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Study No.: 208108/084 (Hib-084)
Title: An open study to evaluate the immunogenicity and reactogenicity of SmithKline Beecham Biologicals' Haemophilus influenzae type b vaccine administered at 2, 4, 6 months to healthy infants over 2 months of age as a primary vaccination course
<i>Hiberix™:</i> GlaxoSmithKline (GSK) Biologicals' <i>Haemophilus influenzae</i> type b, tetanus toxoid conjugate vaccine (Hib).
Rationale: The purpose of the study was to evaluate the immunogenicity and safety of the Hib vaccine in healthy Korean children vaccinated at 2, 4 and 6 months of age as primary vaccination.
Phase: III
Study Period: 6 March 2001 to 2 April 2002.
Study Design: Open, single centre study.
Centers: 1 center in Korea.
Indication: Immunization against <i>Haemophilus influenzae</i> disease.
Treatment: There was one study group (Hib Group) which received 3 doses of the Hib vaccine administered intramuscularly in the anterolateral region in the right thigh.
Objectives: To evaluate the seroconversion rate and the geometric mean concentration (GMC) after primary vaccination, and to evaluate the reactogenicity of the vaccine after each administration.
<p>Primary Outcome/Efficacy Variable:</p> <p><i>Immunogenicity:</i></p> <ul style="list-style-type: none"> • Seroconversion rate* (SCR) after primary vaccination (after 3rd vaccination). <p>*Seroconversion rate is defined as percentage of subjects with anti-PRP antibody concentrations of at least 1.0 µg/mL, and the percentage of subjects with anti-PRP antibody concentrations of at least 0.15 µg/mL.</p> <p><i>Safety:</i></p> <ul style="list-style-type: none"> • Occurrence of solicited local symptoms 4 days (Day 0-3) after vaccination. • Occurrence of solicited general (systemic) symptoms 4 days (Day 0-3) after vaccination. • Occurrence unsolicited adverse event which occurred for 1 month after vaccination. • Occurrence of serious adverse events (SAEs) during the study period.
<p>Secondary Outcome/Efficacy Variable(s):</p> <p><i>Immunogenicity:</i></p> <ul style="list-style-type: none"> • SCR 2-month after 2nd vaccination. • Geometric mean concentration (GMC) 2-month after 2nd vaccination. • Geometric mean concentration (GMC) after primary vaccination (after 3rd vaccination).
<p>Statistical Methods:</p> <p>The analyses were performed on the Intent to Treat (ITT) and Per Protocol Analysis (PP) Cohorts.</p> <ul style="list-style-type: none"> - The ITT Cohort included the subjects who received at least one dose of the investigational vaccine. - The PP Cohort included the subjects conforming to the inclusion and exclusion criteria and who completed the study according to the study protocol. <p><i>Analysis for immunogenicity</i></p> <p>The analysis was performed on the PP Cohort.</p> <p><i>Descriptive analysis</i></p> <p>For each time point, the SCR and the GMCs for anti-PRP antibodies were calculated with 95% confidence interval (CI). Concentrations below the cut-ff (0.15 µg/mL) were given an arbitrary value of considered of half the cut-off value for the purpose of GMC calculation.</p> <p><i>Analysis for safety</i></p> <p>The analysis was performed on the ITT Cohort.</p> <p>The percentage of subjects reporting each individual solicited local and systematic symptom during 4 days (Day 0-3) solicited follow-up period after vaccination was calculated with 95% CI classified according to relationship to vaccination. The percentage of subjects reporting unsolicited adverse events (AE) classified by World Health Organization (WHO) preferred terms and reported during the entire study was tabulated. The occurrence of SAEs during the entire study</p>

period was tabulated according to WHO preferred terms.									
Study Population: Healthy male/female subjects between 8 to 12 weeks of age at the time of first vaccination, born after a normal pregnancy period who had not been vaccinated against <i>Haemophilus influenzae</i> type b before. Written informed consent was obtained from the subjects' parents or guardians.									
Number of Subjects:					Hib Group				
Planned, N					76				
Open, N (ITT Cohort)					73				
Completed, n (%)					66 (90.4)				
Total Number Subjects Withdrawn, n (%)					10 (13.70)				
Withdrawn due to Adverse Events n (%)					0 (0.0)				
Withdrawn due to Lack of Efficacy n (%)					Not Applicable				
Withdrawn for other reasons n (%)					10 (13.70)				
Demographics					Hib Group				
N (ITT)					73				
Females: Males					30:43				
Mean Age, Days (SD)					61.33 (3.92)				
Korean, n (%)					73 (100)				
Primary Efficacy Results: Seroconversion rate after primary vaccination (1.0 µg/mL cut-off) – PP Cohort.									
		Seroconversion		95%CI		Non-seroconversion		Total	
		n	%	LL	UL	n	%	n	%
All Subjects	Males	36	97.3	92.07	100	1	2.70	37	58.73
	Females	26	100	100	100	0	0.0	26	41.27
	Total	62	98.41	95.33	100	1	1.59	63	100
Subject with the baseline value below 1.0 µg/mL		58	98.31	95.01	100	1	1.69	59	100
Subject with the baseline value below 0.15 µg/mL		36	100	100	100	0	0.0	36	100
n(%)= number (percentage) of subjects with anti-PRP antibody concentrations ≥ 1.0 µg/mL. 95%CI = 95% Confidence Interval; LL = Lower limit, UL = Upper limit									
Primary Efficacy Results: SCR after primary vaccination (0.15 µg/mL cut-off) – PP Cohort.									
		Seroconversion		95%CI		Non-seroconversion		Total	
		n	%	LL	UL	n	%	n	%
Total		63	100	100	100	0	0.0	63	100
Subject with the baseline value below 1.0 µg/mL		59	100	100	100	0	0.0	59	100
Subject with the baseline value below 0.15 µg/mL		36	100	100	100	0	0.0	36	100
n(%)= number (percentage) of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL. 95%CI = 95% Confidence Interval; LL = Lower limit, UL = Upper limit									
Primary Efficacy Results: Occurrence of local and systemic symptoms 4 days (Day 0-3) after vaccination, by visit - PP Cohort									
Timing	Symptoms	Case Incidence		95%CI		Frequency			
		n	%	LL	UL	n	%		
1st Vaccination (n=73)	Local	17	23.29	13.59	32.98	27	36.99		
	Systemic	53	72.60	62.37	82.83	147	201.37		
	Total	54	73.97	63.91	84.04	174	238.36		
2nd Vaccination (n=72)	Local	11	15.28	6.97	23.59	19	26.39		
	Systemic	50	69.44	58.80	80.08	126	175.0		
	Total	52	72.22	61.88	82.57	145	201.39		
3rd Vaccination (n=68)	Local	13	19.12	9.77	28.46	19	27.94		
	Systemic	48	70.59	59.76	81.42	147	216.18		
	Total	49	72.06	61.39	82.72	166	244.12		
Total (n=73)	Local	26	35.62	24.63	46.60	65	89.04		
	Systemic	71	97.26	93.52	100	420	575.34		

	Total	71	97.26	93.52	100	485	664.38					
n(%)= number (percentage) of subjects. 95%CI = 95% Confidence Interval; LL = Lower limit, UL = Upper limit												
Secondary Outcome Variable(s): SCR after the 2 nd vaccination (prior to the 3 rd vaccination) (1.0 µg/mL cut-off) – PP Cohort												
Subjects		Seroconversion		95%CI		Non-seroconversion		Total				
		n	%	LL	UL	n	%	n	%			
All Subjects	Males	27	72.97	58.66	87.28	10	27.03	37	58.73			
	Females	22	84.62	70.75	98.48	4	15.38	26	41.27			
	Total	49	77.78	67.51	88.04	14	22.22	63	100			
Subject with the baseline value below 1.0 µg/mL		45	76.27	65.42	87.13	14	23.73	59	100			
Subject with the baseline value below 0.15 µg/mL		27	75.0	60.85	89.15	9	25.0	36	100			
n(%)= number (percentage) of subjects with anti-PRP antibody concentrations ≥ 1.0 µg/mL . 95%CI = 95% Confidence Interval; LL = Lower limit, UL = Upper limit												
Secondary Outcome Variable(s): Seroconversion rate after the 2 nd vaccination (0.15 µg/mL cut-off) – PP Cohort												
		Seroconversion		95%CI		Non-seroconversion		Total				
		n	%	LL	UL	n	%	n	%			
Total		62	98.41	95.33	100	1	1.59	63	100			
Subject with the baseline value below 1.0 µg/mL		58	98.31	95.01	100	1	1.69	59	100			
Subject with the baseline value below 0.1 µg/mL		35	97.22	91.85	100	1	2.78	36	100			
n(%)= number (percentage) of subjects with anti-PRP antibody concentrations ≥ 0.15 µg/mL within the specified range. 95%CI = 95% Confidence Interval; LL = Lower limit, UL = Upper limit												
Secondary Outcome Variable(s): Change in antibody concentration – PP												
Timing	Male				Female				Total			
	n	GMC (µg/mL)	95%CI		n	GMC (µg/mL)	95%CI		n	GMC (µg/mL)	95%CI	
			LL	UL			LL	UL			LL	UL
Baseline (2 months)	37	0.18	0.12	0.27	26	0.14	0.10	0.20	63	0.17	0.13	0.22
Prior to 3 rd vaccination (6 months)	37	2.91	1.62	5.21	26	6.87	3.44	13.72	63	4.14	2.65	6.48
After 3 rd vaccination (6 months)	37	11.90	7.85	18.05	26	19.68	12.72	30.43	63	14.65	10.83	19.81
n= number of subjects with available results. 95%CI = 95% Confidence Interval GMC = Geometric Mean Concentration; LL = Lower limit, UL = Upper limit												
Safety results: Number (%) of subjects with unsolicited adverse events (ITT Cohort)												
Most frequent adverse events - On-Therapy (occurring during the entire study period)						Hib Group N* =486						
Cases of resolved AE(s), n (%)						485 (99.79)						
Cases of non-resolved AE(s), n (%)						1 (0.21)						
*Total Number of cases N=number of cases												
Safety results: Number (%) of subjects with SAEs (ITT Cohort)												
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]												
All SAEs						Hib Group N=73						
Subjects with any SAE(s), n (%) [n related]						5 (6.8) [0]						
Urinary tract infection						2 (2.7) [0]						
Aseptic meningitis						1 (1.4) [0]						
Viral infection						1 (1.4) [0]						
Pneumonia						1 (1.4) [0]						

Bronchiolitis	1 (1.4) [0]
Fatal SAEs	Hib Group N=73
Subjects with fatal SAE(s), n (%) [n related]	0 (0) [0]

Conclusion:

Following primary vaccination (after 3rd vaccination), 98.31% of subjects with baseline anti-PRP antibody concentration < 1.0 µg /mL and 100% subjects with baseline anti-PRP antibody concentration < 0.15 µg/mL had anti-PRP antibody concentrations ≥ 1.0 µg/mL. All subjects had anti-PRP antibody concentrations ≥ 0.15 µg /mL. During the 4 days after vaccination, local symptoms were reported by 26 subjects and systemic symptoms were reported by 71 subjects. 486 unsolicited AEs were reported. All unsolicited AEs resolved except 1 case. At least one SAE was reported by 5 subjects. No fatal SAEs were reported. Please refer also to the publication below.

Publications: Eun Hee Chung et al. (2003) Immunogenicity and safety of a Haemophilus influenzae type b polysaccharide-tetanus toxoid conjugate vaccine in Korean infants. Korean J Pediatr Infect Dis. 10(3):71-80.

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