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<b>Study No.:</b> 371594/006
<b>Title:</b> A phase II, open, randomized study to assess the immune memory induced by a primary vaccination course of an investigational vaccination regimen and the immunogenicity and reactogenicity of a fourth dose of an investigational vaccination regimen, to healthy toddlers primed in study 371594/004.
<b>Rationale:</b> The aim of this study was to evaluate the immunological memory induced by primary vaccination course with an investigational vaccination regimen and to assess the safety and immune response induced by a booster dose of an investigational vaccination regimen. The control group (primed with 3 doses of Hiberix) received a booster dose of Hiberix at 12-18 months of age. Hiberix (Hib): GSK Biologicals' <i>Haemophilus influenzae</i> type b conjugate vaccine.
<b>Phase:</b> II
<b>Study Period:</b> 20 July 2000 to 21 March 2001
<b>Study Design:</b> Open, randomized (1:1:2 allocation), multi-centre study with 3 parallel groups. Data from the group receiving the currently registered vaccine are presented. Data from the investigational vaccination regimen, which is not yet approved or marketed, are not reported at this time.
<b>Centers:</b> 2 study centers in Myanmar.
<b>Indication:</b> Primary and booster vaccination of healthy infants against <i>Haemophilus influenzae</i> type b disease.
<b>Treatment:</b> The treatment groups were as follows: <ul style="list-style-type: none"> <li>• 2 groups received an investigational vaccination regimen.</li> <li>• Hib Group: subjects primed and boosted with Hib.</li> </ul> The Hib vaccine was administered intramuscularly into the left thigh.
<b>Objectives:</b> Not applicable to the licensed vaccine.
<b>Primary Outcome/Efficacy Variable:</b> Not applicable to the licensed vaccine.
<b>Secondary Outcome/Efficacy Variable(s):</b> <i>Only outcome variables related to the licensed vaccine are presented.</i>
<b>Safety</b> <ul style="list-style-type: none"> <li>• Occurrence of any late serious adverse events (SAEs) since one month after the administration of the last vaccine dose of the primary vaccination course prior to the administration of the booster dose.</li> <li>• Occurrence and intensity of solicited local symptoms registered within 8 days (Day 0-7) following vaccination.</li> <li>• Occurrence, intensity and relationship to vaccination of solicited general symptoms registered within 8 days (Day 0-7) following vaccination.</li> <li>• Nature, intensity and relationship to vaccination of unsolicited non-serious adverse events (AEs) within 31 days (Day 0-30) following vaccination.</li> <li>• Nature, intensity and relationship to vaccination of any SAEs occurring up to 1 month after the last vaccine dose.</li> <li>• Nature, intensity and relationship to vaccination of any late SAEs occurring from 1 month up to 6 months after the last vaccine dose.</li> </ul>
<b>Statistical Methods:</b> The analyses were performed on the ATP cohort for safety. Analyses of SAEs were performed on the Total Cohort. <ul style="list-style-type: none"> <li>• The Total Cohort included all subjects for whom safety data were available.</li> <li>• The ATP cohort for safety included all subjects who received the study vaccine, who had documented safety follow-up data, for whom administration site and route of study vaccination was known and who had not received a vaccine not specified or forbidden in the protocol.</li> </ul> <b>Analysis of safety</b> The analysis of safety was performed on the ATP cohort for safety and the analyses of SAEs were performed on the Total cohort. The percentage of subjects with solicited local symptoms (any and Grade 3) and general symptoms (any, Grade 3 and related) during the 8-day (Day 0-7) follow-up period after vaccination was tabulated with exact 95% CI. The occurrence, intensity and relationship to vaccination of unsolicited non-serious AEs within 31 days (Day 0-30) following vaccination was tabulated, according to the World Health organization (WHO) preferred terms. The occurrence of any late SAEs since one month after the administration of the last vaccine dose of the primary vaccination course prior to the administration of the booster dose, the occurrence of any SAEs up to 1 month after the last vaccine dose and the occurrence of any late SAEs from 1 month up to 6 months after the last vaccine dose were tabulated according to WHO preferred terms.

**Study Population:** Healthy toddlers, 12-18 months of age, free of obvious health problems as established by medical history and clinical examination before entering into the study, who had participated in study 371594/004. Written informed consent was obtained from the parents or guardians of the subject prior to study entry.

<b>Number of subjects</b>		<b>Hib Group</b>
Planned, N		67
Randomized, N (Total Cohort)		67
Completed, n (%)		66 (98.5)
Total Number Subjects Withdrawn, n (%)		1 (1.5)
Withdrawn due to Adverse Events, n (%)		0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)		Not applicable
Withdrawn for other reasons, n (%)		1 (1.5)
<b>Demographics</b>		<b>Hib Group</b>
N (Total Cohort)		67
Females:Males		33:34
Mean Age, months (SD)		13.9 (0.72)
Oriental, n (%)		67 (100)

**Primary Efficacy Results:**

Not applicable.

**Secondary Outcome Variable(s):**

Incidence of solicited local symptoms reported during the 8-day (Day 0-7) post-vaccination period (ATP cohort for safety)

Symptom	Intensity	Hib Group				
		N	n	%	95% CI	
					LL	UL
Pain	Any	65	13	20.0	11.1	31.8
	Grade 3	65	0	0.0	0.0	5.4
Redness	Any	65	4	6.2	1.7	15.0
	> 30 mm	65	0	0.0	0.0	5.5
Swelling	Any	65	8	12.3	5.5	22.8
	> 30 mm	65	0	0.0	0.0	5.5

N = number of subjects with a documented dose

n (%) = number (percentage) of subjects for whom the symptom was reported at least once

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

Any= incidence of a particular symptom regardless of grade

Grade 3 pain= cried when limb was moved / spontaneously painful

**Secondary Outcome Variable (s):**

Incidence of solicited general symptoms reported during the 8-day (Day 0-7) post-vaccination period (ATP cohort for safety)

Symptom	Intensity/ relationship	Hib Group				
		N	n	%	95 % CI	
					LL	UL
Drowsiness	Any	65	10	15.4	7.6	26.5
	Grade 3	65	0	0.0	0.0	5.5
	Related	65	6	9.2	3.5	19.0
Irritability	Any	65	5	7.7	2.5	17.0
	Grade 3	65	0	0.0	0.0	5.5
	Related	65	3	4.6	1.0	12.9
Loss of appetite	Any	65	2	3.1	0.4	10.7
	Grade 3	65	0	0.0	0.0	5.5
	Related	65	1	1.5	0.0	8.3
Fever (rectal)	≥ 38.0°C	65	16	24.6	14.8	36.9
	> 40.0°C	65	1	1.5	0.0	8.3
	Related	65	9	13.8	6.5	24.7

N = number of subjects with a documented dose

n (%) = number (percentage) of subjects for whom the symptom was reported at least once

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

Any = incidence of a particular symptom regardless of grade or relationship to study vaccination

Grade 3 drowsiness = drowsiness that prevented normal everyday activities	
Grade 3 irritability = crying that could not be comforted	
Grade 3 loss of appetite = not eating at all	
Related = symptom considered by the investigator to have a causal relationship to study vaccination	
<b>Safety Results:</b> Number (%) of subjects with unsolicited adverse events (AEs) (ATP Cohort for safety)	
<b>Most frequent adverse events - On-Therapy (occurring within Day 0-30 following vaccination)</b>	<b>Hib Group N = 65</b>
Subjects with any AE(s), n (%)	11 (16.9)
Subjects with related AE(s), n (%)	0 (0.0)
Subjects with severe AE(s), n (%)	0 (0.0)
Upper respiratory tract infection	4 (6.2)
Viral infection	4 (6.2)
Infection	2 (3.1)
Gastroenteritis	1 (1.5)
<b>Safety Results:</b> Number (%) of subjects with Serious Adverse Events (SAEs) one month after the administration of the last vaccine dose of the primary vaccination course and prior to the administration of the booster dose (Total Cohort)	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>Hib Group N = 67</b>
Subjects with any SAE(s), n (%) [n related]	1 (1.5) [0]
Febrile Convulsion	1 (1.5) [0]
<b>Fatal SAEs</b>	<b>Group 3 N = 67</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Safety Results:</b> Number (%) of subjects with Serious Adverse Events (SAEs) occurring up to 1 month after the last vaccine dose (Total Cohort)	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>Hib Group N = 67</b>
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Fatal SAEs</b>	<b>Hib Group N = 67</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Safety Results:</b> Number (%) of subjects with Serious Adverse Events (SAEs) occurring from 1 month up to 6 months after the last vaccine dose (Total Cohort)	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>Hib Group N = 67</b>
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]
<b>Fatal SAEs</b>	<b>Hib Group N = 67</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]

**Conclusion:** Pain and fever were the most frequently reported solicited local and general symptoms, respectively. At least one unsolicited AE was reported for 11 (16.9%) subjects in the Hib Group. One late SAE occurring between the end of the primary vaccination course and the booster vaccination was reported for 1 subject in the Hib Group. It was considered by the investigator not to be related to the study vaccination. No SAEs were reported from the booster dose up to 6 months after the booster vaccination. No fatal SAEs were reported during the whole course of the study.

**Publications:** No publications

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