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Study No.: 101222 (DTPw-HBV=Hib Kft-001)
Title: Phase III, partially blinded, randomized, controlled, primary vaccination study to demonstrate the non-inferiority of GlaxoSmithKline (GSK) Biologicals' DTPw-HBV/Hib Kft. vaccine compared to GSK Biologicals' <i>Tritanrix</i> TM -HepB/ <i>Hiberix</i> TM vaccine and to separate administration of DTPw-HBV Kft. and <i>Hiberix</i> TM vaccines with respect to the immunogenicity of all antigens, when administered to healthy infants at 6, 10 and 14 weeks of age. The immunogenicity of GSK Biologicals' DTPw-HBV/Hib Kft. administered after a birth dose of Hepatitis B vaccine will also be assessed. <i>Tritanrix</i> TM -HepB/ <i>Hiberix</i> TM (DTPw-HBV/Hib): combined diphtheria, tetanus, whole cell <i>Bordetella pertussis</i> , hepatitis B and <i>Haemophilus Influenzae</i> type b vaccine DTPw-HBV/Hib Kft.: GSK Biologicals' combined diphtheria, tetanus, whole cell <i>Bordetella pertussis</i> , hepatitis B and <i>Haemophilus Influenzae</i> type b vaccine produced at GSK Biologicals Kft., Gödöllő, Hungary. DTPw-HBV Kft.: GSK Biologicals' combined diphtheria, tetanus, whole cell <i>Bordetella pertussis</i> and hepatitis B vaccine produced at GSK Biologicals Kft., Gödöllő, Hungary. <i>Hiberix</i> TM : GSK Biologicals' <i>Haemophilus Influenzae</i> type b vaccine
Rationale: To demonstrate the non-inferiority of the DTPw-HBV/Hib Kft. vaccine compared to the DTPw-HBV/Hib vaccine and to separate administration of DTPw-HBV Kft. and Hib vaccines with respect to the immunogenicity of all vaccine antigens. The safety of all the study vaccines was also assessed.
Phase: III
Study Period: 23 March 2004 to 25 October 2004
Study Design: Multicentric, partially blinded, randomized (2:2:3:2) study with 4 parallel groups. The study was single blind with respect to groups DTPw-HBV/Hib Kft. and DTPw-HBV/Hib (Control), and open with respect to groups HBV + DTPw-HBV/Hib Kft. and DTPw-HB Kft.+ Hib.
Centers: Three study centers in the Philippines.
Indication: Three-dose primary immunization of healthy infants in the first year of life against diphtheria, tetanus, pertussis, hepatitis B and <i>Haemophilus influenzae</i> type b diseases
Treatment: The study groups were as follows: <ul style="list-style-type: none"> • DTPw-HBV/Hib Kft. without Hepatitis B vaccine (HBV) at birth (DTPw-HBV/Hib Kft. Group) • DTPw-HBV Kft.+ Hib without HBV at birth (DTPw-HB Kft.+ Hib Group) • DTPw-HBV/Hib Kft. with HBV given at birth (HBV + DTPw-HBV/Hib Kft. Group) • DTPw-HBV/Hib without HBV at birth (Control Group) All vaccines were administered intramuscularly in the left anterolateral thigh (except for the Hib vaccine in the DTPw-HB Kft.+ Hib Group, which was given in the right anterolateral thigh) at 6, 10 and 14 weeks of age. In 800 subjects (200 per group), one blood sample was taken prior to the first dose of study vaccine and a second blood sample was taken one month after the third vaccine dose. In the remaining 100 subjects in the DTPw-HBV/Kft.+ Hib group, no blood sample was taken. These subjects were evaluated for safety only.
Objectives: <ul style="list-style-type: none"> • To demonstrate the non-inferiority of DTPw-HBV/Hib Kft. vaccine compared to DTPw-HBV/Hib vaccine (without Hepatitis B vaccine administered at birth) with respect to the antibody response to all vaccine antigens. • To demonstrate the non-inferiority of DTPw-HBV/Hib Kft. vaccine compared to DTPw-HBV Kft.+ Hib vaccines (without Hepatitis B vaccine administered at birth) with respect to the antibody response to all vaccine antigens.
Primary Outcome/Efficacy Variable: <i>Immunogenicity:</i> One month after the third dose of the primary vaccination (i.e. Month 4.5): <ul style="list-style-type: none"> • Seroprotection rates: <ul style="list-style-type: none"> - Anti-diphtheria antibody concentrations ≥ 0.1 IU/mL by ELISA assay or ≥ 0.016 IU/mL by neutralization assay on Vero cells (for subjects seronegative by ELISA). - Anti-tetanus antibody concentrations ≥ 0.1 IU/mL. - Anti-polyribosil-ribitol-phosphate (PRP) antibody concentrations ≥ 0.15 μg/mL. - Anti-HBs antibody (antibodies against hepatitis B surface antigen) concentrations ≥ 10 mIU/mL. • Vaccine response rates to the <i>Bordetella pertussis</i> antigen (BPT), defined as the appearance of antibodies (concentrations ≥ 15 EL.U/mL) in initially seronegative subjects or post-vaccination antibody concentrations \geq pre-

vaccination in initially seropositive subjects.				
Secondary Outcome/Efficacy Variable(s):				
<i>Immunogenicity:</i>				
One month after the third dose of the primary vaccination (i.e. Month 4.5):				
<ul style="list-style-type: none"> • Geometric mean concentrations (GMCs) for antibodies against all vaccine antigens • Anti-PRP antibody concentrations $\geq 1 \mu\text{g/mL}$ • Anti-BPT antibody concentrations $\geq 15 \text{ EL.U/mL}$ 				
<i>Safety:</i>				
<ul style="list-style-type: none"> • Occurrence of solicited local and general symptoms during the 4-day (Day 0-3) follow-up period after each DTPw-combination vaccine dose. • Occurrence of unsolicited adverse events (AEs) during the 31-day (Day 0-30) follow-up period after each DTPw-combination vaccine dose. • Occurrence of serious adverse events (SAEs) during the entire study period. 				
Statistical Methods:				
The analyses were performed on the According-to-Protocol (ATP) cohort for Immunogenicity and the Total Vaccinated Cohort.				
<ul style="list-style-type: none"> - The Total Vaccinated Cohort included all the subjects who received the combined vaccine and for whom data were available. - The ATP Cohort for Immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) with available immunogenicity data. 				
<i>Analysis of Immunogenicity:</i>				
The analysis of immunogenicity was performed on the ATP cohort for Immunogenicity.				
For each group, before the first vaccine dose (i.e. at pre-vaccination), antibody GMCs and seropositivity rates were tabulated with 95% confidence interval (CI) for anti-diphtheria, anti-HBs and anti-BPT antibodies.				
For each group, one month after the third vaccine dose (i.e. Month 4.5), GMCs with 95% CIs were tabulated for antibodies against each antigen. Seropositivity/ seroprotection rates with exact 95% CIs were calculated. The vaccine response to BPT (with exact 95% CI) was calculated.				
Standardized asymptotic 95% CIs for the differences in seroprotection/ vaccine response rates (Control group minus DTPw-HBV/Hib Kft. group and DTPw-HB Kft.+ Hib minus DTPw-HBV/Hib Kft. group) one month after the third vaccine dose were computed.				
The objectives of non-inferiority were reached if, one month after the third vaccine dose, the upper limits of the 95% CI for the differences between groups (as indicated above) in terms of vaccine response rates for pertussis and seroprotection rates for the other antigens, were all below 10%.				
<i>Analysis of Safety:</i>				
The analysis of safety was performed on the Total Vaccinated Cohort.				
The incidence of any and Grade 3 solicited local symptom during the 4-day (Day 0-3) follow-up period was tabulated. The incidence of any, Grade 3 and related solicited general symptoms during the 4-day (Day 0-3) solicited follow-up period was tabulated.				
The percentage of subjects with at least one report of unsolicited adverse event during the 31-day (Day 0-30) follow-up period after each vaccination was tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Serious adverse events reported after enrolment but before the first administration of the combined vaccine and SAEs reported after administration of the study vaccine were tabulated by the MedDRA preferred terms.				
Study Population: Healthy male or female infants ≤ 3 days (72 hours) of age at the time of randomization into study groups. Written informed consent was obtained from the parent or guardian of the subject prior to study entry. Subjects were born after a gestation period of 36 to 42 weeks to mothers proven seronegative for HBsAg. Subjects were excluded if hepatitis B vaccination at birth was given outside the study.				
Number of subjects:	DTPw-HBV/Hib Kft.	DTPw-HB Kft.+ Hib	HBV + DTPw-HBV/Hib Kft.	Control
Planned, N	200	300	200	200
Total Enrolled Cohort*	205	301	205	202
Randomized, N (Total Vaccinated Cohort)	182	285	188	187
Completed, n (%)	181 (99.5)	277 (97.2)	185 (98.4)	183 (97.9)
Total Number Subjects Withdrawn, n (%)	1 (0.5)	8 (2.8)	3 (1.6)	4 (2.1)

Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)								
Withdrawn due to Lack of Efficacy, n (%)	Not applicable											
Withdrawn for other reasons, n (%)	1 (0.5)	8 (2.8)	3 (1.6)	4 (2.1)								
Demographics	DTPw-HBV/Hib Kft.	DTPw-HB Kft.+ Hib	HBV + DTPw-HBV/Hib Kft.	Control								
N (Total Vaccinated Cohort)	182	285	188	187								
Females: Males	82:100	140:145	99:89	90:97								
Mean Age, days (SD)**	46.6 (5.20)	47.1 (5.50)	46.2 (5.02)	46.8 (5.12)								
East/Southeast Asian, n (%)	182 (100)	285 (100)	188 (100)	187 (100)								
* 2 enrolled subjects had a fatal SAE before receiving DTPw vaccine; one of them (HBV + DTPw-HBV/Hib Kft group) had received HBV at birth.												
** Age at the time of first DTPw combination vaccination												
Primary Efficacy Results:												
Comparison of DTPw-HBV/Hib Kft. vs. DTPw-HBV/Hib (Control): Differences in the percentage of subjects with seroprotection/vaccine response rates (with 95% CI) one month after the third vaccine dose (ATP cohort for immunogenicity)												
Antibody	DTPw-HBV/Hib Kft.				Control				Control minus DTPw-HBV/Hib Kft.			
	N	%	95% CI		N	%	95% CI		Difference	95% CI		
			LL	UL			LL	UL		LL	UL	
Anti-diphtheria *	170	95.9	91.7	98.3	172	90.1	84.6	94.1	-5.8	-11.6	-0.4**	
Anti-tetanus \geq 0.1 IU/mL	171	100	97.9	100	172	100	97.9	100	0.0	-2.2	2.2**	
Anti-HBs \geq 10 mIU/mL	170	87.6	81.7	92.2	171	90.6	85.3	94.6	3.0	-3.7	9.8**	
Anti-BPT VR	164	97.6	93.9	99.3	166	95.8	91.5	98.3	-1.8	-6.3	2.4**	
Anti-PRP \geq 0.15 μg/mL	171	99.4	96.8	100	172	99.4	96.8	100	0.0	-2.7	2.7**	
N = Number of subjects with available results												
% = percentage of subjects with specified antibody concentrations												
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit												
* Anti-diphtheria \geq 0.1 IU/mL by ELISA or \geq 0.016 IU/mL on Vero cell assay												
VR = appearance of antibodies in subjects who were initially seronegative or maintenance of pre-vaccination antibody concentration in those who were initially seropositive												
**Upper limit of the 95% CIs below the pre-defined limit of non-inferiority of 10%												
Primary Efficacy Results:												
Comparison of DTPw-HBV/Hib Kft. vs. DTPw-HB Kft. + Hib: Differences in the percentage of subjects with seroprotection/vaccine response rates (with 95% CI) one month after the third vaccine dose (ATP cohort for immunogenicity)												
Antibody	DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib				DTPw-HB Kft.+ Hib minus DTPw-HBV/Hib Kft.			
	N	%	95% CI		N	%	95% CI		Difference	95% CI		
			LL	UL			LL	UL		LL	UL	
Anti-diphtheria*	170	95.9	91.7	98.3	175	99.4	96.9	100	3.6	0.5	7.8**	
Anti-tetanus \geq 0.1 IU/mL	171	100	97.9	100	175	99.4	96.9	100	-0.6	-3.2	1.6**	
Anti-HBs \geq 10 mIU/mL	170	87.6	81.7	92.2	175	92.0	86.9	95.6	4.4	-2.1	11.0	
Anti-BPT VR	164	97.6	93.9	99.3	162	95.7	91.3	98.2	-1.9	-6.5	2.3**	
Anti-PRP \geq 0.15 μg/mL	171	99.4	96.8	100	175	99.4	96.9	100	0.0	-2.6	2.7**	
N: number of subjects with available results												
% = percentage of subjects with specified antibody concentrations												
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit												
VR = appearance of antibodies in subjects who were initially seronegative or maintenance of pre-vaccination antibody concentration in those who were initially seropositive												
\geq 0.1 IU/mL by ELISA or \geq 0.016 IU/mL on Vero cell assay												
**Upper limit of the 95% CIs below the pre-defined limit of non-inferiority of 10%												
Primary Efficacy Results:												
Anti-PRP seroprotection rates and antibody GMCs one month after the third vaccine dose (ATP cohort for immunogenicity)												
Group	N	\geq 0.15 μg/mL*			\geq 1.0 μg/mL**			GMC** (μg/mL)				
		n	%	95% CI	n	%	95% CI	Value	95% CI			

				LL	UL			LL	UL		LL	UL
DTPw-HBV/Hib Kft.	171	170	99.4	96.8	100	161	94.2	89.5	97.2	11.374	9.328	13.869
DTPw-HB Kft.+ Hib	175	174	99.4	96.9	100	169	96.6	92.7	98.7	18.855	15.156	23.457
HBV + DTPw-HBV/Hib Kft.	179	179	100	98.0	100	172	96.1	92.1	98.4	10.496	8.732	12.617
Control	172	171	99.4	96.8	100	166	96.5	92.6	98.7	14.686	12.000	17.974

N = number of subjects with available results

n(%) = number(percentage) of subjects with anti-PRP concentration $\geq 0.15 \mu\text{g/mL}$ or $\geq 1\mu\text{g/mL}$

95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

* Primary Efficacy Results

** Secondary Outcome Variables

Primary Efficacy Results:

Anti-HBs seroprotection rates and antibody GMCs (ATP cohort for immunogenicity)

Group	Timing	N	$\geq 10 \text{ mIU/mL}^*$				GMC** (mIU/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
DTPw-HBV/Hib Kft.	Pre	168	37	22.0	16.0	29.1	11.3	8.7	14.7
	PIII	170	149	87.6	81.7	92.2	114.0	87.5	148.5
DTPw-HB Kft.+ Hib	Pre	168	47	28.0	21.3	35.4	12.9	9.8	16.8
	PIII	175	161	92.0	86.9	95.6	127.0	101.8	158.4
HBV + DTPw-HBV/Hib Kft.	Pre	172	46	26.7	20.3	34.0	11.2	8.9	14.1
	PIII	176	166	94.3	89.8	97.2	226.5	179.9	285.2
Control	Pre	169	46	27.2	20.7	34.6	12.8	9.9	16.6
	PIII	171	155	90.6	85.3	94.6	91.5	73.6	113.7

N = number of subjects with available results

n(%) = number(percentage) of subjects with specified antibody concentrations

95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

Pre: pre-vaccination

PIII: at 4.5 months i.e. one month after third vaccine dose

* Primary Efficacy Results

** Secondary Outcome Variables

Primary Efficacy Results:

Anti-tetanus seroprotection rates and antibody GMCs one month after the third vaccine dose (ATP cohort for immunogenicity)

Group	N	$\geq 0.1 \text{ IU/mL}^*$				GMC** (IU/mL)		
		n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
DTPw-HBV/Hib Kft.	171	171	100	97.9	100	3.996	3.464	4.609
DTPw-HB Kft.+ Hib	175	174	99.4	96.9	100	2.924	2.487	3.439
HBV + DTPw-HBV/Hib Kft.	179	179	100	98.0	100	4.200	3.644	4.840
Control	172	172	100	97.9	100	3.378	2.932	3.891

N = number of subjects with available results

n(%) = number(percentage) of subjects with specified antibody concentrations

95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit

* Primary Efficacy Results

** Secondary Outcome Variables

Primary Efficacy Results:

Anti-diphtheria seroprotection rates (by ELISA) and antibody GMCs (ATP cohort for immunogenicity)

Group	Timing	N	$\geq 0.1 \text{ IU/mL}^*$				GMC** (IU/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
DTPw-HBV/Hib Kft.	Pre	169	47	27.8	21.2	35.2	0.075	0.067	0.084
	PIII	170	162	95.3	90.9	97.9	1.056	0.884	1.260
DTPw-HB Kft.+ Hib	Pre	173	34	19.7	14.0	26.4	0.068	0.061	0.076
	PIII	175	171	97.7	94.3	99.4	1.416	1.203	1.666

HBV + DTPw-HBV/Hib Kft.	Pre	174	50	28.7	22.1	36.1	0.081	0.071	0.093
	P111	179	176	98.3	95.2	99.7	1.294	1.105	1.516
Control	Pre	170	45	26.5	20.0	33.8	0.080	0.069	0.093
	P111	172	149	86.6	80.6	91.3	0.529	0.440	0.636

N = number of subjects with available results
n(%) = number(percentage) of subjects with specified antibody concentrations
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
Pre: pre-vaccination.
P111: at 4.5 months i.e. one month after third vaccine dose
* Primary Efficacy Results
** Secondary Outcome Variables

Primary Efficacy Results:

Seroprotection rate to diphtheria taking into account ELISA and Vero-cell assay for subjects seronegative by ELISA one month after the third vaccine dose (ATP cohort for immunogenicity)

Group	N	Seronegativity assessed by ELISA		Seronegativity assessed by Vero-cell assay for subjects seronegative by ELISA		Overall seronegativity for anti-diphtheria antibodies		Estimated seroprotection rate		
		n/N	%	n/N'	%	n/N x n/N'	%	SP	95% CI	
									LL	UL
DTPw-HBV/Hib Kft.	170	8/170	4.7	7/8	87.5	8/170x7/8	4.1	95.9	91.7	98.3
DTPw-HB Kft.+ Hib	175	4/175	2.3	1/4	25	4/175x1/4	0.6	99.4	96.9	100
HBV + DTPw-HBV/Hib Kft.	179	3/179	1.7	2/3	66.7	3/179x2/3	1.1	98.9	96.0	99.9
Control	172	23/172	13.4	17/23	73.9	23/172x17/23	9.9	90.1	84.6	94.1

N = number of subjects tested by ELISA.
n/N = number of subjects with concentrations below 0.1 IU/mL / number of subjects tested by ELISA
n/N' = number of subjects with concentrations below 0.016 IU/mL / number of subjects tested by Vero-cell assay
% = proportion of subjects with concentrations below the considered cut-off (0.1 IU/mL for ELISA and 0.016 IU/mL for Vero-cell assay)
n/N x n/N' = the multiplication of the two proportions = overall seronegativity for diphtheria
Overall = based on both the ELISA and the Vero-cell assay
SP = estimated proportion of subjects with protective antibodies
95% CI = exact 95% confidence interval; LL = Lower Limit; UL = Upper Limit

Primary Efficacy Results:

Vaccine response to BPT one month after the third vaccine dose (ATP cohort for immunogenicity)

Group	Pre-vaccination antibody status	N [^]	Responders			
			n	%	95% CI	
					LL	UL
DTPw-HBV/Hib Kft.	S+	8	8	100	63.1	100
	S-	156	152	97.4	93.6	99.3
	Total	164	160	97.6	93.9	99.3
DTPw-HB Kft.+ Hib	S+	5	5	100	47.8	100
	S-	157	150	95.5	91	98.2
	Total	162	155	95.7	91.3	98.2
HBV + DTPw-HBV/Hib Kft.	S+	7	7	100	59	100
	S-	164	156	95.1	90.6	97.9
	Total	171	163	95.3	91	98
Control	S+	9	8	88.9	51.8	99.7
	S-	157	151	96.2	91.9	98.6
	Total	166	159	95.8	91.5	98.3

N[^] = number of subjects with both pre and post vaccination results available
n (%) = number (percentage) of responders. Vaccine response = the appearance of antibodies (concentration ≥ cut-off) in

initially seronegative subjects or post-vaccination antibody concentration \geq pre-vaccination concentration in initially seropositive subjects										
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit										
S-/S+ = seronegative/seropositive subjects at pre vaccination										
Total = subjects either seropositive or seronegative at pre-vaccination										
Secondary Outcome Variables:										
Anti-BPT seropositivity rates and antibody GMCs (ATP cohort for immunogenicity)										
Group	Timing	N	≥ 15 EL.U/mL				GMC (EL.U/mL)			
			n	%	95% CI		Value	95% CI		
					LL	UL		LL	UL	
DTPw-HBV/Hib Kft.	Pre	168	8	4.8	2.1	9.2	7.9	7.6	8.2	
	PIII	167	163	97.6	94.0	99.3	54.2	48.2	60.9	
DTPw-HB Kft.+ Hib	Pre	175	5	2.9	0.9	6.5	7.7	7.5	7.9	
	PIII	162	155	95.7	91.3	98.2	61.8	54.3	70.2	
HBV + DTPw-HBV/Hib Kft.	Pre	174	7	4.0	1.6	8.1	7.8	7.6	8.1	
	PIII	176	168	95.5	91.2	98.0	55.1	48.9	62.1	
Control	Pre	170	9	5.3	2.4	9.8	8.0	7.7	8.4	
	PIII	168	161	95.8	91.6	98.3	66.1	58.2	75.1	
N = number of subjects with available results										
n(%) = number(percentage) of subjects with specified antibody concentrations										
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit										
Pre: pre-vaccination.										
PIII: at 4.5 months i.e. one month after third vaccine dose.										
Secondary Outcome Variable(s):										
Incidence of solicited local symptoms reported during the 4-day (Days 0-3) post-vaccination period (Total Vaccinated Cohort)										
Symptom	Intensity	n	%	95% CI		n	%	95% CI		
				LL	UL			LL	UL	
Dose 1										
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib				
		N = 179				N = 277				
Pain	Any	143	79.9	73.3	85.5	201	72.6	66.9	77.7	
	Grade 3	22	12.3	7.9	18.0	30	10.8	7.4	15.1	
Redness	Any	103	57.5	49.9	64.9	167	60.3	54.3	66.1	
	> 20 mm	24	13.4	8.8	19.3	59	21.3	16.6	26.6	
Swelling	Any	106	59.2	51.6	66.5	169	61.0	55.0	66.8	
	> 20 mm	40	22.3	16.5	29.2	81	29.2	24.0	35.0	
		HBV + DTPw-HBV/Hib Kft.				Control				
		N = 185				N = 183				
Pain	Any	146	78.9	72.3	84.6	144	78.7	72.0	84.4	
	Grade 3	24	13.0	8.5	18.7	22	12.0	7.7	17.6	
Redness	Any	115	62.2	54.8	69.2	103	56.3	48.8	63.6	
	> 20 mm	31	16.8	11.7	22.9	19	10.4	6.4	15.7	
Swelling	Any	116	62.7	55.3	69.7	118	64.5	57.1	71.4	
	> 20 mm	54	29.2	22.8	36.3	46	25.1	19.0	32.1	
Dose 2										
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib				
		N = 181				N = 279				
Pain	Any	126	69.6	62.4	76.2	203	72.8	67.1	77.9	
	Grade 3	14	7.7	4.3	12.6	23	8.2	5.3	12.1	
Redness	Any	102	56.4	48.8	63.7	170	60.9	54.9	66.7	
	> 20 mm	19	10.5	6.4	15.9	43	15.4	11.4	20.2	
Swelling	Any	99	54.7	47.1	62.1	163	58.4	52.4	64.3	
	> 20 mm	28	15.5	10.5	21.6	65	23.3	18.5	28.7	
		HBV + DTPw-HBV/Hib Kft.				Control				

		N = 186				N = 184			
Pain	Any	123	66.1	58.8	72.9	128	69.6	62.4	76.1
	Grade 3	14	7.5	4.2	12.3	14	7.6	4.2	12.4
Redness	Any	106	57.0	49.5	64.2	102	55.4	47.9	62.7
	> 20 mm	19	10.2	6.3	15.5	12	6.5	3.4	11.1
Swelling	Any	106	57.0	49.5	64.2	111	60.3	52.9	67.4
	> 20 mm	34	18.3	13.0	24.6	34	18.5	13.1	24.9
Dose 3									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
		N = 181				N = 279			
Pain	Any	116	64.4	57.0	71.4	187	67.3	61.4	72.8
	Grade 3	12	6.7	3.5	11.4	12	4.3	2.3	7.4
Redness	Any	107	59.4	51.9	66.7	176	63.3	57.3	69.0
	> 20 mm	19	10.6	6.5	16.0	30	10.8	7.4	15.0
Swelling	Any	98	54.4	46.9	61.9	152	54.7	48.6	60.6
	> 20 mm	23	12.8	8.3	18.6	39	14.0	10.2	18.7
		HBV + DTPw-HBV/Hib Kft.				Control			
		N = 186				N = 184			
Pain	Any	119	64.0	56.6	70.9	118	64.1	56.7	71.1
	Grade 3	11	5.9	3.0	10.3	7	3.8	1.5	7.7
Redness	Any	106	57.0	49.5	64.2	113	61.4	54.0	68.5
	> 20 mm	18	9.7	5.8	14.9	11	6.0	3.0	10.4
Swelling	Any	103	55.4	47.9	62.7	107	58.2	50.7	65.4
	> 20 mm	26	14.0	9.3	19.8	23	12.5	8.1	18.2
Across Doses									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
		N = 182				N = 285			
Pain	Any	160	87.9	82.3	92.3	248	87.0	82.6	90.7
	Grade 3	37	20.3	14.7	26.9	50	17.5	13.3	22.5
Redness	Any	142	78.0	71.3	83.8	227	79.6	74.5	84.2
	> 20 mm	46	25.3	19.1	32.2	91	31.9	26.6	37.7
Swelling	Any	139	76.4	69.5	82.3	210	73.7	68.2	78.7
	> 20 mm	58	31.9	25.2	39.2	113	39.6	33.9	45.6
		HBV + DTPw-HBV/Hib Kft.				Control			
		N = 186				N = 184			
Pain	Any	170	90.4	85.3	94.2	162	86.6	80.9	91.2
	Grade 3	41	21.8	16.1	28.4	28	15.0	10.2	20.9
Redness	Any	150	79.8	73.3	85.3	148	79.1	72.6	84.7
	> 20 mm	49	26.1	19.9	33.0	31	16.6	11.6	22.7
Swelling	Any	147	78.2	71.6	83.9	150	80.2	73.8	85.7
	> 20 mm	72	38.3	31.3	45.7	64	34.2	27.5	41.5
<p>N = number of subjects with a symptom sheet completed n (%) = number (percentage) of subjects for whom the symptom was reported 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Any = incidence of a specified solicited local symptom irrespective of intensity grade Grade 3 pain: cried when limb was moved/spontaneously painful</p>									
Secondary Outcome Variable(s):									
Incidence of solicited general symptoms reported during the 4-day (Day 0-3) post-vaccination period (Total Vaccinated Cohort)									
Symptom	Intensity	n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
Dose 1									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
		N = 179				N = 277			

Drowsiness	Any	93	52.0	44.4	59.5	136	49.1	43.1	55.1
	Grade 3	6	3.4	1.2	7.2	7	2.5	1.0	5.1
	Related	91	50.8	43.3	58.4	132	47.7	41.6	53.7
Irritability	Any	134	74.9	67.8	81.0	198	71.5	65.8	76.7
	Grade 3	2	1.1	0.1	4.0	5	1.8	0.6	4.2
	Related	129	72.1	64.9	78.5	191	69.0	63.1	74.4
Loss of appetite	Any	46	25.7	19.5	32.8	64	23.1	18.3	28.5
	Grade 3	1	0.6	0.0	3.1	4	1.4	0.4	3.7
	Related	44	24.6	18.5	31.6	59	21.3	16.6	26.6
Fever (axillary)	Any	139	77.7	70.8	83.5	200	72.2	66.5	77.4
	Grade 3	0	0.0	0.0	2.0	1	0.4	0.0	2.0
	Related	137	76.5	69.6	82.5	193	69.7	63.9	75.0
		HBV + DTPw-HBV/Hib Kft.				Control			
		N = 185				N = 183			
Drowsiness	Any	100	54.1	46.6	61.4	97	53.0	45.5	60.4
	Grade 3	8	4.3	1.9	8.3	5	2.7	0.9	6.3
	Related	97	52.4	45.0	59.8	94	51.4	43.9	58.8
Irritability	Any	137	74.1	67.1	80.2	128	69.9	62.7	76.5
	Grade 3	7	3.8	1.5	7.6	3	1.6	0.3	4.7
	Related	134	72.4	65.4	78.7	124	67.8	60.5	74.5
Loss of appetite	Any	56	30.3	23.7	37.4	39	21.3	15.6	28.0
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
	Related	54	29.2	22.8	36.3	38	20.8	15.1	27.4
Fever (axillary)	Any	129	69.7	62.6	76.3	120	65.6	58.2	72.4
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
	Related	125	67.6	60.3	74.3	116	63.4	56.0	70.4
Dose 2									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
Drowsiness	Any	77	42.5	35.2	50.1	129	46.2	40.3	52.3
	Grade 3	3	1.7	0.3	4.8	4	1.4	0.4	3.6
	Related	76	42.0	34.7	49.5	129	46.2	40.3	52.3
Irritability	Any	105	58.0	50.5	65.3	173	62.0	56.0	67.7
	Grade 3	2	1.1	0.1	3.9	3	1.1	0.2	3.1
	Related	103	56.9	49.4	64.2	173	62.0	56.0	67.7
Loss of appetite	Any	40	22.1	16.3	28.9	69	24.7	19.8	30.2
	Grade 3	2	1.1	0.1	3.9	2	0.7	0.1	2.6
	Related	40	22.1	16.3	28.9	69	24.7	19.8	30.2
Fever (axillary)	Any	110	60.8	53.3	67.9	169	60.6	54.6	66.3
	Grade 3	1	0.6	0.0	3.0	1	0.4	0.0	2.0
	Related	107	59.1	51.6	66.4	168	60.2	54.2	66.0
		HBV + DTPw-HBV/Hib Kft.				Control			
Drowsiness	Any	76	40.9	33.7	48.3	76	41.3	34.1	48.8
	Grade 3	4	2.2	0.6	5.4	2	1.1	0.1	3.9
	Related	76	40.9	33.7	48.3	74	40.2	33.1	47.7
Irritability	Any	109	58.6	51.2	65.8	121	65.8	58.4	72.6
	Grade 3	5	2.7	0.9	6.2	1	0.5	0.0	3.0
	Related	109	58.6	51.2	65.8	120	65.2	57.9	72.1
Loss of appetite	Any	41	22.0	16.3	28.7	36	19.6	14.1	26.0
	Grade 3	1	0.5	0.0	3.0	0	0.0	0.0	2.0
	Related	41	22.0	16.3	28.7	36	19.6	14.1	26.0
Fever	Any	99	53.2	45.8	60.6	87	47.3	39.9	54.8

(axillary)	Grade 3	1	0.5	0.0	3.0	0	0.0	0.0	2.0
	Related	98	52.7	45.3	60.0	87	47.3	39.9	54.8
Dose 3									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
Drowsiness	Any	67	37.2	30.1	44.7	115	41.4	35.5	47.4
	Grade 3	3	1.7	0.3	4.8	5	1.8	0.6	4.1
	Related	67	37.2	30.1	44.7	112	40.3	34.5	46.3
Irritability	Any	102	56.7	49.1	64.0	160	57.6	51.5	63.4
	Grade 3	1	0.6	0.0	3.1	5	1.8	0.6	4.1
	Related	101	56.1	48.5	63.5	157	56.5	50.4	62.4
Loss of appetite	Any	34	18.9	13.5	25.4	58	20.9	16.2	26.1
	Grade 3	1	0.6	0.0	3.1	1	0.4	0.0	2.0
	Related	34	18.9	13.5	25.4	55	19.8	15.3	25.0
Fever (axillary)	Any	94	52.2	44.7	59.7	136	48.9	42.9	55.0
	Grade 3	1	0.6	0.0	3.1	0	0.0	0.0	1.3
	Related	94	52.2	44.7	59.7	135	48.6	42.5	54.6
		HBV + DTPw-HBV/Hib Kft.				Control			
Drowsiness	Any	72	38.7	31.7	46.1	83	45.1	37.8	52.6
	Grade 3	6	3.2	1.2	6.9	0	0.0	0.0	2.0
	Related	71	38.2	31.2	45.6	82	44.6	37.3	52.1
Irritability	Any	106	57.0	49.5	64.2	116	63.0	55.6	70.0
	Grade 3	2	1.1	0.1	3.8	1	0.5	0.0	3.0
	Related	103	55.4	47.9	62.7	115	62.5	55.1	69.5
Loss of appetite	Any	32	17.2	12.1	23.4	31	16.8	11.7	23.1
	Grade 3	1	0.5	0.0	3.0	0	0.0	0.0	2.0
	Related	31	16.7	11.6	22.8	31	16.8	11.7	23.1
Fever (axillary)	Any	77	41.4	34.2	48.8	78	42.4	35.2	49.9
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.0
	Related	76	40.9	33.7	48.3	77	41.8	34.6	49.3
Across Doses									
		DTPw-HBV/Hib Kft.				DTPw-HB Kft.+ Hib			
Drowsiness	Any	126	69.2	62.0	75.8	192	67.4	61.6	72.8
	Grade 3	10	5.5	2.7	9.9	14	4.9	2.7	8.1
	Related	125	68.7	61.4	75.3	190	66.7	60.9	72.1
Irritability	Any	160	87.9	82.3	92.3	242	84.9	80.2	88.9
	Grade 3	4	2.2	0.6	5.5	13	4.6	2.5	7.7
	Related	160	87.9	82.3	92.3	242	84.9	80.2	88.9
Loss of appetite	Any	79	43.4	36.1	50.9	126	44.2	38.4	50.2
	Grade 3	4	2.2	0.6	5.5	7	2.5	1.0	5.0
	Related	77	42.3	35.0	49.8	123	43.2	37.3	49.1
Fever (axillary)	Any	163	89.6	84.2	93.6	241	84.6	79.8	88.6
	Grade 3	2	1.1	0.1	3.9	2	0.7	0.1	2.5
	Related	162	89.0	83.5	93.2	239	83.9	79.1	87.9
		HBV + DTPw-HBV/Hib Kft.				Control			
Drowsiness	Any	132	70.2	63.1	76.6	136	72.7	65.7	79.0
	Grade 3	16	8.5	4.9	13.5	7	3.7	1.5	7.6
	Related	130	69.1	62.0	75.7	136	72.7	65.7	79.0
Irritability	Any	159	84.6	78.6	89.4	160	85.6	79.7	90.3
	Grade 3	12	6.4	3.3	10.9	4	2.1	0.6	5.4

	Related	157	83.5	77.4	88.5	160	85.6	79.7	90.3
Loss of appetite	Any	86	45.7	38.5	53.2	77	41.2	34.0	48.6
	Grade 3	2	1.1	0.1	3.8	0	0.0	0.0	2.0
	Related	85	45.2	38.0	52.6	76	40.6	33.5	48.1
Fever (axillary)	Any	158	84.0	78.0	89.0	158	84.5	78.5	89.4
	Grade 3	1	0.5	0.0	2.9	0	0.0	0.0	2.0
	Related	157	83.5	77.4	88.5	157	84.0	77.9	88.9
<p>N = number of subjects with a symptom sheet completed n (%) = number (percentage) of subjects for whom the symptom was reported 95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit Any = incidence of a specified general symptom irrespective of intensity grade or relationship to vaccination Related = symptoms considered by the investigator to have a causal relationship to study vaccination Grade 3 Drowsiness: drowsiness that prevented normal activity. Grade 3 Loss of appetite: Not eating at all Grade 3 Irritability : Crying that could not be comforted</p>									
Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort)									
Most frequent adverse events - On-Therapy (occurring within Day 0-30 after vaccination)			DTPw-HBV/Hib Kft. N = 182	DTPw-HB Kft.+ Hib N = 285	HBV + DTPw-HBV/Hib Kft. N = 188		Control N = 187		
Subjects with any AE(s), n (%)			86 (47.3)	115 (40.4)	90 (47.9)		82 (43.9)		
Upper respiratory tract infection			45 (24.7)	52 (18.2)	42 (22.3)		39 (20.9)		
Rhinitis			16 (8.8)	10 (3.5)	17 (9.0)		13 (7.0)		
Pyrexia			8 (4.4)	10 (3.5)	7 (3.7)		7 (3.7)		
Pneumonia			10 (5.5)	6 (2.1)	7 (3.7)		7 (3.7)		
Gastroenteritis			10 (5.5)	5 (1.8)	4 (2.1)		4 (2.1)		
Viral upper respiratory tract infection			2 (1.1)	9 (3.2)	8 (4.3)		3 (1.6)		
Bronchitis acute			6 (3.3)	7 (2.5)	1 (0.5)		5 (2.7)		
Safety results: Number (%) of subjects with serious adverse events after enrolment but before first administration of the combined vaccine (Total Enrolled Cohort)									
n (%) [n considered by the investigator to be related to study medication]									
All SAEs			DTPw-HBV/Hib Kft. N = 205	DTPw-HB Kft.+ Hib N = 301	HBV + DTPw-HBV/Hib Kft. N = 203†		Control N = 202		
Sepsis			2 (1.0) [0]	1 (0.3) [0]	0 (0.0) [0]		0 (0.0) [0]		
Pneumonia			1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]		0 (0.0) [0]		
Cyanosis			0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]		0 (0.0) [0]		
Sepsis neonatal			0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]		0 (0.0) [0]		
Viral infection			0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]		0 (0.0) [0]		
Gastroenteritis			0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]		0 (0.0) [0]		
Pneumonia aspiration			0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]		0 (0.0) [0]		
Fatal SAEs			DTPw-HBV/Hib Kft. N = 205	DTPw-HB Kft.+ Hib N = 301	HBV + DTPw-HBV/Hib Kft. N = 203†		Control N = 202		
Subjects with fatal SAE(s), n (%) [n related]			0 (0.0) [0]	1 (0.3) [0]	1 (0.5) [0]		0 (0.0) [0]		
Cyanosis			0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]		0 (0.0) [0]		
Pneumonia aspiration			0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]		0 (0.0) [0]		
† The subjects from the HBV + DTPw-HBV/Hib Kft. Group received a birth dose of HBV vaccine.									
Safety results: Number (%) of subjects with serious adverse events after administration of the combined vaccine (Total Vaccinated Cohort)									
n (%) [n considered by the investigator to be related to study medication]									
All SAEs			DTPw-HBV/Hib Kft. N = 182	DTPw-HB Kft.+ Hib N = 285	HBV + DTPw-HBV/Hib Kft. N = 188		Control N = 187		
Subjects with any SAE(s), n (%) [n related]			7 (3.8) [0]	6 (2.1) [0]	4 (2.1) [0]		1 (0.5) [0]		

Pneumonia	1 (0.5) [0]	1 (0.4) [0]	1 (0.5) [0]	1 (0.5) [0]
Gastroenteritis	2 (1.1) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Sepsis neonatal	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]
Bronchiolitis	0 (0.0) [0]	1 (0.4) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchitis viral	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Bronchopneumonia	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Interstitial lung disease	0 (0.0) [0]	0 (0.0) [0]	1 (0.5) [0]	0 (0.0) [0]
Pyelonephritis acute	1 (0.5) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	DTPw- HBV/Hib Kft. N = 182	DTPw-HB Kft.+ Hib N = 285	HBV + DTPw- HBV/Hib Kft. N = 188	Control N = 187
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Please refer to the publication below.

Publications:

Gatchalian S, *et al.* (2005) A new DTPw-HBV/Hib vaccine is immunogenic and safe when administered according to the EPI (Expanded Programme for Immunization) schedule and following hepatitis B vaccination at birth. *Human Vaccines*; 1(5): 198-203.

Gatchalian et al. A new DTPw-HBV/Hib vaccine: Immunogenic and safe for primary vaccination and booster dosing in the second year of life - 5th World Congress WSPID, Bangkok, Thailand, 15-18 Nov 2007.

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