



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Tritanrix HepB

(diphtheria (d), tetanus (t), pertussis (whole cell) (pw) and hepatitis b (rdna) (hbv) vaccine (adsorbed))

Procedure No. EMEA/H/C/000093/P45/0039

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**



1. Recommendation

No further action required.

2. Introduction

The MAH submitted 2 completed paediatric studies for Tritanrix-Hep B, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. Two short critical expert overviews have also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Tritanrix-Hep B that there is no consequential regulatory action.

3. Scientific Discussion

3.1. Information on the pharmaceutical formulation used in the clinical studies

Tritanrix HepB, suspension for injection

Diphtheria (D), tetanus (T), pertussis (whole cell) (Pw) and hepatitis B (rDNA) (HBV) vaccine (adsorbed)

3.2. Non-clinical aspects

Not applicable.

3.3. Clinical aspects

3.3.1. Introduction

The MAH submitted reports for and synopsis for:

- Study DTP-HBV-006 (2 reports) (Thailand)
 - **208139/003** final study report
 - The immunogenicity and reactogenicity of combined tetravalent diphtheria, tetanus, whole-cell pertussis, hepatitis B (DTPwHBV) candidate vaccine in healthy infants.
 - **208139/003** erratum annex and additional report on 18 month booster
 - The immunogenicity and reactogenicity of combined tetravalent diphtheria, tetanus, whole-cell pertussis, hepatitis B (DTPwHBV) candidate vaccine in healthy infants. This annex: results of the booster dose administered at 18 months of age.
- Study DTP-HBV-028 (1 report) (Thailand)

- **208139/018** Month 30, Years 4 and 5 long term follow-up
 - **208139/051** Year 6 long term follow-up
 - **208139/054** Year 7 Annex 2 Development Phase II
 - An open randomised study in healthy infants vaccinated at birth with Engerix™-B (10 µg) to evaluate the immunogenicity and the reactogenicity of the following GlaxoSmithKline (GSK) Biologicals' vaccines:
 - combined DTP-HB vaccine (10 µg HBsAg)
 - combined DTP-HB vaccine (5 µg HBsAg)
 - simultaneous administration of Engerix™-B (10 µg) vaccine in right thigh and whole-cell DTP vaccine in left thigh
- when administered at 2, 4 and 6 months of age.

3.3.2. Clinical studies

3.3.2.1. Clinical study: 208139/003 (DTP-HBV-006) - (Thailand)

3.3.2.1.1. Description

This open, randomized feasibility study with 160 healthy infants at 2 to 3 months of age started in Thailand on 11/02/1992. It was performed to evaluate the immunogenicity and reactogenicity of two formulations of a combined DTPwHBV vaccine, against a commercial DTPw vaccine starting at 6-12 weeks of age. An amendment (22/06/1993) to the protocol of the study DTPw-HBV-006 was approved to evaluate a booster dose administered at 18 months of age (annex report).

3.3.2.1.2. Methods

- **Objectives**

The primary objective of the study was to evaluate and compare the antibody responses elicited by the hepatitis B component of two formulations of a combined DTPwHBV vaccine when administered according to a 0, 2, 4 month schedule. Other objectives include the evaluation of the antibody responses to diphtheria and tetanus toxoid and whole cell B. pertussis components and the reactogenicity of the formulations. A control group was included which received a commercial DTPw vaccine. The aim of the annex report study was to evaluate the immunogenicity and reactogenicity of booster vaccination at 18 months of age. Reactions to vaccinations were subjectively evaluated.

- **Study design**

160 infants were randomized to receive either one of the two formulations of SmithKline Beecham Biologicals' combined diphtheria, tetanus, whole-cell pertussis, hepatitis B candidate vaccine (DTP_wHBV) (Groups 1 and 2) or a commercial DTPw vaccine (Berna) (Group 3) according to a 0,2,4 month schedule. Antibody titers were measured in blood samples obtained just before vaccination and 4 weeks after the third dose. For ethical reasons group 3 received a hepatitis B vaccination course, according to a 0, 1 and 6 months schedule after the primary vaccination. An amendment (annex report) was approved to administer a booster dose at 18 months of age. The annex report provides the

results of blood samplings taken at 18, 19 and 30 months of age as well as solicited and unsolicited symptoms reported following the booster vaccination.

- **Study population /Sample size**

160 healthy infants of 2 to 3 months of age

- **Treatments**

Group 1 received the combined DTP_WHBV vaccine lot 15707A2 with 0.5 ml dose (containing 0.75 mg of aluminium) and a booster dose of SB Bio's DTP_WHBV lot 15724B2, 0.5ml at 18 months of age.

Group 2 received the combined DTP_WHBV vaccine lot 15720A2 with 0.6 ml dose (containing 0.676 mg of aluminium) and the same booster dose as group 1.

Group 3 received commercial DTP_W Berna with 0.5 doses and a booster dose Berna-DTP_W vaccine both without hepatitis B. A hepatitis B vaccine course according to a 0, 1 and 6 months schedule was given for ethical reasons.

- **Outcomes**

The immunogenicity outcomes were titers of antibodies against the hepatitis B surface antigen (anti-HBs), diphtheria toxoid (anti-diphtheria), tetanus toxoid (anti-tetanus) and whole-cell B. pertussis bacteria (anti-B. Pertussis) were measured in pre and post III vaccination serum samples. For the booster dose serum antibody titers against vaccine antigen components assessed in blood samples taken before the booster dose, one month after the booster dose and one year later (18, 19 and 30 months of age)

Concerning the safety outcomes the reactogenicity was evaluated after each dose administered, involving 30 minutes observing for adverse events and parent reports of symptoms of local, general and possible other reactions. The investigator evaluated subjectively the feverishness of the infants based on parent's comments. No objective measurements were taken for any reaction.

- **Endpoints**

The presence of **anti-HBs** titers was determined using radioimmunoassay (AUSAB, Abbott) and titers were calculated in mIU/ml as described by Hollinger, et al, titered against a WHO reference standard. The assay cut-off used for this study was 1 mIU/ml. (titers \geq 10 mIU/ml)

Anti-diphtheria and anti-tetanus titers were measured by Elisa and expressed in international units per ml (IU/ml), with respect to a reference serum. The assay cut-off was 0. IU/ml. (titers \geq 0.1IU/ml)

Anti-B. pertussis antibody titers were determined by ELISA Units (EI.U/ml). The assay cut-off was 15 EL.U/ml. (post-vaccination titer \geq pre- vaccination titer)

For the booster the same assay cut-offs were used.

- **Statistical Methods**

All analyses were descriptive only. The demographics were analysed for age and sex. The reactogenicity data are presented in terms of type, incidence and intensity. The immunogenicity analysis was performed on data from sera collected at pre and post III vaccination for those subjects who conformed to specific criteria with respect to vaccination. Further statistical comparisons were not made nor were additional details were given.

3.3.2.1.3. Results

- **Recruitment/number analyzed**

160 healthy infants of 2 to 3 months of age were enrolled. 133 subjects were eligible for inclusion in the immunogenicity analysis. Compliance for the booster dose at 18 months: 119 subjects (mean age of the infants at this moment was 17.7 months)

- **Efficacy results**

For the primary study the immunogenicity results were as follows. One month after the full vaccination course, all of the subjects in group 1 and all except for one subject (97.6%) in group 2 had protective levels of anti-HBs. At this time, all subjects in all three groups had protective levels of antibodies against diphtheria and tetanus as well as satisfactory levels of pertussis antibodies.

Table 3B: Immunogenicity: anti-HBs titers (analyzable group)

Group	Blood sample	N	Subjects with protective titer		GMT (mIU/ml)	CL 95% lower limit	CL 95% upper limit
			n	%			
1	Pre	52	12	23.1	11	7	19
	Post	42	42	100.0	234	149	367
2	Pre	52	15	28.8	10	7	15
	Post	42	41	97.6	416	256	676

Table 3C: Immunogenicity: anti-diphtheria titers (analyzable group)

Group	Blood sample	N	Subjects with protective titers		GMT (IU/ml)	CL 95% lower limit	CL 95% upper limit
			n	%			
1	Pre	52	22	42.3	0.092	0.074	0.116
	Post	42	42	100.0	3.941	2.861	5.429
2	Pre	52	18	34.6	0.084	0.067	0.106
	Post	42	42	100.0	3.622	2.684	4.888
3	Pre	29	10	34.5	0.088	0.065	0.119
	Post	24	24	100.0	2.741	1.772	4.239

Table 3D: Anti-tetanus antibody titres of subjects included in the analysis of immunogenicity

Group	Timing	N	Subjects with Seropositive titres	n	%	GMT	CL 95% lower	CL 95% upper	Min titre	Max titre
1	Pre B (m 18)	38	34	89.5	0.285	0.207	0.393	<0.1	3.360	
	Post B (m 19)	38	38	100.0	9.652	7.950	11.717	1.551	20.139	
	Post B (m 30)	28	27	96.4	1.020	0.717	1.451	<0.1	3.355	
2	Pre B (m 18)	36	35	97.2	0.347	0.261	0.459	<0.1	4.219	
	Post B (m 19)	35	35	100.0	10	8.601	12.761	2.103	29.549	
	Post B (m 30)	25	25	100.0	1.000	0.737	1.357	0.276	5.144	
3	Pre B (m 18)	22	21	95.5	0.673	0.391	1.158	<0.1	28.838	
	Post B (m 19)	21	21	100.0	29	19.393	42.057	3.525	169.760	
	Post B (m 30)	11	11	100.0	3.024	1.696	5.394	0.269	9.376	

For the booster dose amendment the immunogenicity results were as follows. % subjects greater than assay cut-off.

	Pre-booster Group 1, 2, 3	1 year after Group 1, 2, 3
Antibody titers	68.4%, 69.4% and 54.5%,	96.4%, 100.0%, 81.8%
Antitetanus	89.5%; 97.2% and 95.5%	96-100% in all groups
Anti-BPT	2.1%, 77.8 and 68.2%	100%, 100%, 90, 9%

- **Safety results**

No serious adverse experiences were reported in this study and reactions were not essentially different from what is usually reported following vaccination with DTPw. Local reactions were reported by approximately 10% of the subjects, general reactions in approximately 55% (more in group 1 and 2). After the booster dose, the only reported solicited symptom was fever in 77.8%, 62.2%, 64% in the 3 groups, but no fever was scored as severe.

3.3.2.1.4. Conclusion

In conclusion, the results of the primary study indicate that both formulations of the DTPw-HBV candidate vaccine were safe when administered to these healthy infants, with the first dose administered between 2 to 3 months of age, according to a 0, 2, 4 month schedule. The immunological response to the diphtheria, tetanus and B. pertussis antigens in the combined vaccines were similar to those obtained with the commercial DTPw vaccine. The response to the hepatitis B component of the combined candidate vaccines meets the criteria proposed by a WHO task force (May, 1992) that a combined vaccine could be judged acceptable if the minimum protective level for hepatitis B is achieved in more than 95% of the vaccinees.

The conclusion for the booster doses amendment states that the SmithKline Beecham Biologicals's combination DTPwHBV vaccine is both safe and immunogenic and elicits similar results as those obtained with commercially available DTPw vaccine when used as a booster dose to vaccinate previously primed 18-month children.

3.3.2.1.5. Clinical Expert statement

GlaxoSmithKline has reviewed the results of this study and has concluded that they are in accordance with the approved SPC for Tritanrix™-HepB.

3.3.2.1.6. Rapporteur's conclusion study DTP-HBV-006

The quality of this trial seems to be rather poor: the statistical analysis of this open label feasibility study was seriously limited and the method for retrieving safety results was also far from quality research design. Nevertheless the conclusion of the MAHs is endorsed in so far that the outcome of this trial does not alter the risk – benefit analysis of Tritanrix-HepB. Furthermore the data found do not contest the existing SPC, so no changes are needed as the MAH expert advices.

3.3.2.2. Clinical Study: 208139/(018/051/054) (DTP-HBV-028) - (Thailand)

3.3.2.2.1. Description

This clinical phase III study is a long term follow-up of the primary study DTPw-HBV-028. In the primary study subjects got a 3-dose primary vaccination course with DTPw-HBV, DTPw and HBV vaccines and a booster of the same vaccines at 18 months of age, followed by a booster of DTPw Vaccine at 4 years of age. The aim of this study (018, 051, 054) is to evaluate the long-term persistence of antibodies against hepatitis B, diphtheria, tetanus and *Bordetella pertussis*. Report number 018 stands for the follow-up at Month 30 and at years 4 and 5, report number 051 stands for the follow-up at year 6 and report number 054 for the year 7 follow-up at development phase II.

3.3.2.2.2. Methods

- Objectives

The objective of this long-term follow-up was to evaluate the long-term persistence of antibodies against hepatitis B (anti-HBs), diphtheria (anti-diphtheria), tetanus (anti-tetanus) and *Bordetella pertussis* (anti-BPT) in subjects who had completed the 3-dose primary vaccination course with DTPw-HBV vaccine and DTPw and HBV vaccines and received two booster doses of the same vaccines as the primary study.

- Study design

The primary study was an open, randomised study with three groups. All infants received a dose of hepatitis B vaccine, Engerix™-B, at birth. In the primary study,

- | | |
|----------------|--|
| Group 1 | received DTPw-HBV vaccine (10 µg HBsAg) |
| Group 2 | received DTPw-HBV vaccine (5 µg HBsAg) |
| Group 3 | received DTPw vaccine and HBV as concomitant injections. |

A booster dose of the same vaccine that was given in the primary study was administered at **18 months** of age. At **4 years** of age, all subjects who returned for a follow-up visit received a booster dose of DTPw vaccine. During each of the follow-up visits at 30 months, 4, 5, 6 and 7 years of age, a blood sample was taken to evaluate long-term persistence. Reactogenicity and safety were evaluated for primary vaccination and for the 18 months' booster.

- **Study population /Sample size**

Number of subjects enrolled in the primary study: 124

- **Treatments**

The study vaccine was given at 2-4-6 months of age, the booster at 18 months of age. At 4 years of age, all subjects received a booster dose of the local DTPw vaccine under the EPI program. Lot numbers of these DTPw vaccines were not recorded. All vaccines were administered intramuscularly in the anterolateral thigh. Following vaccines were given:

- GSK Biologicals' candidate combined DTPw-HBV(10 µg) vaccine: one dose (0.5ml)
- 2. GSK Biologicals' candidate combined DTPw-HBV (5 µg) vaccine: one dose (0.5 ml),
- 3. GSK Biologicals' recombinant hepatitis B vaccine (Engerix™-B), given at birth: one dose (0.5 ml)

The reference vaccine was given at 2-4-6 months of age during the primary vaccination course and at 18 months of age during the booster study. All vaccines were administered intramuscularly in the anterolateral thigh. Following vaccines were given:

- Left thigh: GSK Biologicals' DTPw vaccine: one dose (0.5 ml), Lot numbers 13114E7/M (primary) and 13119B9 (18 months)
- Right thigh: GSK Biologicals' recombinant hepatitis B vaccine (Engerix™-B): one dose (0.5 ml), Lot numbers 1080A2 (primary) and 11486A2 (18 months)

- **Duration of the Study**

Long-term follow-up: up to Year 7.

- **Criteria for evaluation**

Anti-HBs antibody concentrations ≥ 10 mIU/ml, anti-diphtheria and anti-tetanus antibody concentrations ≥ 0.1 IU/ml by enzyme linked immunosorbent assay (ELISA) were considered as protective. Anti-BPT antibody concentrations were determined by ELISA with an assay cut-off of 15 IU/ml determining seropositivity.

NOTE: Anti-HBs antibodies were measured by a Radioimmunoassay (AUSAB RIA -Abbott) until availability of the test kit i.e. up to Year 5 and partially up to Year 6 time point. Due to the unavailability of this assay, a new assay, an Enzyme-linked Immunosorbent assay (AUSAB EIA from Abbott Laboratories), was used for testing Year 6 and Year 7 blood samples.

- **Statistical Methods**

Analyses were performed on the total vaccinated cohort, ATP cohort and the kinetic cohort. The following analyses were performed for blood samples taken at Months 18 and 30 and at Years 4, 5, 6 and 7: Seroprotection rates for anti-HBs, anti-diphtheria and anti-tetanus antibodies and their exact 95% confidence intervals (CIs) were calculated. Seropositivity rates and their exact 95% CIs were

tabulated for anti-BPT antibodies. GMCs and their 95% CIs were calculated for anti-HBs, anti-diphtheria, anti-tetanus and anti-BPT antibodies. Difference/similarity between groups was not evaluated and therefore similarity/comparability is based on clinical judgement.

3.3.2.2.3. Results

- **Number of subjects**

In group 1 and 3 the proportion male/female is significantly higher in comparison than group 2, from 30 months throughout the entire study.

Number of subjects:	Group 1	Group 2	Group 3	Total
Number of subjects enrolled in the primary study	41	42	41	124
Number of subjects in the total vaccinated cohort (TVC) at Month 18	30	30	33	93
Number of subjects in the according to protocol (ATP) Cohort at Month 18	20	23	29	72
Number of subjects in the TVC at Month 30	25	23	31	79
Number of subjects in the ATP Cohort at Month 30	18	20	27	65
Number of subjects in the TVC at Year 4	18	23	28	69
Number of subjects in the ATP Cohort at Year 4	15	17	25	57
Number of subjects in the TVC at Year 5	14 (17*)	19 (22*)	21 (25*)	54 (64*)
Number of subjects in the ATP Cohort at Year 5	12 (15*)	15 (17*)	19 (23*)	46 (55*)
Number of subjects in the TVC at Year 6	15	19	25	59
Number of subjects in the ATP Cohort at Year 6	14	15	23	52
Number of subjects in the TVC at Year 7	11	18	17	46
Number of subjects in the ATP Cohort at Year 7	10	13	16	39

(*) Year 5 time point there were a total of 10 subjects in the TVC and 9 subjects in the ATP who had immunogenicity results but did not have demography results or visit dates.

- **Efficacy results**

Hepatitis B results: approximately 5½ years after the last dose of HBV given in the second year of life, the percentage of subjects with anti-HBs antibody seroprotection rates was 90.9% (95%CI: 58.7; 99.8) and 81.3% (95%CI: 54.4; 96.0) in Groups 1 and 3 respectively and 55.6% (95%CI: 30.8; 78.5) in Group 2. Also anti-HBs GMCs continued to be higher in Groups 1 and 3 than in Group 2. Subjects in Group 2 (who received half the dosage of HBsAg as the other two groups at both primary and booster vaccination time points in the first two years of life) had the lowest anti-HBs GMCs.

D, T and Pw results: three years after the DTPw booster (given at Year 4), at least 94.1% of all subjects had seroprotective levels of anti-diphtheria and anti-tetanus antibodies and at least 88.0% of subjects were seropositive for anti-BPT antibodies. The anti-diphtheria and anti-BPT antibody GMCs were comparable in all three groups. The point estimate of the anti-tetanus antibody GMC was lower in Group 1 as compared to Group 2 and Group 3 but the CIs largely overlapped between groups.

- **Effectiveness results**

Not assessed in this study.

- **Safety results**

Not assessed in this study.

3.3.2.2.4. Conclusion

Long-term persistence of anti-HBs antibodies after primary vaccination with DTPw-HBV (10 µg HBsAg) was high (90% of the vaccinees continued to have seroprotective antibody concentrations of anti-HBs antibodies at Year 7) and comparable to that after vaccination with HBV (10 µg HBsAg) vaccine administered separately but concomitantly from the DTPw vaccine. Majority of subjects (at least 81.3%) in the three groups continued to have seroprotective/seropositive antibody levels to the diphtheria, tetanus and whole cell pertussis antigens, at Year 7, i.e. three years after the last booster dose at Year 4.

3.3.2.2.5. Clinical Expert statement

GlaxoSmithKline has reviewed the results of this study and has concluded that they are in accordance with the approved SPC for TritanrixTM-HepB.

3.3.2.2.6. Rapporteur's conclusion study DTP-HBV-028

Although this is an open label clinical trial (no blinding), the conclusion of the MAH is endorsed and although only immunogenicity data are evaluated and the effectiveness and the safety was not assessed in this study. The data found do not contest the existing SPC, so no changes are needed as the MAH expert advices.

3.3.3. Discussion on clinical aspects

Not applicable.

4. Rapporteur's Overall Conclusion and recommendation

4.1. Overall conclusion

The data found in the studies do not contest the currently approved SPC, so no changes are needed as the MAH expert advices.

4.2. Recommendation

No further action required.

5. Request for supplementary information

Not applicable