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Study No.: 104124 (Hib-095)		
Title: An open, randomised post-marketing clinical trial to assess the safety and reactogenicity of GlaxoSmithKline Biologicals' <i>Haemophilus influenzae</i> type b (Hib) tetanus conjugate vaccine (Hiberix™) co-administered with Chinese local DTPw vaccine when compared to Chinese local DTPw vaccine administered alone, in healthy infants at 3, 4 and 5 months of age		
Rationale: The aim of this study was to evaluate the safety of Hib vaccine when co-administered with DTPw vaccine to infants as compared to administration of DTPw vaccine alone when given as a primary vaccination course at 3, 4, 5 months of age. DTPw: Diphtheria, tetanus, whole cell pertussis; Hib: <i>Haemophilus influenzae</i> type b		
Phase: IV		
Study Period: 11 January 2005 to 28 July 2005		
Study Design: Open, randomised (1:1 ratio), single centre study with 2 groups.		
Centres: One study centre in China		
Indication: Primary immunisation of healthy infants at 3, 4 and 5 months of age against Hib, diphtheria, tetanus and pertussis diseases.		
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • DTPw + Hib Group: received DTPw vaccine and Hib vaccine co-administered at different injection sites at 3, 4 and 5 months of age. • DTPw Group: received only DTPw vaccine at 3, 4 and 5 months of age. All vaccines were administered by deep intramuscular injections, DTPw vaccine in the left anterolateral thigh and the Hib vaccine in the right anterolateral thigh.		
Objectives: To compare the safety of Hib vaccine co-administered with DTPw vaccine to that of DTPw vaccine alone, in terms of grade 3 (severe) solicited symptoms.		
Primary Outcome/Efficacy Variable: <ul style="list-style-type: none"> • Occurrence of grade 3 solicited symptoms during the 4-day follow-up period (Day 0 to Day 3) after vaccination. 		
Secondary Outcome/Efficacy Variable(s): <ul style="list-style-type: none"> • Occurrence of solicited symptoms during the 4-day follow-up period (Day 0 to Day 3) after vaccination. • Occurrence of unsolicited adverse events (AEs) during the 31-day follow-up period (Day 0 to Day 30) after vaccination. • Occurrence of serious adverse events (SAEs) during the study period. 		
Statistical Methods: The analyses were performed on the Total Vaccinated cohort. <ul style="list-style-type: none"> - The Total Vaccinated cohort included all subjects with at least one vaccine administration documented. Analysis of safety: The analysis of safety was performed on the Total Vaccinated cohort. For each solicited symptom, the percentage of subjects with the symptom reported during the 4-day (Day 0 to Day 3) follow-up period was summarised after each dose and across doses for each group with exact 95% Confidence Interval (CI). The percentage of subjects reporting unsolicited AEs within 31 days (Day 0 to Day 30) following administration of vaccine(s) was tabulated according to the Medical Dictionary for Adverse Events (MedDRA) preferred term for each group. The occurrence of serious adverse events was tabulated according to the MedDRA preferred term for each group during the entire study period.		
Study Population: Primary immunisation of healthy infants between 11 and 17 weeks of age (inclusive) at the time of first vaccination, free of obvious health problems as established by medical history and clinical examination before entering into the study and born after a gestation period of 36-42 weeks. Written informed consent was obtained from the parents/guardians of the subjects.		
Number of subjects	DTPw + Hib	DTPw
Planned, N	230	230
Randomised, N (Total Vaccinated cohort)	238	234
Completed, n (%)	226 (95.0)	228 (97.4)

Total Number Subjects Withdrawn, n (%)		12 (5.0)	6 (2.6)						
Withdrawn due to Adverse Events, n (%)		2 (0.8)	1 (0.4)						
Withdrawn due to Lack of Efficacy, n (%)		Not applicable	Not applicable						
Withdrawn for other reasons, n (%)		10 (4.2)	5 (2.1)						
Demographics		DTPw + Hib	DTPw						
N (Total Vaccinated Cohort)		238	234						
Females:Males		105:133	112:122						
Mean Age, months (SD)		3.0 (0.16)	3.0 (0.20)						
East/south east Asia, n (%)		238 (100)	233 (99.6)						
Primary Efficacy Results:									
Number and percentage of subjects reporting solicited local symptoms during the 4-day (Day 0-Day 3) follow-up period (Total Vaccinated cohort)									
Symptom	Intensity	DTPw + Hib				DTPw			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
		Dose 1				Dose 2			
		N = 232				N = 230			
Pain	Any	53	22.8	17.6	28.8	49	21.2	16.1	27.1
	Grade 3*	3	1.3	0.3	3.7	3	1.3	0.3	3.7
Redness	Any	66	28.4	22.7	34.7	61	26.4	20.8	32.6
	>20mm*	2	0.9	0.1	3.1	0	0.0	0.0	1.6
Swelling	Any	39	16.8	12.2	22.3	35	15.2	10.8	20.4
	>20mm*	4	1.7	0.5	4.4	2	0.9	0.1	3.1
		Dose 2				Dose 3			
		N = 226				N = 228			
Pain	Any	50	22.1	16.9	28.1	45	19.6	14.6	25.3
	Grade 3*	1	0.4	0.0	2.4	1	0.4	0.0	2.4
Redness	Any	66	29.2	23.4	35.6	53	23.0	17.8	29.0
	>20mm*	3	1.3	0.3	3.8	0	0.0	0.0	1.6
Swelling	Any	40	17.7	13.0	23.3	32	13.9	9.7	19.1
	>20mm*	5	2.2	0.7	5.1	0	0.0	0.0	1.6
		Dose 3				Across Doses			
		N = 226				N = 231			
Pain	Any	47	20.8	15.7	26.7	41	18.0	13.2	23.6
	Grade 3*	5	2.2	0.7	5.1	3	1.3	0.3	3.8
Redness	Any	55	24.3	18.9	30.5	54	23.7	18.3	29.7
	>20mm*	0	0.0	0.0	1.6	1	0.4	0.0	2.4
Swelling	Any	43	19.0	14.1	24.8	38	16.7	12.1	22.2
	>20mm*	5	2.2	0.7	5.1	3	1.3	0.3	3.8
		Across Doses				Across Doses			
		N = 232				N = 231			
Pain	Any	85	36.6	30.4	43.2	81	35.1	28.9	41.6
	Grade 3*	9	3.9	1.8	7.2	7	3.0	1.2	6.1
Redness	Any	107	46.1	39.6	52.8	89	38.5	32.2	45.1
	>20mm*	4	1.7	0.5	4.4	1	0.4	0.0	2.4
Swelling	Any	72	31.0	25.1	37.4	68	29.4	23.6	35.8
	>20mm*	10	4.3	2.1	7.8	5	2.2	0.7	5.0
N: number of subjects with a symptom sheet completed n (%): number (percentage) of subjects for whom a specific local 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 * Primary endpoint									
Primary Efficacy Results:									
Number and percentage of subjects reporting solicited general symptoms during the 4-day (Day 0-Day 3) follow-up period									

(Total Vaccinated cohort)									
Symptom	Intensity/ Relationship	DTPw + Hib				DTPw			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
		Dose 1							
		N = 232				N = 232			
Drowsiness	Any	39	16.8	12.2	22.3	40	17.2	12.6	22.7
	Grade 3*	1	0.4	0.0	2.4	6	2.6	1.0	5.5
	Related	19	8.2	5.0	12.5	20	8.6	5.3	13.0
Fever (Axillary)	≥37.5°C	18	7.8	4.7	12.0	16	6.9	4.0	11.0
	>39.5°C *	0	0.0	0.0	1.6	0	0.0	0.0	1.6
	Related	7	3.0	1.2	6.1	12	5.2	2.7	8.9
Irritability	Any	63	27.2	21.5	33.4	58	25.0	19.6	31.1
	Grade 3*	2	0.9	0.1	3.1	7	3.0	1.2	6.1
	Related	31	13.4	9.3	18.4	31	13.4	9.3	18.4
Loss of appetite	Any	31	13.4	9.3	18.4	37	15.9	11.5	21.3
	Grade 3*	0	0.0	0.0	1.6	1	0.4	0.0	2.4
	Related	17	7.3	4.3	11.5	22	9.5	6.0	14.0
		Dose 2							
		N = 227				N = 231			
Drowsiness	Any	33	14.5	10.2	19.8	31	13.4	9.3	18.5
	Grade 3*	5	2.2	0.7	5.1	3	1.3	0.3	3.7
	Related	21	9.3	5.8	13.8	19	8.2	5.0	12.5
Fever (Axillary)	≥37.5°C	27	11.9	8.0	16.8	21	9.1	5.7	13.6
	>39.5°C *	0	0.0	0.0	1.6	0	0.0	0.0	1.6
	Related	21	9.3	5.8	13.8	13	5.6	3.0	9.4
Irritability	Any	55	24.2	18.8	30.3	41	17.7	13.0	23.3
	Grade 3*	1	0.4	0.0	2.4	1	0.4	0.0	2.4
	Related	32	14.1	9.8	19.3	30	13.0	8.9	18.0
Loss of appetite	Any	27	11.9	8.0	16.8	31	13.4	9.3	18.5
	Grade 3*	0	0.0	0.0	1.6	1	0.4	0.0	2.4
	Related	20	8.8	5.5	13.3	21	9.1	5.7	13.6
		Dose 3							
		N = 226				N = 228			
Drowsiness	Any	35	15.5	11.0	20.9	32	14.0	9.8	19.2
	Grade 3*	1	0.4	0.0	2.4	1	0.4	0.0	2.4
	Related	18	8.0	4.8	12.3	22	9.6	6.1	14.2
Fever (Axillary)	≥37.5°C	43	19.0	14.1	24.8	30	13.2	9.1	18.2
	>39.5°C *	0	0.0	0.0	1.6	1	0.4	0.0	2.4
	Related	29	12.8	8.8	17.9	22	9.6	6.1	14.2
Irritability	Any	48	21.2	16.1	27.2	44	19.3	14.4	25.0
	Grade 3*	0	0.0	0.0	1.6	2	0.9	0.1	3.1
	Related	25	11.1	7.3	15.9	30	13.2	9.1	18.2
Loss of appetite	Any	39	17.3	12.6	22.8	31	13.6	9.4	18.7
	Grade 3*	0	0.0	0.0	1.6	0	0.0	0.0	1.6
	Related	23	10.2	6.6	14.9	19	8.3	5.1	12.7
		Across Doses							
		N = 232				N = 232			
Drowsiness	Any	73	31.5	25.5	37.9	72	31.0	25.1	37.4
	Grade 3*	7	3.0	1.2	6.1	10	4.3	2.1	7.8
	Related	42	18.1	13.4	23.7	45	19.4	14.5	25.1
Fever (Axillary)	≥37.5°C	76	32.8	26.8	39.2	60	25.9	20.4	32.0
	>39.5°C *	0	0.0	0.0	1.6	1	0.4	0.0	2.4
	Related	52	22.4	17.2	28.3	43	18.5	13.8	24.1
Irritability	Any	101	43.5	37.1	50.2	97	41.8	35.4	48.4

	Grade 3*	3	1.3	0.3	3.7	10	4.3	2.1	7.8
	Related	61	26.3	20.7	32.5	65	28.0	22.3	34.3
Loss of appetite	Any	63	27.2	21.5	33.4	72	31.0	25.1	37.4
	Grade 3*	0	0.0	0.0	1.6	2	0.9	0.1	3.1
	Related	47	20.3	15.3	26.0	47	20.3	15.3	26.0

N: number of subjects with at least one symptom sheet completed
n (%): number (percentage) of subjects for whom a specific general symptom was reported
Any: incidence of a particular symptom regardless of grade and relationship to vaccination
Grade 3 drowsiness: prevented normal everyday activities
Grade 3 irritability: crying that could not be comforted
Grade 3 loss of appetite: not eating at all
95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit
* Primary endpoint

Safety Results: Number (%) of subjects with Unsolicited AEs (Total Vaccinated cohort)

Most Frequent AEs - On-Therapy (occurring within Day 0-30 following vaccination)	DTPw + Hib N = 238	DTPw N = 234
Subjects with any AE(s), n(%)	49 (20.6)	45 (19.2)
Nasopharyngitis	16 (6.7)	19 (8.1)
Upper respiratory tract infection	16 (6.7)	13 (5.6)
Diarrhoea	8 (3.4)	9 (3.8)
Pyrexia	9 (3.8)	8 (3.4)
Cough	4 (1.7)	5 (2.1)
Dyspepsia	5 (2.1)	3 (1.3)
Tracheitis	4 (1.7)	4 (1.7)
Eczema	2 (0.8)	5 (2.1)
Rhinorrhoea	3 (1.3)	4 (1.7)
Vomiting	0 (0.0)	5 (2.1)
Dermatitis allergic	0 (0.0)	3 (1.3)
Bronchitis	2 (0.8)	0 (0.0)

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 + Hib N = 238	DTPw N = 234
Subjects with any SAE(s), n(%) [n related]	0 (0.0) [0]	0 (0.0) [0]
Fatal SAEs	DTPw + Hib N = 238	DTPw N = 234
Subjects with any fatal SAE(s), n(%) [n related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: A maximum of 4.3% of subjects in both groups reported at least one Grade 3 solicited symptom during the 4-day follow-up period. A total of 49 subjects in DTPw + Hib group and 45 subjects in DTPw group reported at least one unsolicited AE. No unsolicited AEs of grade 3 intensity were reported. There were no SAEs (fatal or non-fatal) reported in this study.

Publications: No Publication

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