

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

<b>Study No.:</b> 347414/023
<b>Title:</b> A phase II, single-blind, randomized, controlled study to evaluate the immunogenicity and safety of four different formulations of an investigational vaccination regimen when given intramuscularly as primary vaccination in infants at 3, 4 ½ and 6 months of age.
<b>Rationale:</b> The aim of this study was to evaluate the immunogenicity and safety of 4 different formulations of an investigational vaccination regimen. A control group received DTPa-IPV + Hib. DTPa-IPV: combined diphtheria, tetanus, acellular pertussis, and enhanced potency inactivated poliovirus vaccine; Hib: <i>Haemophilus influenzae</i> type b vaccine
<b>Phase:</b> II
<b>Study Period:</b> 06 February 2001 to 21 November 2001.
<b>Study Design:</b> Single-blind, randomized (1:1:1:1:1), controlled, multicenter clinical study with 5 parallel groups. Data from the group receiving currently registered vaccines are presented. Data from the investigational vaccination regimen, which is not yet approved or marketed, are not reported at this time.
<b>Centers:</b> Five study centers in Lithuania.
<b>Indication:</b> Primary immunization against diphtheria tetanus, pertussis, poliomyelitis and Hib diseases.
<b>Treatment:</b> Study groups were as follows: <ul style="list-style-type: none"> <li>• 4 groups received a different formulation of the investigational vaccination regimen.</li> <li>• 1 control group received DTPa-IPV + Hib. Hib and DTPa-IPV vaccines were administered intramuscularly into the right and left thigh, respectively.</li> </ul> Three doses of hepatitis B vaccine were given to all subjects at 0, 1 and 7 months of age, according to the national immunization schedule. The investigational vaccination regimen and DTPa-IPV + Hib. Hib and DTPa-IPV vaccines were administered at 3, 4,5 and 6 months of age.
<b>Objectives:</b> To evaluate the immune response induced by an investigational vaccination regimen.
<b>Primary Outcome/Efficacy Variable:</b> <i>Only outcome variables related to the licensed vaccines are presented</i> Not applicable.
<b>Secondary Outcome/Efficacy Variable(s):</b> <i>Only outcome variables related to the licensed vaccines are presented</i> <b>Immunogenicity</b> <i>In half of the subjects of each group, one month after Dose 3:</i> <ul style="list-style-type: none"> <li>• Seroprotection status, defined as anti-polio types 1, 2 and 3 antibody titers <math>\geq 8</math></li> <li>• Anti-polio types 1, 2 &amp; 3 antibody GMTs.</li> </ul> <i>In other half of the subjects of each group, one month after Dose 3:</i> <ul style="list-style-type: none"> <li>• Seroprotection status, defined as: <ul style="list-style-type: none"> <li>- Anti-diphtheria and anti-tetanus antibody concentrations <math>\geq 0.1</math> IU/mL.</li> <li>- Anti-polyribosyl ribitol phosphate (anti-PRP) antibody concentrations <math>\geq 0.15</math> <math>\mu</math>g/mL and <math>\geq 1.0</math> <math>\mu</math>g/mL.</li> </ul> </li> <li>• Seropositivity rate, defined as: <ul style="list-style-type: none"> <li>- Anti-pertussis toxoid (anti-PT), Anti-filamentous haemagglutinin (anti-FHA) and Anti-pertactin (anti-PRN) antibody concentrations <math>\geq 5</math> EL.U/mL.</li> </ul> </li> <li>• Antibody GMCs against all vaccine antigens</li> <li>• Vaccine response to PT, FHA, and PRN one month after Dose 3 defined as appearance of antibodies in subjects who were initially seronegative, and at least maintenance of pre-vaccination antibody concentrations in those who were initially seropositive.</li> </ul> <b>Safety</b> <ul style="list-style-type: none"> <li>• Occurrence and intensity of each solicited local and general symptom within 8 days (Day 0-7) after each vaccination.</li> <li>• Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0-30) after each vaccination.</li> <li>• Occurrence of serious adverse events (SAEs) occurring during the whole study.</li> </ul>
<b>Statistical Methods:</b> The analyses were performed on the Total Vaccinated Cohort. The Total Vaccinated Cohort included all subjects who received at least one dose of the vaccine.

**Analysis of immunogenicity:**

The analyses of immunogenicity were performed on all subjects of the Total Vaccinated Cohort for whom immunogenicity data were available. Geometric Mean concentrations (GMCs) or Geometric Mean titers (GMTs) and seropositivity/seroprotection rate for antibodies against all vaccine antigens were calculated before Dose 1 and one month after Dose 3 with 95% confidence intervals (CI). Vaccine response to PT, FHA and PRN were calculated one month after Dose 3 with exact 95% CI.

**Analysis of safety:**

The analyses of safety were performed on all subjects of the Total Vaccinated Cohort for whom safety data were available. For each solicited local and general symptom, the percentage of subjects with the symptom reported during the 8-day (Day 0-7) follow-up period was summarized with exact 95% CI by dose and across doses. The percentage of subjects reporting unsolicited AEs within 31 days (Day 0-30) following vaccination was tabulated according to the WHO preferred term. The occurrence of the SAEs occurring up to 31 days after the administration of the last vaccine dose was tabulated according to the World Health Organization (WHO) preferred term.

**Study Population:** Male or female infants between, and including, 11 and 17 weeks of age at the time of the first vaccination, born after a gestation period between 36 and 42 weeks and having received 2 doses of hepatitis B vaccine (at birth and 1 month of age). Subjects were free of obvious health problems as established by medical history and clinical examination before entering into the study. Written informed consent was obtained from the parent(s) or guardian(s) of the subject prior to study entry.

Number of subjects	Control
Planned, N	80
Randomized, N (Total Vaccinated Cohort)	80
Total Number Subjects Withdrawn, n (%)	4 (5.0)
Withdrawn due to Adverse Events, n (%)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable
Withdrawn for other reasons, n (%)	4 (5.0)
Demographics	Control
N (Total Vaccinated Cohort)	80
Females:Males	43:37
Mean Age, weeks (SD)	13.4 (1.11)
White/Caucasian, n (%)	80 (100)

**Primary Efficacy Results:** Not Applicable.

**Secondary Outcome Variable(s):** Seroprotection rate and GMCs for anti-diphtheria and anti-tetanus antibodies (Total Vaccinated Cohort).

Antibody	Timing	N	≥ 0.1 IU/mL				GMC (IU/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
Anti-diphtheria	PRE	39	19	48.7	32.4	65.2	0.104	0.079	0.137
	PIII(M4)	35	35	100	90.0	100	1.443	1.078	1.933
Anti-tetanus	PRE	39	26	66.7	49.8	80.9	0.177	0.127	0.245
	PIII(M4)	36	36	100	90.3	100	1.929	1.446	2.572

N: number of subjects with available results

n (%): number (percentage) of subjects with specified antibody concentrations

95%CI: 95% confidence interval; LL: lower limit; UL: upper limit

PRE: pre-vaccination

PIII(M4): 1 month after Dose 3

**Secondary Outcome Variable(s):** Seropositivity rate and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (Total Vaccinated Cohort).

Antibody	Timing	N	≥ 5 EL.U/mL				GMC (EL.U/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
Anti-PT	PRE	36	13	36.1	20.8	53.8	3.9	3.1	4.9
	PIII(M4)	35	35	100	90.0	100	72.2	61.1	85.3
Anti-FHA	PRE	38	26	68.4	51.3	82.5	8.9	6.2	12.8
	PIII(M4)	34	34	100	89.7	100	238.5	185.4	307.0
Anti-PRN	PRE	39	11	28.2	15.0	44.9	4.3	3.0	6.0
	PIII(M4)	35	35	100	90.0	100	178.1	132.4	239.7

N: number of subjects with available results  
n (%): number (percentage) of subjects with specified antibody concentrations  
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit  
PRE: pre-vaccination  
PIII(M4): 1 month after Dose 3

**Secondary Outcome Variable(s):** Vaccine response to PT, FHA and PRN one month after Dose 3 (Total Vaccinated Cohort).

Antibody	Pre-vaccination status	Number of subjects*	Responders			
			n	%	95% CI	
					LL	UL
Anti-PT	S+	11	11	100	-	-
	S-	20	20	100	-	-
	Total	31	31	100	88.8	100
Anti-FHA	S+	21	21	100	-	-
	S-	12	12	100	-	-
	Total	33	33	100	89.4	100
Anti-PRN	S+	9	7	77.8	-	-
	S-	25	25	100	-	-
	Total	34	32	94.1	80.3	99.3

\* number of subjects with both pre-and post-vaccination results available  
n (%): number (percentage) of responders. Vaccine response was defined as appearance of antibodies in subjects who were initially seronegative, and at least maintenance of pre-vaccination antibody concentrations in those who were initially seropositive  
S/S+: seronegative/ seropositive subjects at pre-vaccination  
Total: subjects either seropositive or seronegative at pre-vaccination  
95%CI: exact 95% confidence interval; LL: lower limit; UL: upper limit

**Secondary Outcome Variable(s):** Seroprotection rate and GMTs for anti-poliovirus types 1, 2 and 3 antibodies (Total Vaccinated Cohort).

Antibody	Timing	N	≥ 8				GMT			
			n	%	95% CI		Value	95% CI		
					LL	UL		LL	UL	
Anti-poliovirus type 1	PRE	35	22	62.9	44.9	78.5	14.2	9.2	22.0	
	PIII(M4)	27	27	100	87.2	100	258.9	148.1	452.6	
Anti-poliovirus type 2	PRE	36	16	44.4	27.9	61.9	8.5	6.2	11.7	
	PIII(M4)	27	26	96.3	81.0	99.9	208.2	120.8	358.8	
Anti-poliovirus type 3	PRE	36	3	8.3	1.8	22.5	4.5	3.9	5.2	
	PIII(M4)	21	21	100	83.9	100	565.4	350.6	912.0	

N: number of subjects with available results  
n (%): number (percentage) of subjects with specified antibody titers  
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit  
PRE: pre-vaccination  
PIII(M4): 1 month after Dose 3

**Secondary Outcome Variable(s):** Seroprotection rate and GMCs for anti-PRP antibodies (Total Vaccinated Cohort).

Timing	N	≥ 0.15 µg/mL				≥ 1.0 µg/mL				GMC (µg/mL)		
		n	%	95% CI		n	%	95% CI		Value	95% CI	
				LL	UL			LL	UL		LL	UL
PRE	40	15	37.5	22.7	54.2	1	2.5	0.1	13.2	0.143	0.106	0.193
PIII(M4)	36	35	97.2	85.5	99.9	33	91.7	77.5	98.2	8.922	5.388	14.775

N: number of subjects with available results  
n (%): number (percentage) of subjects with specified antibody concentrations  
95%CI: 95% confidence interval; LL: lower limit; UL: upper limit  
PRE: pre-vaccination  
PIII(M4): 1 month after Dose 3

**Secondary Outcome Variable(s):** Percentage of subjects with solicited local symptoms within the 8-day (Day 0-7) follow-up period (Total Vaccinated Cohort).

Symptom	Intensity	n	%	95% CI	n	%	95% CI
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				LL	UL			LL	UL
		Dose 1 (N = 78)				Dose 2 (N = 78)			
Pain	Any	10	12.8	6.3	22.3	17	21.8	13.2	32.6
	Grade 3	1	1.3	0.0	6.9	2	2.6	0.3	9.0
Redness	Any	29	37.2	26.5	48.9	35	44.9	33.6	56.6
	> 30 mm	2	2.6	0.3	9.0	0	0.0	0.0	4.6
Swelling	Any	16	20.5	12.2	31.2	15	19.2	11.2	29.7
	> 30 mm	1	1.3	0.0	6.9	0	0.0	0.0	4.6
		Dose 3 (N = 78)				Across Doses (N = 78)			
Pain	Any	7	9.0	3.7	17.6	21	26.9	17.5	38.2
	Grade 3	1	1.3	0.0	6.9	4	5.1	1.4	12.6
Redness	Any	34	43.6	32.4	55.3	47	60.3	48.5	71.2
	> 30 mm	2	2.6	0.3	9.0	4	5.1	1.4	12.6
Swelling	Any	16	20.5	12.2	31.2	30	38.5	27.7	50.2
	> 30 mm	1	1.3	0.0	6.9	2	2.6	0.3	9.0

N: number of subjects with a symptom sheet completed

n (%): number (percentage) of subjects for whom a specific symptom was reported at least once

Any: incidence of a particular symptom regardless of intensity grade

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

95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit

**Secondary Outcome Variable(s):** Percentage of subjects reporting solicited general symptoms within the 8-day (Day 0-7) follow-up period (Total Vaccinated Cohort).

Symptom	Intensity/ Relationship	n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
		Dose 1 (N = 78)				Dose 2 (N = 78)			
Drowsiness	Any	38	48.7	37.2	60.3	29	37.2	26.5	48.9
	Grade 3	5	6.4	2.1	14.3	2	2.6	0.3	9.0
	Related	36	46.2	34.8	57.8	28	35.9	25.3	47.6
Irritability	Any	48	61.5	49.8	72.3	37	47.4	36.0	59.1
	Grade 3	7	9.0	3.7	17.6	8	10.3	4.5	19.2
	Related	45	57.7	46.0	68.8	36	46.2	34.8	57.8
Loss of Appetite	Any	22	28.2	18.6	39.5	17	21.8	13.2	32.6
	Grade 3	2	2.6	0.3	9.0	0	0.0	0.0	4.6
	Related	20	25.6	16.4	36.8	17	21.8	13.2	32.6
Fever (rectal)	≥ 38°C	6	7.7	2.9	16.0	13	16.7	9.2	26.8
	> 40°C	0	0.0	0.0	4.6	0	0.0	0.0	4.6
	Related	5	6.4	2.1	14.3	12	15.4	8.2	25.3
		Dose 3 (N = 78)				Across Doses (N = 78)			
Drowsiness	Any	18	23.1	14.3	34.0	49	62.8	51.1	73.5
	Grade 3	3	3.8	0.8	10.8	10	12.8	6.3	22.3
	Related	17	21.8	13.2	32.6	48	61.5	49.8	72.3
Irritability	Any	33	42.3	31.2	54.0	62	79.5	68.8	87.8
	Grade 3	2	2.6	0.3	9.0	16	20.5	12.2	31.2
	Related	32	41.0	30.0	52.7	62	79.5	68.8	87.8
Loss of Appetite	Any	12	15.4	8.2	25.3	37	47.4	36.0	59.1
	Grade 3	1	1.3	0.0	6.9	3	3.8	0.8	10.8
	Related	11	14.1	7.3	23.8	35	44.9	33.6	56.6
Fever (rectal)	≥ 38°C	9	11.5	5.4	20.8	24	30.8	20.8	42.2
	> 40°C	0	0.0	0.0	4.6	0	0.0	0.0	4.6
	Related	9	11.5	5.4	20.8	23	29.5	19.7	40.9

N: number of subjects with a symptom sheet completed

n (%): number (percentage) of subjects reporting a specific symptom

Any: incidence of a particular symptom regardless of grade and relationship to vaccination

Related: symptoms considered by the investigator to have a causal relationship to study vaccination

Grade 3 drowsiness: drowsiness which prevented normal everyday activities

Grade 3 irritability: crying that could not be comforted/prevented normal everyday activities	
Grade 3 loss of appetite: not eating at all	
95% CI: exact 95% confidence interval; LL: lower limit, UL: upper limit	
<b>Safety Results:</b> Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort).	
<b>Most frequent adverse events - On-Therapy (occurring within Day 0-30 following vaccination)</b>	<b>Control N = 79*</b>
Subjects with any AE(s), n (%)	50 (63.3)
Pharyngitis	27 (34.2)
Dermatitis	11 (13.9)
Rhinitis	8 (10.1)
Vitamin D deficiency	7 (8.9)
Injection site reaction	6 (7.6)
Upper respiratory tract infection	6 (7.6)
Otitis media	5 (6.3)
Stomatitis	4 (5.1)
Anemia	3 (3.8)
Diarrhea	3 (3.8)
Dyspepsia	3 (3.8)
Dystonia	3 (3.8)
Laryngitis	3 (3.8)
Pneumonia	3 (3.8)
* One subject was lost to follow-up without any safety information reported	
<b>Safety results:</b> Number (%) of subjects with serious adverse events (Total Vaccinated Cohort).	
<b>Serious adverse event, n (%) [n considered by the investigator to be related to study medication]</b>	
<b>All SAEs</b>	<b>Control N = 79*</b>
Subjects with any SAE(s), n (%) [n related]	8 (10.1) [0]
Pneumonia	3 (3.8) [0]
Dyspepsia	1 (1.3) [0]
Gastritis	1 (1.3) [0]
Gastroenteritis	1 (1.3) [0]
Infection bacterial	1 (1.3) [0]
Infection viral	1 (1.3) [0]
Otitis media	1 (1.3) [0]
Upper respiratory tract infection	1 (1.3) [0]
* One subject was lost to follow-up without any safety information reported	
<b>Fatal SAEs</b>	<b>Control N = 79*</b>
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]
* One subject was lost to follow-up without any safety information reported	

**Conclusion:** One month after Dose 3, at least 96.3% of the subjects had antibody levels against poliovirus types 1, 2 and 3  $\geq$  the cut-off value. At the same time point, all subjects had anti-diphtheria, anti-tetanus, anti-PT, anti-FHA and anti-PRN antibody concentrations were  $\geq$  cut-off value. One month after Dose 3, 97.2% of the subjects had anti-PRP antibody concentrations  $\geq$  0.15  $\mu$ g/mL. The most frequently reported solicited local symptom across doses was redness (60.3%). Irritability was the most frequently reported solicited general symptom across doses (79.5%). At least one unsolicited AE was reported for 63.3% of the subjects. Eight SAEs were reported during the study period. None of the SAEs were considered by the investigator to be related to the study vaccination. No fatal SAEs were reported during the entire course of this study.

**Publications:** No Publication

Date updated: 19-Apr-2007