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Study No.: 208140 (DTPa-HBV-020)
Title: Open clinical study to assess the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV and dtpa-HBV vaccines when administered with SB Biologicals' Hib vaccine, either mixed in one syringe and given in one single injection or given in two simultaneous injections into opposite limbs, as a booster vaccination at the age of 15 to 22 months to healthy children, previously primed with a three-dose primary vaccination course using the DTPa-HBV vaccine. DTPa-HBV: GlaxoSmithKline (GSK) Biologicals' (formerly Smith Kline Beecham [SB]) combined diphtheria tetanus acellular pertussis and hepatitis B vaccine. dtpa-HBV: GSK Biologicals' reduced antigen content combined diphtheria tetanus acellular pertussis and hepatitis B vaccine. Hib: GSK Biologicals' <i>Haemophilus influenzae</i> type B conjugate vaccine.
Rationale: In previous clinical studies healthy infants received a primary vaccination course of combined DTPa-HBV and Hib conjugate vaccines at 3, 4 and 5 months of age. The study vaccines were administered either in 2 simultaneous injections into opposite limbs, or mixed in one syringe, according to the study group. The aim of the present study was to evaluate the immunogenicity and safety of the DTPa-HBV and the dtpa-HBV vaccines, when given with Hib as a booster dose during the second year of life, and injected according to the same mode as during primary vaccination.
Phase: IIIb
Study Period: 28 June 1995 to 28 February 1996.
Study Design: Open, randomised study with 4 groups.
Centres: Single centre in Germany.
Indication: Booster vaccination of healthy children against diphtheria, tetanus, pertussis, hepatitis B and Hib.
Treatment: The study groups were as followed: <ul style="list-style-type: none"> • DTPa-HBV + Hib Group: subjects were primed (3-dose vaccination course) and boosted with DTPa-HBV and Hib vaccines concomitantly administered at separate injection sites • dtpa-HBV + Hib Group: subjects were primed (3-dose vaccination course) and boosted (1 dose) with dtpa-HBV and Hib vaccines concomitantly administered at separate injection sites • DTPa-HBV/Hib Group: subjects were primed (3-dose vaccination course) and boosted with the combined DTPa-HBV/Hib vaccine • dtpa-HBV/Hib Group: subjects were primed (3-dose vaccination course) and boosted with of the combined dtpa-HBV/Hib vaccine All vaccines were administered as a single dose intramuscularly into the anterolateral thigh (the right thigh for DTPa-HBV and dTpa-HBV administered alone or mixed with Hib, the left thigh for Hib vaccine when administered separately).
Objectives: To assess the immunogenicity of the fourth dose of Hib and DTPa-HBV, dtpa-HBV vaccines.
Primary Outcome/Efficacy Variable: <i>Immunogenicity:</i> One month after the booster vaccination in all subjects: <ul style="list-style-type: none"> • Anti-diphtheria and anti-tetanus toxoid antibody concentration ≥ 0.1 IU/mL and geometric mean concentrations (GMCs). • Vaccine response to pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) and GMCs. <i>Vaccine response was defined as follows:</i> - For initially seronegative subjects, a post-vaccination antibody concentrations ≥ 5 EL.U/mL.

- For initially seropositive subjects, a post-vaccination antibody concentrations at least twice that of the pre- vaccination concentration

- Anti hepatitis B virus surface (anti-HBs) antibody concentrations $\geq 10\text{mIU/mL}$ and GMCs.
- Anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations $\geq 0.15 \mu\text{g/mL}$ and $\geq 1.0 \mu\text{g/mL}$ and GMCs.

Secondary Outcome/Efficacy Variable(s):

Safety:

- Incidence and intensity of solicited local symptoms during the 4-day (Day 0-Day 3) follow-up period after booster vaccination.
- Incidence, intensity and relationship of solicited general symptoms during the 4-day (Day 0-Day 3) follow-up period after booster vaccination.
- Incidence and relationship of unsolicited symptoms within 30 days post vaccination.
- Occurrence of serious adverse events (SAEs) occurring during the 31-day follow-up period after vaccination.

Statistical Methods:

The analyses were performed on the Total Cohort, According-to-Protocol (ATP) cohort for immunogenicity.

- The Total Cohort included all vaccinated subjects 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 and with no elimination code assigned) who had received the complete primary vaccination course and for whom immunogenicity data were available.
- The ATP cohort for analysis of safety included all vaccinated subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol and with no elimination code assigned) who had received the complete primary vaccination course

Analysis of Immunogenicity

The analysis was performed on the ATP cohort for immunogenicity.

The percentages of subjects with antibody concentrations above a specified level were calculated (with 95% confidence interval [CI]) per group for each vaccine antigen, as well as vaccine response rates to each of the pertussis antigens. Pre- and post-vaccination GMCs were calculated with 95% CI for each vaccine antigen. For GMC calculations, antibody concentrations below the assay cut-off were given an arbitrary value of one half of the cut-off value.

Analysis of safety

The analysis was performed on the ATP cohort for analysis of safety.

The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 0-3) solicited follow-up was tabulated with 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited adverse events classified by the World Health Organization (WHO) preferred term and reported up to 31 days (Day 0-30) after vaccination was tabulated. The occurrence of SAEs during the 31-day follow-up period after vaccination was tabulated according to WHO preferred terms.

Study Population: Healthy male or female subjects aged 15-22 months at the time of vaccination who had received a complete primary vaccination course of 3 consecutive doses of GSK Biologicals' DTPa-HBV and Hib vaccines, were enrolled in the study. Written informed consent was obtained from the parents/guardians of the subjects prior to study entry.

Number of Subjects:	DTPa-HBV + Hib Group	dtpa-HBV + Hib Group	DTPa-HBV/Hib Group	dtpa-HBV/Hib Group
Planned, N	150	150	150	150
Randomised, N (Total cohort)	138	140	137	138
Completed, n (%)	138 (100)	140 (100)	136 (99.3)	138 (100)
Total Number Subjects Withdrawn,	0 (0.0)	0 (0.0)	1 (0.73)	0 (0.0)

n (%)				
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	Not Applicable	Not Applicable	Not Applicable
Withdrawn for other reasons n (%)	0 (0.0)	0 (0.0)	1 (0.73)	0 (0.0)
Demographics	DTPa-HBV + Hib Group	dtpa-HBV + Hib Group	DTPa-HBV/Hib Group	dtpa-HBV/Hib Group
N (Total cohort)	138	140	137	138
Females: Males	68:70	74:66	66:71	64:74
Mean Age, months (SD)	18.69 (1.38)	18.76 (1.45)	17.02 (1.36)	17.03 (1.28)
Race, n (%)	Not Available	Not Available	Not Available	Not Available

Primary Efficacy Results: Seropositivity rates and GMCs of anti-diphtheria antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥0.1 IU/mL		95% CI		GMC IU/mL	95% CI	
			n	%	LL	UL		L.L	U.L
DTPa-HBV + Hib	Pre	108	60	55.6	(45.7-	65.4)	0.127	(0.105-	0.153)
	PI(d30)	108	108	100.0	(95.7-	100.0)	6.055	(5.005-	7.327)
dtpa-HBV + Hib	Pre	103	56	54.4	(44.3-	64.5)	0.135	(0.109-	0.167)
	PI(d30)	104	103	99.0	(94.0-	99.9)	2.301	(1.923-	2.754)
DTPa-HBV/Hib	Pre	121	55	45.5	(36.2-	54.7)	0.097	(0.084-	0.112)
	PI(d30)	122	122	100.0	(96.2-	100.0)	4.458	(3.794-	5.239)
dtpa-HBV/Hib	Pre	113	51	45.1	(35.5-	54.8)	0.099	(0.084-	0.117)
	PI(d30)	113	112	99.1	(94.5-	100.0)	1.483	(1.253-	1.756)

N = total number of subjects tested
n = number of subjects within the given range
Pre = pre booster vaccination (day 0)
PI(d30) = approximately one month after booster vaccination
95% CI = 95% confidence interval; LL = Lower limit; UL = Upper limit

Primary Efficacy Results: Seropositivity rates and GMCs for anti-tetanus antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥0.1 IU/mL		95% CI		GMC IU/mL	95% CI	
			n	%	LL	UL		LL	UL
DTPa-HBV + Hib	Pre	108	99	91.7	(84.4	95.9)	0.266	(0.23-	0.31)
	PI(d30)	108	108	100.0	(95.7	100.0)	15.875	(13.42-	18.78)
dtpa-HBV + Hib	Pre	104	96	92.3	(85.0	96.4)	0.279	(0.24-	0.33)
	PI(d30)	104	104	100.0	(95.6	100.0)	18.490	(15.11-	22.62)
DTPa-HBV/Hib	Pre	121	105	86.8	(79.1	92.0)	0.252	(0.22-	0.29)
	PI(d30)	122	122	100.0	(96.2	100.0)	6.471	(5.63-	7.44)

dtpa-HBV/Hib	Pre	113	104	92.0	(85.0 -	96.1)	0.273	(0.24-	0.32)
	PI(d30)	113	113	100.0	(95.9 -	100.0)	9.622	(8.03-	11.54)

N = total number of subjects tested
n = number of subjects within the given range
Pre = pre booster vaccination (day 0)
PI(d30) = approximately one month after booster vaccination
95% CI = 95% confidence interval; LL = Lower limit; UL = Upper limit

Primary Efficacy Results: Vaccine response to pertussis components (ATP analysis of immunogenicity)

Antibody	Group	Pre- vaccination serological status	N	Vaccine response		
				n	%	[95% CI]
Anti-PT	DTPa-HBV + Hib	Seronegative	25	25	100.0	[90.2 -98.8]
		Seropositive	83	79	95.2	
		All	108	104	96.3	
	dtpa-HBV + Hib	Seronegative	26	26	100.0	[88.6 -98.2]
		Seropositive	78	73	93.6	
		All	104	99	95.2	
	DTPa- HBV/Hib	Seronegative	36	36	100.0	[92.4 - 99.4]
		Seropositive	86	83	96.5	
		All	122	119	97.5	
	dtpa-HBV/Hib	Seronegative	32	32	100.0	[86.1 - 96.7]
		Seropositive	81	73	90.1	
		All	113	105	92.9	
Anti-FHA	DTPa-HBV + Hib	Seronegative	3	3	100.0	[95.3 -100]
		Seropositive	96	96	100.0	
		All	99	99	100.0	
	dtpa-HBV + Hib	Seronegative	0	0	-	[93.5 -99.9]
		Seropositive	96	95	99.0	
		All	96	95	99.0	
	DTPa- HBV/Hib	Seronegative	1	1	100.0	[96.0 -100]
		Seropositive	114	114	100.0	
		All	115	115	100.0	
	dtpa-HBV/Hib	Seronegative	1	1	100.0	[93.9 -99.9]
		Seropositive	102	101	99.0	
		All	103	102	99.0	
Anti-PRN	DTPa-HBV + Hib	Seronegative	9	9	100.0	[95.7 -100]
		Seropositive	99	99	100.0	
		All	108	108	100.0	
	dtpa-HBV + Hib	Seronegative	10	10	100.0	[95.6 -100]
		Seropositive	94	94	100.0	
		All	104	104	100.0	
	DTPa- HBV/Hib	Seronegative	19	19	100.0	[96.2 -100]
		Seropositive	103	103	100.0	
		All	122	122	100.0	
	dtpa-HBV/Hib	Seronegative	18	17	94.4	[94.5 -100]
		Seropositive	95	95	100	
		All	113	112	99.1	

N = number of subjects tested
n = number of subjects with a vaccine response

95% CI = 95% confidence interval

Vaccine response definition:

-Pre-vaccination seronegative subjects: appearance of the antibodies concentrations \geq cut-off (5 EL.U/mL)

-Pre-vaccination seropositive subjects: post-vaccination concentrations at least twice pre-vaccination concentrations

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PT antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥ 5 EL.U/mL		95% CI		GMC EL.U/m	95% CI	
			n	%	LL	UL		LL	UL
DTPa-HBV + Hib	Pre	108	83	76.9	(67.6 -	84.2)	8.0	(6.9 -	9.3)
	PI(d30)	108	108	100.0	(95.7 -	100.0)	76.3	(67.4 -	86.3)
dtpa-HBV + Hib	Pre	104	78	75.0	(65.4 -	82.7)	8.6	(7.2 -	10.2)
	PI(d30)	104	104	100.0	(95.6 -	100.0)	60.2	(52.2 -	69.4)
DTPa-HBV/Hib	Pre	122	86	70.5	(61.4 -	78.2)	7.4	(6.3 -	8.6)
	PI(d30)	122	122	100.0	(96.2 -	100.0)	64.1	(56.3 -	73.0)
dtpa-HBV/Hib	Pre	113	81	71.7	(62.3 -	79.6)	7.0	(6.0 -	8.1)
	PI(d30)	113	113	100.0	(95.9 -	100.0)	50.2	(43.8 -	57.6)

N = total number of subjects tested

n = number of subjects with concentrations ≥ 5 EL.U/mL

Pre = pre booster vaccination (day 0)

PI(d30) = approximately one month after booster vaccination

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

Primary Efficacy Results: Seropositivity rates and GMCs of anti-FHA antibodies (ATP analysis of

Group	Timing	N	≥ 5 EL.U/mL		95% CI		GMC EL.U/m	95% CI	
			n	%	LL	UL		LL	UL
DTPa-HBV + Hib	Pre	99	96	97.0	(90.8 -	99.2)	29.9	(24.7 -	36.3)
	PI(d30)	99	99	100.0	(95.3 -	100.0)	972.9	(837.8 -	1129.9)
dtpa-HBV + Hib	Pre	102	102	100.0	(95.5 -	100.0)	35.6	(30.1 -	42.2)
	PI(d30)	96	96	100.0	(95.2 -	100.0)	562.0	(482.2 -	654.9)
DTPa-HBV/Hib	Pre	116	115	99.1	(94.6 -	100.0)	29.3	(25.5 -	33.8)
	PI(d30)	115	115	100.0	(96.0 -	100.0)	679.1	(594.5 -	775.8)
dtpa-HBV/Hib	Pre	109	108	99.1	(94.3 -	100.0)	28.3	(24.1 -	33.2)
	PI(d30)	103	103	100.0	(95.5 -	100.0)	398.9	(345.6 -	460.5)

N = total number of subjects tested

n = number of subjects with concentrations ≥ 5 EL.U/mL

Pre = pre booster vaccination (day 0)

PI(d30) = approximately one month after booster vaccination

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

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PRN antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥ 5 EL.U/mL		95% CI		GMCs EL.U/m	95% CI	
			n	%	LL	UL		LL	UL

DTPa-HBV + Hib	Pre	108	99	91.7	(84.4-	95.9)	17.8	(14.6 -	21.7)
	PI(d30)	108	108	100.0	(95.7-	100.0)	928.9	(794.3 -	1086.3)
dtpa-HBV + Hib	Pre	104	94	90.4	(82.6-	95.0)	18.5	(15.1 -	22.6)
	PI(d30)	104	104	100.0	(95.6-	100.0)	572.7	(484.7 -	676.7)
DTPa-HBV/Hib	Pre	122	103	84.4	(76.5-	90.1)	15.8	(13.2 -	19.1)
	PI(d30)	122	122	100.0	(96.2-	100.0)	731.8	(625.3 -	856.5)
dtpa-HBV/Hib	Pre	113	95	84.1	(75.7-	90.0)	15.4	(12.6 -	18.8)
	PI(d30)	113	112	99.1	(94.5-	100.0)	487.2	(407.9 -	581.9)

N = total number of subjects tested

n = number of subjects with concentrations ≥ 5 EL.U/mL

Pre = pre booster vaccination (day 0)

PI(d30) = approximately one month after booster vaccination

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

Primary Efficacy Results: Seropositivity rates and GMCs for anti-HBs antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥ 10 mIU/mL		95% CI		GMC mIU/mL	95% CI	
			n	%	LL	UL		LL	UL
DTPa-HBV + Hib	Pre	108	96	88.9	(81.0-	93.9)	78.9	(60.6-	102.8)
	PI(d30)	108	108	100.0	(95.7-	100.0)	3889.2	(2869.7 -	5271.0)
dtpa-HBV + Hib	Pre	104	90	86.5	(78.1-	92.2)	81.0	(59.8-	109.9)
	PI(d30)	104	103	99.0	(94.0-	99.9)	3573.0	(2478.8 -	5150.3)
DTPa-HBV/Hib	Pre	122	107	87.7	(80.2-	92.7)	73.4	(55.7-	96.7)
	PI(d30)	122	121	99.2	(94.8-	100.0)	2648.2	(1956.6 -	3584.2)
dtpa-HBV/Hib	Pre	113	100	88.5	(80.8-	93.5)	78.2	(59.1-	103.5)
	PI(d30)	113	113	100.0	(95.9-	100.0)	2657.6	(1923.1 -	3672.7)

N = total number of subjects tested

n = number of subjects with specified concentration

Pre = pre booster vaccination (day 0)

PI(d30) = approximately one month after booster vaccination

95% CI = confidence interval

LL, UL = lower and upper confidence limits

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PRP antibodies (ATP analysis of immunogenicity)

Group	Timing	N	≥ 0.15 $\mu\text{g/mL}$		95% CI		GMC $\mu\text{g/mL}$	95% CI	
			n	%	LL	UL		LL	UL
DTPa-HBV + Hib	Pre	108	84	77.8	(68.6 -	85.0)	0.585	(0.430 -	0.797)
	PI(d30)	108	108	100.0	(95.7 -	100.0)	96.119	(74.074 -	124.726)
dtpa-HBV + Hib	Pre	104	80	76.9	(67.4 -	84.4)	0.560	(0.405 -	0.773)
	PI(d30)	104	104	100.0	(95.6 -	100.0)	110.899	(84.658 -	145.273)
DTPa-HBV/Hib	Pre	122	74	60.7	(51.6 -	69.7)	0.222	(0.181 -	0.271)
	PI(d30)	122	122	100.0	(96.2 -	100.0)	26.327	(20.682 -	33.513)

dtpa-HBV/Hib	Pre	113	64	56.6	(47.1 - 66.2)	0.204	(0.165 - 0.252)
	PI(d30)	113	113	100.0	(95.9 - 100.0)	48.590	(39.322 - 60.043)

N = total number of subjects tested
n = subjects with concentrations ≥ 0.15 $\mu\text{g/mL}$
Pre = pre booster vaccination (day 0)
PI(d30) = approximately one month after booster vaccination
95% CI = 95% confidence interval; LL = Lower limit; UL = Upper limit

Primary Efficacy Results: Distribution of individual anti-PRP antibody concentrations (ATP analysis of immunogenicity)

Group	Timing	N	≥ 0.15	%	≥ 1	%
DTPa-HBV + Hib	Pre	108	84	77.8	35	32.4
	PI(d30)	108	108	100.0	108	100.0
dtpa-HBV + Hib	Pre	104	80	76.9	29	27.9
	PI(d30)	104	104	100.0	104	100.0
DTPa-HBV/Hib	Pre	122	74	60.7	10	8.2
	PI(d30)	122	122	100.0	121	99.2
dtpa-HBV/Hib	Pre	113	64	56.6	10	8.8
	PI(d30)	113	113	100.0	113	100.0

N = number of subjects with available data
Pre = pre booster
PI(d30) = one month after booster dose

Secondary Outcome Variable(s): Incidence of all and grade 3 solicited local symptoms during the 4-day follow-up period after vaccination (ATP analysis of safety)

Symptom	Intensity	DTPa-HBV + Hib Group (N = 128)		dtpa-HBV + Hib Group (N = 125)		DTPa-HBV/Hib Group (N = 135)		dtpa-HBV/Hib Group (N = 133)	
		n	%	n	%	n	%	n	%
Pain	All	24	18.8	22	17.6	43	31.9	26	19.5
	Grade 3	1	0.8	3	2.4	3	2.2	1	0.8
Redness	All	44	34.4	50	40	64	47.4	43	32.3
	>20 mm	6	4.7	6	4.8	13	9.6	7	5.3
Swelling	All	34	26.6	36	28.8	56	41.5	27	20.3
	>20 mm	3	2.3	7	5.6	10	7.4	6	4.5

N = number of documented doses
n = number of documented doses followed by the specified symptom
Grade 3 = pain which prevented everyday activities

Secondary Outcome Variable(s): Incidence of solicited general symptoms (all, grade 3, related/possibly related) (ATP analysis of safety)

Symptom	Intensity	DTPa-HBV + Hib Group (N = 128)		dtpa-HBV + Hib Group (N = 125)		DTPa-HBV/Hib Group (N = 135)		dtpa-HBV/Hib Group (N = 133)	
		n	%	n	%	n	%	n	%
Diarrhoea	Total	15	11.7	21	16.8	23	17.0	12	9.0
	Grade 3	1	0.8	1	0.8	1	0.7	0	0.0
	R/PR	10	7.8	17	13.6	20	14.8	8	6.0
Loss of appetite	Total	23	18.0	18	14.4	27	20.0	19	14.3
	Grade 3	0	0.0	0	0.0	2	1.5	0	0.0
	R/PR	21	16.4	16	12.8	26	19.3	15	11.3

Restlessness	Total	27	21.1	25	20.0	37	27.4	32	24.1
	Grade 3	2	1.6	2	1.6	0	0.0	2	1.5
	R/PR	26	20.3	22	17.6	37	27.4	29	21.8
Fever (rectal temperature)	≥38.0°C	37	28.9	27	21.6	42	31.1	41	30.8
	≥39.5°C	2	1.6	0	0.0	1	0.7	1	0.8
	R/PR	37	28.9	27	21.6	40	29.6	38	28.6
Unusual crying	Total	11	8.6	10	8.0	10	7.4	15	11.3
	Grade 3	0	0.0	0	0.0	1	0.7	2	1.5
	R/PR	10	7.8	10	8.0	9	6.7	13	9.8
Vomiting	Total	3	2.3	3	2.4	3	2.2	5	3.8
	Grade 3	0	0.0	1	0.8	1	0.7	1	0.8
	R/PR	2	1.6	3	2.4	2	1.5	3	2.3

N = number of documented doses

n = number of documented doses followed by the specified symptom

Total = all reports of a general solicited symptom, irrespective of the relationship to vaccination

Grade 3 = symptom preventing everyday activities

R/PR = 'related' or 'possibly related' to vaccination

Safety results: Number (%) of subjects with unsolicited AEs (ATP analysis of safety)

Most frequent adverse events - On-Therapy (occurring within Day 0-30 following vaccination)	DTPa-HBV + Hib Group N=128	dtpa-HBV + Hib Group N=125	DTPa-HBV/Hib Group N=135	dtpa-HBV/Hib Group N=133
Subjects with any AE(s), n (%)	24 (18.8)	25 (20.0)	44 (32.6)	43 (32.3)
Subjects with Grade 3 AE(s), n (%)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.5)
Subjects with related AE(s), n (%)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Fever	3 (2.3)	7 (5.6)	10 (7.4)	12 (9.0)
Upper resp tract infection	4 (3.1)	3 (2.4)	10 (7.4)	6 (4.5)
Rash erythematous	2 (1.6)	-	3 (2.2)	5 (3.8)
Rhinitis	-	-	5 (3.7)	4 (3.0)
Otitis media	-	2 (1.6)	6 (4.4)	-
Bronchitis	1 (0.8)	2 (1.6)	-	4 (3.0)
Diarrhoea	3 (2.3)	-	-	-
Gastroenteritis	3 (2.3)	2 (1.6)	2 (1.5)	1 (0.8)
Pharyngitis	-	1 (0.8)	3 (2.2)	3 (2.3)
Tooth ache	2 (1.6)	1 (0.8)	1 (0.7)	1 (0.8)
Oedema legs	-	-	3 (2.2)	-
Injection site reaction	-	-	3 (2.2)	-

Grade 3 AE: AE that prevented normal activities

Related AE: assessed by the investigator as related or possibly related to vaccination

-: Adverse event not present or not meeting the AE counting rules.

Detail of rule: > 30 subjects/treatment group and > 3 groups, display the most frequent 5 events in each treatment group

Safety results: Number (%) of subjects with SAEs (ATP analysis of safety)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]				
All SAEs	DTPa-HBV + Hib Group N=128	dtpa-HBV + Hib Group N=125	DTPa-HBV/Hib Group N=135	dtpa-HBV/Hib Group N=133
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Gastroenteritis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Pharyngitis	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]

Pneumonia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Fatal SAEs	DTPa-HBV + Hib Group N=128	dtpa-HBV + Hib Group N=125	DTPa- HBV/Hib Group N=135	dtpa- HBV/Hib Group N=133
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: One month after booster vaccination, all subjects had antibody concentrations \geq assay cut-off for anti-tetanus, anti-PT, anti-FHA and anti-PRP; at least 99.0%, 99.1% and 99.0% of subjects had anti-diphtheria, anti-PRN and anti-HBs antibody concentrations \geq assay cut-off, respectively.

During the 31-day follow-up period after vaccination, unsolicited AEs were reported for 24 (18.8%), 25 (20.0%), 44 (32.6%) and 43 (32.3%) subjects in the DTPa-HBV + Hib, dtpa-HBV + Hib, DTPa-HBV/Hib and dtpa-HBV/Hib groups, respectively. SAEs were reported for 1 subject from the dtpa-HBV/Hib Group; it was not considered by the investigator as related to the study vaccination. No fatal SAEs were reported during the study.

Publications: None.

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