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Study No.: 208108/087 (Hib-087)
Title: Phase II open randomized primary vaccination study to assess the immunogenicity and reactogenicity of GlaxoSmithKline Biologicals (GSK) <i>Haemophilus influenzae</i> type b (Hib) conjugate vaccine administered either mixed or in two separated injections with commercially available DTPw vaccine (Government Pharmaceutical Organization: GPO) as compared to GSK Biologicals' Hib administered mixed with GSK Biologicals' DTPw vaccine in healthy infants, aged 2, 4 and 6 months DTPw I: commercially available diphtheria, tetanus, whole cell pertussis vaccine; DTPw II: GSK Biologicals' diphtheria, tetanus, whole cell pertussis vaccine; Hib: <i>Haemophilus influenzae</i> type b
Rationale: This study assessed the immunogenicity and safety of mixed and separate administration of Hib vaccine with DTPw I or DTPw II vaccines.
Phase: II
Study Period: 4 September 2001 to 23 April 2002
Study Design: Open, randomized, controlled study with 3 parallel groups (1:1:1 ratio).
Centers: One center in Thailand
Indication: Immunization against Hib, diphtheria, tetanus and pertussis diseases in the first year of life.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • Group DTPw I + Hib received DTPw I vaccine concomitantly with Hib vaccine. • Group DTPw I/Hib received DTPw I vaccine mixed with Hib vaccine. • Group DTPw II/Hib received DTPw II vaccine mixed with Hib vaccine. All vaccines were administered by deep intramuscular injections. DTPw vaccines in the left anterolateral thigh and the Hib vaccine in the right anterolateral thigh.
Objectives: To demonstrate that infants receiving Hib vaccine either mixed or administered simultaneously at 2 separate sites with DTPw I vaccine produced an immune response with respect to the polysibosyl ribitol phosphate (PRP) antigen 1 month after the third dose of the primary vaccination course (% of subjects with anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$) equivalent to that observed in a control group of infants receiving mixed Hib and DTPw II vaccines.
Primary Outcome/Efficacy Variable: One month after the third dose of the study vaccines: <ul style="list-style-type: none"> • Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$.
Secondary Outcome/Efficacy Variable(s): One month after the third dose of the study vaccines: <ul style="list-style-type: none"> • Antibody concentrations against all vaccine antigen components: anti-diphtheria, anti-tetanus, anti-<i>Bordetella Pertussis</i> toxoids (BPT), anti-PRP. After each vaccine dose: <ul style="list-style-type: none"> • Occurrence of any solicited local and/or general symptoms within 4 days (Day 0-3) of each dose of the study vaccines. • Occurrence of unsolicited adverse events (AEs) within 30 days (Day 0-29) of each dose of the study vaccines. • Occurrence of serious adverse events (SAEs) throughout the entire study period.
Statistical Methods: The analyses were performed on the Total Vaccinated Cohort, the According-To-Protocol (ATP) cohort for immunogenicity and the ATP cohort for safety. <ul style="list-style-type: none"> - The Total Vaccinated Cohort included all subjects who received at least one vaccine dose. - The ATP cohort for immunogenicity included all vaccinated subjects who complied with the procedures defined in the protocol and for whom immunogenicity data were available.

- The ATP cohort for safety included all subjects who received at least one dose of study vaccine, who had not received a vaccine not specified or forbidden in the protocol and with sufficient data to perform an analysis of safety.

Analysis of immunogenicity:

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

Geometric Mean concentrations (GMCs) and Seroprotection or Seropositivity rates for antibodies against all vaccine antigens were summarized at pre-vaccination and one month after the third vaccine dose with 95% confidence interval (CI). Seroprotection and seropositivity rates were defined as the percentage of subjects with antibody concentrations \geq a protective level (seroprotection) or and assay cut-off (seropositivity) respectively. The cut-off values were the following:

- Anti-diphtheria and anti-tetanus antibody concentrations \geq 0.1 IU/mL (seroprotection)
- Anti-*Bordetella Pertussis* toxoid (BPT) antibody concentrations \geq 15 EL.U/mL (seropositivity)
- Anti-PRP antibody concentrations \geq 0.15 μ g/mL and \geq 1 μ g/mL (seroprotection)

The equivalence between each treatment group and the control group was shown if the confidence limits of the difference in anti-PRP seroprotection rates were within the pre-defined clinical limits [-10%, 10%].

Analysis of safety:

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

For each solicited local and general symptom, the percentage of subjects with the symptom reported during the 4-day (Day 0-3) follow-up period was summarized after the vaccination for each group with exact 95% CI.

The percentage of subjects with unsolicited AEs within 30 days (Day 0-29) following each dose was tabulated according to the World Health Organization (WHO) preferred term for each group.

The occurrence of SAEs was tabulated according to the WHO preferred term for each group during the entire study period.

Study Population: Male or female subjects aged between and including 6 to 12 weeks at the time of the first vaccination, born after a normal gestation period (between 36 and 42 weeks), free of obvious health problems as established by medical history and clinical examination before entering into the study and who were previously primed with vaccines in Extended Program on Immunization (EPI) according to the local schedule. Written informed consent was obtained from parents/guardians of the subjects prior to study entry. Subjects with history of or intercurrent, diphtheria, tetanus, pertussis, and/or Hib disease or vaccination were excluded.

Number of subjects	DTPw I + Hib	DTPw I/Hib	DTPw II /Hib
Planned, N	120	120	120
Randomized, N (Total Vaccinated Cohort)	120	120	120
Completed, n (%)	113 (94.2)	115 (95.8)	112 (93.3)
Total Number Subjects Withdrawn, n (%)	7 (5.8)	5 (4.2)	8 (6.7)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	7 (5.8)	5 (4.2)	8 (6.7)
Demographics	DTPw I + Hib	DTPw I/Hib	DTPw II /Hib
N (Total Vaccinated Cohort)	120	120	120
Females:Males	53:67	68:52	54:66
Mean Age, weeks (SD)	9.2 (0.66)	9.1 (0.52)	9.1 (0.74)
Oriental, n (%)	120 (100)	120 (100)	120 (100)

Primary Efficacy Results:

Difference between groups in anti-PRP seroprotection rates one month after the last vaccine dose (ATP cohort for immunogenicity)

Group	N	%	Group	N	%	Inference			
						Difference	Value	95% CI	
							%	LL	UL
DTPw I + Hib	112	100	DTPw II /Hib	110	100	DTPwII/Hib -DT Pw I + Hib	0.0	-	3.3*
DTPw I /Hib	111	100	DTPw II /Hib	110	100	DTPwII/Hib -DT Pw I /Hib	0.0	-	3.3*

N: Number of subjects with available results
 %: percentage of subjects with antibody concentrations ≥ 0.15 g /mL
 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
 * As the confidence limits were within the pre-defined clinical limits [-10%, 10%], the equivalence between groups was shown.

Primary Efficacy Results:

Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity)

Group	Timing	N	≥ 0.15 g/ mL			≥ 1.0 g/mL			GMC				
			n	%	95% CI		n	%	95% CI		g/mL	95% CI	
					LL	UL			LL	UL		LL	UL
DTPw I + Hib	Pre	111	101	91.0	84.1	95.6	16	14.4	8.5	22.4	0.356	0.296	0.428
	Post	112	112	100*	96.8	100	112	100	96.8	100	17.655	14.495	21.504
DTPw I/Hib	Pre	110	97	88.2	80.6	93.6	18	16.4	10.0	24.6	0.352	0.290	0.426
	Post	111	111	100*	96.7	100	109	98.2	93.6	99.8	15.285	12.253	19.068
DTPw II /Hib	Pre	110	100	90.9	83.9	95.6	21	19.1	12.2	27.7	0.408	0.338	0.492
	Post	110	110	100*	96.7	100	110	100	96.7	100	15.447	13.298	17.943

N: Number of subjects with available results
 n(%): Number (percentage) of subjects with the specified antibody concentrations
 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
 Pre: Pre-vaccination
 Post: One month after the third vaccine dose
 * Primary outcome

Secondary Outcome Variable (s):

Seropositivity rates and GMCs for anti-BPT antibodies (ATP cohort for immunogenicity)

Group	Timin g	N	≥ 15 EL.U/mL				GMC		
			n	%	95% CI		EL.U/mL	95% CI	
					LL	UL		LL	UL
DTPw I + Hib	Pre	112	2	1.8	0.2	6.3	7.735	7.390	8.095
	Post	111	110	99.1	95.1	100	75.527	67.156	84.941
DTPw I /Hib	Pre	114	4	3.5	1.0	8.7	7.861	7.495	8.245
	Post	113	110	97.3	92.4	99.4	66.087	57.743	75.636
DTPw II /Hib	Pre	110	3	2.7	0.6	7.8	7.765	7.462	8.081
	Post	105	103	98.1	93.3	99.8	72.761	63.276	83.668

N: Number of subjects with available results
 n(%): Number(percentage) of subjects with the specified antibody concentrations
 95%CI: 95% confidence interval; LL: lower limit; UL: upper limit
 Pre: Pre-vaccination
 Post: One month after the third vaccine dose

Secondary Outcome Variable (s):

Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (ATP cohort for immunogenicity)

Antibody	Group	Timin g	N	≥ 0.1 IU/mL			GMC			
				n	%	95% CI		IU/mL	95% CI	
						LL	UL		LL	UL

Pain	Any	63	56.3	46.6	65.6	62	52.5	43.1	61.8	66	57.9	48.3	67.1
	Grade 3	10	8.9	4.4	15.8	6	5.1	1.9	10.7	12	10.5	5.6	17.7
Redness	Any	53	47.3	37.8	57.0	58	49.2	39.8	58.5	57	50.0	40.5	59.5
	>20mm	0	0.0	0.0	3.2	0	0.0	0.0	3.1	0	0.0	0.0	3.2
Swelling	Any	29	25.9	18.1	35.0	41	34.7	26.2	44.1	38	33.3	24.8	42.8
	>20mm	3	2.7	0.6	7.6	1	0.8	0.0	4.6	0	0.0	0.0	3.2
		Across Doses											
		N = 119				N = 120				N = 118			
Pain	Any	98	82.4	74.3	88.7	103	85.8	78.3	91.5	111	94.1	88.2	97.6
	Grade 3	26	21.8	14.8	30.4	22	18.3	11.9	26.4	29	24.6	17.1	33.4
Redness	Any	80	67.2	58.0	75.6	82	68.3	59.2	76.5	86	72.9	63.9	80.7
	>20mm	0	0.0	0.0	3.1	6	5.0	1.9	10.6	5	4.2	1.4	9.6
Swelling	Any	57	47.9	38.7	57.2	61	50.8	41.6	60.1	72	61.0	51.6	69.9
	>20mm	3	2.5	0.5	7.2	5	4.2	1.4	9.5	10	8.5	4.1	15.0
<p>N: number of subjects with a symptom sheet completed n (%): number (percentage) of subjects for whom a specific symptom was reported Any: incidence of a particular symptom regardless of grade Grade 3 pain: cried when limb was moved / spontaneously painful 95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit</p>													
Secondary Outcome Variable (s):													
Number and percentage of subjects with solicited general symptoms during 4-day (Day 0- 3) follow-up period (ATP cohort for safety)													
Symptoms	Intensity/ Relationship	DTPw I + Hib				DTPw I/Hib				DTPw II /Hib			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
		Dose 1											
		N = 119				N = 120				N = 118			
Drowsiness	Any	72	60.5	51.1	69.3	86	71.7	62.7	79.5	86	72.9	63.9	80.7
	Grade 3	4	3.4	0.9	8.4	7	5.8	2.4	11.6	8	6.8	3.0	12.9
	Related	63	52.9	43.6	62.2	77	64.2	54.9	72.7	84	71.2	62.1	79.2
Irritability	Any	91	76.5	67.8	83.8	102	85.0	77.3	90.9	98	83.1	75.0	89.3
	Grade 3	12	10.1	5.3	17.0	6	5.0	1.9	10.6	11	9.3	4.7	16.1
	Related	77	64.7	55.4	73.2	85	70.8	61.8	78.8	91	77.1	68.5	84.3
Loss of appetite	Any	41	34.5	26.0	43.7	47	39.2	30.4	48.5	45	38.1	29.4	47.5
	Grade 3	2	1.7	0.2	5.9	3	2.5	0.5	7.1	0	0.0	0.0	3.1
	Related	36	30.3	22.2	39.3	40	33.3	25.0	42.5	43	36.4	27.8	45.8
Fever (axillary)	≥ 37.5°C	58	48.7	39.5	58.1	67	55.8	46.5	64.9	80	67.8	58.6	76.1
	> 39.5°C	0	0.0	0.0	3.1	1	0.8	0.0	4.6	0	0.0	0.0	3.1
	Related	54	45.4	36.2	54.8	66	55.0	45.7	64.1	80	67.8	58.6	76.1
		Dose 2											
		N = 117				N = 118				N = 116			
Drowsiness	Any	55	47.0	37.7	56.5	69	58.5	49.0	67.5	68	58.6	49.1	67.7
	Grade 3	2	1.7	0.2	6.0	3	2.5	0.5	7.3	0	0.0	0.0	3.1
	Related	53	45.3	36.1	54.8	67	56.8	47.3	65.9	67	57.8	48.2	66.9
Irritability	Any	82	70.1	60.9	78.2	84	71.2	62.1	79.2	90	77.6	68.9	84.8
	Grade 3	3	2.6	0.5	7.3	8	6.8	3.0	12.9	5	4.3	1.4	9.8
	Related	79	67.5	58.2	75.9	79	66.9	57.7	75.3	87	75.0	66.1	82.6
Loss of appetite	Any	32	27.4	19.5	36.4	38	32.2	23.9	41.4	42	36.2	27.5	45.6
	Grade 3	2	1.7	0.2	6.0	3	2.5	0.5	7.3	0	0.0	0.0	3.1
	Related	29	24.8	17.3	33.6	37	31.4	23.1	40.5	41	35.3	26.7	44.8

Fever (axillary)	≥ 37.5°C	48	41.0	32.0	50.5	52	44.1	34.9	53.5	65	56.0	46.5	65.2
	> 39.5°C	1	0.9	0.0	4.7	3	2.5	0.5	7.3	1	0.9	0.0	4.7
	Related	48	41.0	32.0	50.5	52	44.1	34.9	53.5	65	56.0	46.5	65.2
		Dose 3											
		N = 112				N = 118				N = 114			
Drowsiness	Any	69		51.9	70.6	64	54.2	44.8	63.4	70	61.4	51.8	70.4
	Grade 3	2	1.8	0.2	6.3	2	1.7	0.2	6.0	4	3.5	1.0	8.7
	Related	68	60.7	51.0	69.8	64	54.2	44.8	63.4	70	61.4	51.8	70.4
Irritability	Any	87	77.7	68.8	85.0	87	73.7	64.8	81.4	83	72.8	63.7	80.7
	Grade 3	10	8.9	4.4	15.8	7	5.9	2.4	11.8	3	2.6	0.5	7.5
	Related	87	77.7	68.8	85.0	87	73.7	64.8	81.4	83	72.8	63.7	80.7
Loss of appetite	Any	43	38.4	29.4	48.1	40	33.9	25.4	43.2	44	38.6	29.6	48.2
	Grade 3	2	1.8	0.2	6.3	1	0.8	0.0	4.6	1	0.9	0.0	4.8
	Related	43	38.4	29.4	48.1	40	33.9	25.4	43.2	44	38.6	29.6	48.2
Fever (axillary)	≥37.5°C	62	55.4	45.7	64.8	65	55.1	45.7	64.3	63	55.3	45.7	64.6
	>39.5°C	1	0.9	0.0	4.9	1	0.8	0.0	4.6	1	0.9	0.0	4.8
	Related	62	55.4	45.7	64.8	65	55.1	45.7	64.3	63	55.3	45.7	64.6
		Across Doses											
		N = 119				N = 120				N = 118			
Drowsiness	Any	97	81.5	73.4	88.0	102	85.0	77.3	90.9	107	90.7	83.9	95.3
	Grade 3	95	79.8	71.5	86.6	100	83.3	75.4	89.5	106	89.8	82.9	94.6
	Related	7	5.9	2.4	11.7	9	7.5	3.5	13.8	10	8.5	4.1	15.0
Irritability	Any	111	93.3	87.2	97.1	115	95.8	90.5	98.6	113	95.8	90.4	98.6
	Grade 3	109	91.6	85.1	95.9	111	92.5	86.2	96.5	112	94.9	89.3	98.1
	Related	21	17.6	11.3	25.7	15	12.5	7.2	19.8	17	14.4	8.6	22.1
Loss of appetite	Any	65	54.6	45.2	63.8	72	60.0	50.7	68.8	78	66.1	56.8	74.6
	Grade 3	63	52.9	43.6	62.2	70	58.3	49.0	67.3	76	64.4	55.1	73.0
	Related	5	4.2	1.4	9.5	5	4.2	1.4	9.5	1	0.8	0.0	4.6
Fever (axillary)	≥ 37.5°C	91	76.5	67.8	83.8	99	82.5	74.5	88.8	103	87.3	79.9	92.7
	> 39.5°C	90	75.6	66.9	83.0	99	82.5	74.5	88.8	103	87.3	79.9	92.7
	Related	2	1.7	0.2	5.9	4	3.3	0.9	8.3	2	1.7	0.2	6.0
<p>N: number of subjects with a symptom sheet completed n (%): number (percentage) of subjects for whom a specific symptom was reported Any: incidence of a particular symptom regardless of grade or relationship to vaccination Grade 3 drowsiness: drowsiness that prevented normal activity Grade 3 irritability: crying that could not be comforted/ prevented normal activity Grade 3 Loss of appetite: not eating at all Related: symptoms determined by the investigator to be related to vaccination 95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit</p>													
Safety Results: Number (%) of subjects with unsolicited AEs (ATP cohort for safety)													
Most Frequent AEs - On-Therapy (occurring within Day 0-29 following vaccination)						DTPw I + Hib N = 119		DTPw I/Hib N = 120		DTPw II/Hib N = 118			
Subjects with any AE(s), n (%)						26 (21.8)		29 (24.2)		27 (22.9)			
Upper respiratory tract infection						2 (1.7)		5 (4.2)		5 (4.2)			
Diarrhea						2 (1.7)		3 (2.5)		6 (5.1)			
Pharyngitis						5 (4.2)		2 (1.7)		3 (2.5)			
Rhinitis						2 (1.7)		3 (2.5)		3 (2.5)			
Infection viral						2 (1.7)		2 (1.7)		3 (2.5)			
Eczema						3 (2.5)		2 (1.7)		1 (0.8)			
Bronchitis						2 (1.7)		3 (2.5)		0 (0.0)			
Pneumonia						2 (1.7)		2 (1.7)		1 (0.8)			
Rash						1 (0.8)		2 (1.7)		1 (0.8)			

Gastritis	1 (0.8)	1 (0.8)	1 (0.8)
Gastroenteritis	1 (0.8)	1 (0.8)	1 (0.8)
Rash erythematous	0 (0.0)	2 (1.7)	1 (0.8)
Conjunctivitis	1 (0.8)	1 (0.8)	0 (0.0)
Dermatitis contact	1 (0.8)	0 (0.0)	1 (0.8)
Moniliasis	1 (0.8)	0 (0.0)	1 (0.8)
Abscess	0 (0.0)	0 (0.0)	1 (0.8)
Dysphonia	1 (0.8)	0 (0.0)	0 (0.0)
Fever	0 (0.0)	0 (0.0)	1 (0.8)
Gastroesophageal reflux	1 (0.8)	0 (0.0)	0 (0.0)
Infection	1 (0.8)	0 (0.0)	0 (0.0)
Injury	1 (0.8)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (0.8)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	1 (0.8)
Safety Results: Number (%) of subjects with SAEs (Total Vaccinated cohort)			
SAEs, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	DTPw I + Hib N = 120	DTPw I/Hib N = 120	DTPwII/Hib N = 120
Subjects with any SAE(s), n (%) [n related]	2 (1.7) [0]	5 (4.2) [0]	1 (0.8) [0]
Gastroenteritis	0 (0.0) [0]	2 (1.7) [0]	0 (0.0) [0]
Pneumonia	1 (0.8) [0]	1 (0.8) [0]	0 (0.0) [0]
Coughing	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]
Dehydration	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]
Fever convulsions	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]
Lymphadenopathy cervical	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Urinary tract infection	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	DTPw I + Hib	DTPw I/Hib	DTPw II /Hib
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Please refer to publication below.

Publications:

Kerdpanich A et al (2007) The Immunological Response of Thai Infants to Haemophilus influenzae Type B Polysaccharide-Tetanus Conjugate Vaccine Co-administered in the Same Syringe with Locally Produced Diphtheria-Tetanus-Pertussis Vaccine. J Med Assoc Thai 90 (7):1330-1336.

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