	43	33	76.7	61.4	88.2	12	27.9	15.3	43.7	9.4	4.9	18.1
	PI(m2)	43	39	90.7	77.9	97.4	24	55.8	39.9	70.9	18.0	9.7	33.7
	PI(m6)	42	41	97.6	87.4	99.9	32	76.2	60.5	87.9	28.8	17.2	48.2
	PII(m7)	42	42	100.0	91.6	100.0	41	97.6	87.4	99.9	2538.8	1282.6	5025.7

Results were also comparable in the age group of 12-20 years with a smaller difference in GMTs after the second doses.

*Table 20: Geometric mean titres (GMT) of anti-HBs antibody titres (in seroconverters), seropositivity rates and seroprotection rates, **in the age group of 12-20 years** (Subjects included in the ATP immunogenicity analysis)*

Group	Timing	N	S+		CI 95%		SP		CI 95%		GMT	CI 95%	
			n	%	L.L.	U.L.	n	%	L.L.	U.L.	(mIU/ml)	L.L.	U.L.
1	PI(m1)	67	52	77.6	65.8	86.9	23	34.3	23.2	46.9	14.7	7.1	30.4
	PI(m2)	69	58	84.1	73.3	91.8	26	37.7	26.3	50.2	12.4	6.6	23.4
	PI(m6)	66	55	83.3	72.1	91.4	32	48.5	36.0	61.1	19.8	11.1	35.3
	PII(m7)	64	64	100.0	94.4	100.0	63	98.4	91.6	100.0	1636.9	967.8	2768.8
2	PI(m1)	30	19	63.3	43.9	80.1	9	30.0	14.7	49.4	21.5	4.3	107.0
	PI(m2)	33	24	72.7	54.5	86.7	13	39.4	22.9	57.9	29.4	7.7	111.6
	PI(m6)	32	28	87.5	71.0	96.5	19	59.4	40.6	76.3	23.2	11.0	49.0
	PII(m7)	31	31	100.0	88.8	100.0	29	93.5	78.6	99.2	1020.3	418.1	2489.9

The results of intention-to-treat analysis of immunogenicity were consistent with those obtained from the analysis performed according to protocol.

- Safety

Group 2 reported a higher number of total and local symptoms (solicited/unsolicited during the 4-day follow-up period) than group 1 but the incidence of general symptoms (solicited/unsolicited) in the 4-day follow-up period was similar in the two groups. There was a decrease in incidence of local and general symptoms (solicited/unsolicited) with subsequent doses in both groups.

Table 22: Incidence and nature of symptoms during the 4-day follow-up period for each vaccine dose and overall (subjects included in the ATP reactogenicity analysis)

	N	Symptoms				General Symptoms				Local Symptoms			
		n	%	95% C.I.		n	%	95% C.I.		n	%	95% C.I.	
Dose 1													
G1	167	57	34.1	27.0	41.9	33	19.8	14.0	26.6	44	26.3	19.8	33.7
G2	79	34	43.0	31.9	54.7	16	20.3	12.0	30.8	28*	35.4	25.0	47.0
Dose 2													
G1	154	39	25.3	18.7	33.0	21	13.6	8.6	20.1	33	21.4	15.2	28.8
G2	73	22	30.1	19.9	42.0	9	12.3	5.8	22.1	22*	30.1	19.9	42.0
Overall													
G1	321	96	29.9	24.9	35.2	54	16.8	12.9	21.4	77	24.0	19.4	29.0
G2	152	56	36.8	29.2	45.0	25	16.4	10.9	23.3	50*	32.9	25.5	41.0

Soreness at injection site was the most frequently reported solicited local symptom in both groups. Only 2 solicited local symptoms of intensity grade 3 were reported. These two were cases of soreness at injection site reported by subjects in group 1. All solicited local symptoms occurred within two days of vaccine administration and all resolved within the 4-day follow-up

Table 23: Overall incidence of solicited local symptoms, with duration of onset and grade "3" solicited local symptoms (Subjects included in the ATP analysis of reactogenicity)

Symptom		Group 1 N = 321		Group 2 N = 152			
				Havrix		Engerix	
		n	%	n	%	n	%
Redness	≤ 1 day	5	1.6	5	3.3	6	3.9
	> 1 day	12	3.7	5	3.3	5	3.3
	Onset 2 days	17	5.3	10	6.6	11	7.2
	Total	17	5.3	10	6.6	11	7.2
	Grade "3"	0	0.0	0	0.0	0	0.0
Soreness	≤ 1 day	38	11.8	16	10.5	15	9.9
	> 1 day	31	9.7	14	9.2	15	9.9
	Onset 2 days	69	21.5	30	19.7	30	19.7
	Total	69	21.5	30	19.7	30	19.7
	Grade "3"	2	0.6	0	0.0	0	0.0
Swelling	≤ 1 day	6	1.9	3	2.0	4	2.6
	> 1 day	12	3.7	3	2.0	6	3.9
	Onset 2 days	18	5.6	6	3.9	10	6.6
	Total	18	5.6	6	3.9	10	6.6
	Grade "3"	0	0.0	0	0.0	0	0.0

Headache was the most frequently reported solicited general symptom in both groups and more than 50% of the reported cases (17/30 in group 1 and 7/13 in group 2) were determined by the investigator to be related/possibly related to the study vaccine(s).

Table 24: Overall and grade "3" incidence of solicited general symptoms and those determined to be 'related'/'possibly related' to the study vaccine(s), (Subjects included in the ATP analysis of reactogenicity)

Symptom		Group 1 N = 321		Group 2 N = 152	
		n	%	n	%
Fatigue	Total	20	6.2	6	3.9
	Grade "3"	1	0.3	0	0.0
	R/PR	10	3.1	4	2.6
	R/PR Grade "3"	1	0.3	0	0.0
Fever	Total	7	2.2	4	2.6
	Grade "3"	0	0.0	0	0.0
	R/PR	6	1.9	2	1.3
	R/PR Grade "3"	0	0.0	0	0.0
Headache	Total	30	9.3	13	8.6
	Grade "3"	0	0.0	0	0.0
	R/PR	17	5.3	7	4.6
	R/PR Grade "3"	0	0.0	0	0.0
Malaise	Total	24	7.5	10	6.6
	Grade "3"	1	0.3	0	0.0
	R/PR	17	5.3	7	4.6
	R/PR Grade "3"	1	0.3	0	0.0
Nausea	Total	14	4.4	6	3.9
	Grade "3"	0	0.0	0	0.0
	R/PR	7	2.2	2	1.3
	R/PR Grade "3"	0	0.0	0	0.0
Vomiting	Total	4	1.2	1	0.7
	Grade "3"	0	0.0	0	0.0
	R/PR	1	0.3	0	0.0
	R/PR Grade "3"	0	0.0	0	0.0

Only 2 solicited general symptoms of intensity grade 3 were reported (both in group 1). These concerned cases of fatigue and malaise following vaccine dose 2. The majority of solicited general symptoms

reported occurred within two days of vaccine administration and all resolved within the 4-day follow-up period.

Overall 19 subjects (9 in group 1 and 10 in group 2) reported 24 unsolicited symptoms during the 30-day follow-up period after the vaccination. Also, 24 doses (12 per group) were followed by at least one report of unsolicited symptoms and 7 doses (3 in group 1, 4 in group 2) were followed by at least one unsolicited symptom determined by the investigator to be related/possibly related to the vaccination. No unsolicited symptoms of intensity grade 3 were reported. All the unsolicited symptoms reported resolved within the 30-day follow-up period after the vaccination.

Table 25: Number of doses followed by at least one report of unsolicited symptom classified by WHO Preferred Term (Subjects included in the ATP reactogenicity analysis)

WHO Body System (Code)	WHO Preferred Term (Code)	G1	G2	All
Body as a whole general (1810)	Allergic Reaction (0712)	1	0	1
	Fever (0725)	1	1	2
	Influenza-Like Symptoms (1222)	2	0	2
Central and peripheral nervous system (410)	Dizziness (0101)	0	1	1
Gastrointestinal system (600)	Abdominal Pain (0268)	4	2	6
	Vomiting (0228)	1	0	1
Psychiatric (500)	Somnolence (0197)	1	2	3
Resistance mechanism (1830)	Infection Viral (0740)	0	1	1
	Upper Resp Tract Infection (0543)	0	3	3
Skin and appendages (100)	Rash (0027)	0	1	1
	Urticaria (0044)	1	0	1
Vision (431)	Eye Pain (0244)	1	1	2
ALL		**12**	**12**	**24**

There were 18 subjects (11 in group 1 and 7 in group 2) who received concomitant medication during the study period but no medication was given prophylactically in anticipation of reaction to vaccination.

One pregnancy was reported to occur at 5 months after the first dose of vaccination. This resulted in a healthy child and no complications occurred either during pregnancy or during delivery. The study vaccination was discontinued.

One subject reported a SAE of fever and urticaria with onset 10 days after the first dose of vaccination. A diagnosis of allergic reaction was made but the investigator determined that the event was unrelated to study vaccination. This subject received the second dose of the vaccine and there were no SAEs following the second dose.

HAB-164 = Ext of original study HAB-038 to Year 10

The first volunteer was enrolled in the primary study on 8 July 1994 and the last study visit in the primary study was 28 March 1995. The long-term follow-up visits at Month 120 were conducted between 20 September 2004 and 18 October 2004. The study completion date was 6 May 2005. The study report is dated February 2006.

The original clinical study protocol 208127/044 (HAB-038) was designed to evaluate the immunogenicity and reactogenicity of two lots of Twinrix Paediatric (360/10) when administered according to a 0, 1, 6 month schedule to healthy children between 6 and 15 years of age.

The original study protocol was amended three times to extend the serological follow up to 60, 90 and then 120 months.

Results from the primary study had shown an anti-HAV seropositivity rate of 100% and anti-HBs seroprotection rate of 100% at Month 7. Data obtained up to Month 90 had shown an anti-HAV seropositivity rate of 100% and an anti-HBs seroprotection rate of 92.9% (for pooled groups).

- Objectives

The objectives of the long-term follow-up study were:
- To evaluate anti-HAV and anti-HBs antibody persistence at Month 120 (i.e. Year 10) after the first dose of the primary series.
- To evaluate immune memory in subjects who became seronegative for anti-HAV (< 15 mIU/ml) or had anti-HBs antibody < 10 mIU/ml at Month 120 by administration of a single dose of Twinrix Adult between 6 to 12 months after the Month 120 visit.

- Study design

See the table below.
The primary study was a double-blind, randomised (to one of two vaccine lots), single centre study.
The long-term follow-up at Month 120 was an open study with the same group allocation as in the primary study i.e.
− Group 1: had received vaccine lot HAB101C2 in the primary study
− Group 2: had received vaccine lot HAB102B2 in the primary study

- Study population and treatment

At Month 120 the single subject who had anti-HBs antibody concentrations < 10 mIU/ml was offered and accepted a dose of Twinrix Adult and was followed up for safety.

Visit Timing Sampling time point	VISIT 11 Month 120 Long-term blood sample	VISIT 12 Month 126 Pre booster	VISIT 13 Month 127 Post booster
Recording of non-participation of subjects in the tracking document	•		
Informed consent	•		
Check elimination criteria	•		•
Check contraindications		•	
Medical history		•	
Physical examination		•	
Pre-vaccination body temperature		•	
Pregnancy test		•	
Blood sampling: for antibody determination (7ml)	•	•	•
Vaccination*		•	
Daily post-vaccination recording of solicited symptoms (Days 0–3) by subjects/ subjects' parents/guardians*		•	
Recording of non-serious adverse events within 30 days post-vaccination, by investigator*		•	•
Record any concomitant medication/vaccination*		•	
Reporting of Serious Adverse Events*	•	•	•
Study Conclusion			•

Note: Please note that all the procedures marked by * were performed only for the subjects who had anti-HBs antibody concentrations < 10 mIU/ml.

- Outcomes/endpoints

Up to Month 60, anti-HBs antibody concentrations were measured by Radioimmunoassay (AUSAB RIA - Abbott) with an assay cut-off of 1 mIU/ml and anti- HAV antibody concentrations were measured by ELISA [Enzymun (Boehringer Mannheim)] with an assay cut-off of 33 mIU/ml.

At Months 90 and 120 anti-HAV antibody was assayed using Enzygnost from Dade Behring with an assay cut-off of 15 mIU/ml and anti-HBs using AUSAB EIA from Abbott Laboratories with an assay cut-off at 3.3 mIU/ml. For bridging purposes the Month 60 samples were re-tested with the new EIA assay kits. Subjects with antibody concentrations above the assay cut-offs were considered seropositive.

Marker	Assay method	Test Kit/ Manufacturer	Assay unit	Assay cut-off	Laboratory
Anti-HAV	EIA	Enzygnost® DADE Behring*	mIU/ml	15 mIU/ml	GSK Biologicals
Anti-HBs	EIA	AUSAB/Abbott*	mIU/ml	3.3 mIU/ml	GSK Biologicals

EIA: Enzyme-linked immunoassay
mIU/ml: milli International Units per millilitre

- Statistical Methods

The immunogenicity analysis was performed on the long-term total cohort and the long-term ATP immunogenicity cohort (= primary analysis).

➢ **Results**

- Recruitment/ Number analysed

Study 038 initially enrolled 120 subjects (60 subjects per group) of which 26 (14 in Group 1 and 12 in Group 2) came back for the long-term follow-up at Month 120 (Year 10).

	Total	Group 1	Group 2
Number of subjects enrolled in the primary study	120	60	60
Number of subjects included in the ATP immunogenicity cohort in the primary study	114	55	59
Number of subjects returning for blood sampling at Month 60	46	25	21
Number of subjects included in the long-term ATP immunogenicity cohort at Month 60	42	23	19
Number of subjects returning for blood sampling at Month 90	48	24	24
Number of subjects included in the long-term ATP immunogenicity cohort at Month 90	42	22	20
Number of subjects returning for blood sampling at Month 120	26	14	12
Number of subjects who returned at Month 120 but were previously eliminated	3	1	2
Number of subjects with abnormal increase in antibody concentrations during the long-term follow-up (code 2120) at Month 120	1	0	1
Number of subjects included in the long-term ATP analysis of immunogenicity at Month 120	22	13	9

Group 1: received vaccine lot HAB101C2 in the primary study
Group 2: received vaccine lot HAB102B2 in the primary study

- Baseline data

Group	Gender	N	Mean	SD	Min	Max
1	Female	7	20.6	3.60	16	26
	Male	6	19.8	2.93	16	23
	Total	13	20.2	3.19	16	26
2	Female	3	18.7	2.31	16	20
	Male	6	21.2	2.04	19	24
	Total	9	20.3	2.35	16	24
ALL	Female	10	20.0	3.27	16	26
	Male	12	20.5	2.50	16	24
	Total	22	20.3	2.81	16	26

- Immunogenicity

At Month 120 on pooling groups all subjects who returned were still seropositive for anti-HAV with only a small decrease in the GMC since Month 90.

Table 6 **Anti-HAV seropositivity rates and GMCs calculated on seropositive subjects (Long-term ATP immunogenicity cohort)**

Group	Timing	N	S+				GMC		
			n	%	95% CI		mIU/ml	95% CI	
					LL	UL		LL	UL
1	PIII(M7)	54	54	100.0	93.4	100.0	8896	7371	10737
	PIII(M36)	43	43	100.0	91.8	100.0	1164	921	1471
	PIII(M48)	30	30	100.0	88.4	100.0	769	581	1018
	PIII(M60)	23	23	100.0	85.2	100.0	860.3	684.7	1080.9
	PIII(M90)	22	22	100.0	84.6	100.0	613.2	499.2	753.3
	PIII(M120)	13	13	100.0	75.3	100.0	645.2	433.4	960.4
2	PIII(M7)	58	58	100.0	93.8	100.0	8145	6291	10547
	PIII(M36)	48	48	100.0	92.6	100.0	1333	1009	1760
	PIII(M48)	36	36	100.0	90.3	100.0	1105	826	1479
	PIII(M60)	19	19	100.0	82.4	100.0	906.6	656.5	1251.9
	PIII(M90)	20	20	100.0	83.2	100.0	814.2	525.6	1261.3
	PIII(M120)	9	9	100.0	66.4	100.0	733.0	428.8	1253.1
All	PIII(M7)	112	112	100.0	96.8	100.0	8499	7247	9968
	PIII(M36)	91	91	100.0	96.0	100.0	1250	1043	1498
	PIII(M48)	66	66	100.0	94.6	100.0	937	765	1148
	PIII(M60)	42	42	100.0	91.6	100.0	880.9	733.2	1058.5
	PIII(M90)	42	42	100.0	91.6	100.0	701.8	558.7	881.7
	PIII(M120)	22	22	100.0	84.6	100.0	679.7	507.0	911.3

In addition, as shown below, all subjects who returned were seropositive for anti-HBs while 21/22 (95.5%) were seroprotected. There was a 44.4% decrease in GMC from Month 90 to Month 120.

The single subject with anti-HBs < 10 mIU/ml at Month 120 and who received Twinrix Adult had a last recorded anti HBs antibody concentration of 13,553 mIU/ml.

The results of the long-term total cohort were consistent with those for the long-term ATP immunogenicity cohort.

Table 7 Anti-HBs seropositivity rates, percentage of subjects with anti-HBs antibody concentrations greater than or equal to 10 mIU/ml and GMCs (calculated on seropositive subjects) (Long-term ATP immunogenicity cohort)

Group	Timing	N	S+				≥ 10 mIU/ML				GMC		
			n	%	95% CI		n	%	95% CI		mIU/ml	95% CI	
					LL	UL			LL	UL		LL	UL
1	PIII(M7)	54	54	100.0	93.4	100.0	54	100.0	93.4	100.0	10886	6846	17311
	PIII(M36)	43	43	100.0	91.8	100.0	43	100.0	91.8	100.0	618	373	1025
	PIII(M48)	30	30	100.0	88.4	100.0	30	100.0	88.4	100.0	428	223	819
	PIII(M60)	23	23	100.0	85.2	100.0	23	100.0	85.2	100.0	383.3	187.8	782.3
	PIII(M90)	22	22	100.0	84.6	100.0	21	95.5	77.2	99.9	355.0	135.5	930.2
	PIII(M120)	13	13	100.0	75.3	100.0	13	100.0	75.3	100.0	148.8	44.7	494.7
2	PIII(M7)	58	58	100.0	93.8	100.0	58	100.0	93.8	100.0	10178	6677	15512
	PIII(M36)	48	48	100.0	92.6	100.0	47	97.9	88.9	99.9	443	266	737
	PIII(M48)	36	36	100.0	90.3	100.0	35	97.2	85.5	99.9	415	230	751
	PIII(m60)	19	19	100.0	82.4	100.0	19	100.0	82.4	100.0	220.3	92.9	522.4
	PIII(m90)	20	20	100.0	83.2	100.0	18	90.0	68.3	98.8	244.1	84.5	705.1
	PIII(M120)	9	9	100.0	66.4	100.0	8	88.9	51.8	99.7	191.4	26.8	1365.9
All	PIII(M7)	112	112	100.0	96.8	100.0	112	100.0	96.8	100.0	10513	7729	14300
	PIII(M36)	91	91	100.0	96.0	100.0	90	98.9	94.0	100.0	518	364	739
	PIII(M48)	66	66	100.0	94.6	100.0	65	98.5	91.8	100.0	421	275	645
	PIII(M60)	42	42	100.0	91.6	100.0	42	100.0	91.6	100.0	298.4	174.8	509.4
	PIII(m90)	42	42	100.0	91.6	100.0	39	92.9	80.5	98.5	297.0	149.7	589.3
	PIII(M120)	22	22	100.0	84.6	100.0	21	95.5	77.2	99.9	164.9	62.6	434.1

- Safety

In the retrospective follow-up, there were no SAEs or pregnancies reported in the study since the last study visit at Month 90.

The subject who received Twinrix Adult did not report any SAEs. The subject returned the diary card and did not report local or general solicited/unsolicited symptoms in the pre-defined follow-up period (Day 0 to Day 3 for solicited symptoms and Day 0 to Day 30 for unsolicited symptoms).

3. Discussion on clinical aspects

The three studies with Ambirix were all comparisons against two doses of adult strength Havrix and Engerix co-administered at the same time points. The relevance of these comparisons to the EU is low since the choice for immunisation of children against both HAV and HBV would lie between three doses of Twinrix Paediatric or two doses of Ambirix (i.e. Twinrix Adult).

However, all three studies indicated that two doses of Ambirix elicited satisfactory immune responses after the second dose. In addition, the safety profile of Ambirix appeared to be at least as good as that of co-administration of adult strength Havrix and Engerix.

In the long-term follow-up of study 038 the interpretation of the 10-year data must be cautious due to the low numbers that returned. However, the fact that all were still seropositive for anti-HAV and all except one was seroprotected against HBV in this population that had been aged 6-15 years old when first vaccinated is in keeping with data from many other studies, including vaccines against HAV and/or HBV produced by other companies.

The data do not raise any concerns and do not require any changes to the prescribing information for Ambirix or Twinrix Paediatric.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submission is satisfactory and Art 45 may be considered fulfilled for these vaccines.

- **Recommendation**

Fulfilled – No further action required

IV. ADDITIONAL CLARIFICATION REQUESTED

Not applicable