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Study No.: 213503/044 (DTPa-IPV-044)
Title: Open study to assess the immunogenicity after two and three doses of GlaxoSmithKline (GSK) Biologicals' Hib vaccine combined with GSK Biologicals' DTPa-IPV vaccine given to Swedish infants in a 3, 5, 12 month schedule. DTPa-IPV/Hib: GSK Biologicals' combined diphtheria, tetanus, acellular pertussis, enhanced potency inactivated polio and <i>Haemophilus influenzae</i> type b vaccine
Rationale: The aim of this study was to collect data on antibody response in Swedish children, in the Swedish 3-5-12 months schedule, after 2 and 3 doses of DTPa-IPV/Hib vaccine.
Phase: IV
Study Period: 23 March 2001 to 12 March 2002
Study Design: Open, multicenter study in Sweden, with one study group.
Centres: 2 study centres in Sweden
Indication: Immunisation against diphtheria, tetanus, pertussis, polio and <i>Haemophilus influenzae</i> type b diseases of healthy children.
Treatment: There was no vaccination given in this study. Subjects receiving a primary vaccination course of GSK Biologicals' DTPa-IPV/Hib vaccine were enrolled after receiving either the second or the third dose.
Objectives: To measure the immune response against Hib, poliovirus types 1, 2 and 3 and diphtheria, one month after the third of three doses of DTPa-IPV/Hib vaccine given according to the Swedish 3, 5, 12 month schedule.
Primary Outcome/Efficacy Variable: One month after the second and third dose of DTPa-IPV/Hib: <ul style="list-style-type: none"> • Anti polyribosyl-ribitol-phosphate (PRP) antibody concentrations as measured by ELISA. Seroprotection status defined as anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$.
Secondary Outcome/Efficacy Variable(s): <ul style="list-style-type: none"> • One month after the second and third dose of DTPa-IPV/Hib: <ul style="list-style-type: none"> - Anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$, - Anti-poliovirus types 1, 2 and 3 antibody titres ≥ 8 (neutralization assay), - Anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/mL}$ and 0.016 IU/mL (ELISA and Vero cell assay, respectively). • Occurrence of serious adverse events (SAEs) throughout the entire study, up to and including 30 days post-dose 3.
Statistical Methods: The analyses were performed on the Total Vaccinated cohort and the According-To-Protocol (ATP) cohort for immunogenicity. <ul style="list-style-type: none"> - The Total Vaccinated cohort included all subjects enrolled in the study who received at least the second 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. <p><i>Analysis of immunogenicity:</i> The analysis of immunogenicity was performed on the ATP cohort for immunogenicity. Geometric Mean titres (GMTs)/Geometric Mean concentrations (GMCs) and Seroprotection/Seropositivity rates for all antibodies were computed one month after the second and the third vaccine dose with 95% confidence interval (CI). Subjects who were enrolled after receiving Dose 2 and for whom immunogenicity results were also available after the third vaccine dose were included in the Post Dose 3 analyses as well.</p> <p><i>Analysis of safety:</i> The analysis of safety was performed on the Total Vaccinated cohort. The percentage of subjects with unsolicited adverse events (AEs) within 31 days (Day 0-30) following vaccine dose was tabulated according to the World Health Organization (WHO) preferred term. The occurrence of SAEs was tabulated throughout the entire study period according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.</p>
Study Population: Male or female children, with written documentation of having received 2 or 3 doses of GSK Biologicals' DTPa-IPV/Hib vaccine in the regular Swedish paediatric vaccination program. Subjects were free of obvious serious health problems. Written informed consent obtained from the parents or guardians of the subject before study entry.

Number of Subjects:										DTPa-IPV/Hib Group		
Planned, N										220		
Entered, N (Total Vaccinated cohort)										221		
Completed, n (%)										215 (97.3)		
Total Number Subjects Withdrawn, n (%)										6 (2.7)		
Withdrawn due to Adverse Events, n (%)										1 (0.4)		
Withdrawn due to Lack of Efficacy, n (%)										Not Applicable		
Withdrawn for other reasons, n (%)										5 (2.3)		
Demographics**										DTPa-IPV/Hib Group		
N (Completed)										215		
Females: Males										101:114		
Mean Age, month (SD)*										13.3 (0.60)		
White, n (%)										207 (96.7)		
* Age calculated at post Dose 3												
** For demographics results, only results on the "Completed" population are available												
Primary Efficacy Results:												
Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity)												
Timing	N	≥ 0.15 µg/mL*				≥ 1 µg/mL				GMC (µg/mL)		
		n	%	95% CI		n	%	95% CI		Value	95% CI	
				LL	UL			LL	UL		LL	UL
P1I(M0)	86	72	83.7	74.2	90.8	44	51.2	40.1	62.1	1.081	0.725	1.612
P1I1(M7)	184	184	100	98.0	100	178	96.7	93.0	98.8	23.172	19.066	28.162
N = Number of subjects with available results												
n (%) = Number (percentage) of subjects with antibody titres ≥ 0.15 µg/mL												
P1I(M0) = one month after the second dose												
P1I1(M7) = one month after the third dose												
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit												
* Primary outcome variable												
Secondary Outcome Variable(s):												
Seroprotection rates and GMTs for anti-poliovirus types 1, 2 and 3 antibodies (ATP cohort for immunogenicity)												
Antibody	Timing	N	≥ 8				GMT					
			n	%	95% CI		Value	95% CI				
					LL	UL		LL	UL			
Anti-poliovirus type 1	P1I(M0)	86	80	93.0	85.4	97.4	106.2	75.5	149.4			
	P1I1(M7)	180	179	99.4	96.9	100	816.8	679.0	982.6			
Anti-poliovirus type 2	P1I(M0)	85	81	95.3	88.4	98.7	125.8	87.8	180.1			
	P1I1(M7)	182	182	100	98.0	100	1042.9	884.7	1229.4			
Anti-poliovirus type 3	P1I(M0)	82	81	98.8	93.4	100	160.0	112.9	226.7			
	P1I1(M7)	180	179	99.4	96.9	100	1109.2	916.9	1341.7			
N = Number of subjects with available results												
n (%) = Number (percentage) of subjects with antibody titres ≥ 8												
P1I(M0) = one month after the second dose												
P1I1(M7) = one month after the third dose												
95% CI = 95% confidence interval; LL = lower limit; UL = upper limit												
Secondary Outcome Variable(s):												
Seroprotection rates and GMCs for anti-diphtheria antibodies by ELISA (ATP cohort for immunogenicity)												
Timing	N	≥ 0.1 IU/mL				GMC (IU/mL)						
		n	%	95% CI		Value	95% CI					
				LL	UL		LL	UL				
P1I(M0)	85	80	94.1	86.8	98.1	0.622	0.480	0.806				
P1I1(M7)	184	184	100	98.0	100	2.732	2.401	3.109				
N = Number of subjects with available results												
n (%) = Number (percentage) of subjects with antibody concentrations ≥ 0.1 IU/mL												
P1I(M0) = one month after the second dose												
P1I1(M7) = one month after the third dose												

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

Secondary Outcome Variable (s):

Seroprotection rates and GMCs for anti-diphtheria antibodies by Vero cell assay (ATP cohort for immunogenicity)

Timing	N	≥ 0.016 IU/mL				GMC (IU/mL)		
		n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
P1I(M0)	86	85	98.8	93.7	100	0.174	0.132	0.230
P1I1(M7)	184	184	100	98.0	100	1.525	1.319	1.763

N = Number of subjects with available results

n (%) = Number (percentage) of subjects with antibody concentrations ≥ 0.016 IU/mL

P1I(M0) = one month after the second dose

P1I1(M7) = one month after the third dose

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

Safety Results: Number (%) of subjects with unsolicited adverse events (AEs) (Total Vaccinated cohort)

**Most Frequent Adverse Events - On-Therapy-
(occurring within Day 0-30 following vaccination)**

**DTPa-IPV/Hib Group
N = 221**

Subjects with any AE(s), n (%)	10 (4.5)
Otitis media	5 (2.3)
Fever	2 (0.9)
Convulsions	1 (0.5)
Coughing	1 (0.5)
Gastroenteritis	1 (0.5)
Upper respiratory tract infection	1 (0.5)

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) (Total Vaccinated cohort)

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]

All SAEs

**DTPa-IPV/Hib Group
N = 221**

Subjects with any SAE(s), n (%) [related]	4 (1.8) [1]
Bronchitis chronic	1 (0.4) [0]
Convulsion	1 (0.4) [1]
Gastroenteritis	2 (0.9) [0]
Otitis media	1 (0.4) [0]

Fatal SAEs

**G DTPa-IPV/Hib Group
N = 221**

Subjects with fatal SAEs, n (%) [related]	0 (0.0) [0]
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Conclusion: One month after the second dose, 83.7% of the subjects had anti-PRP antibody concentrations ≥ 0.15 µg/mL. At the same time point, 93.0%, 95.3% and 98.8% of the subjects had antibody titres ≥ 8 against poliovirus types 1, 2, and 3, respectively and 98.8% of the subjects had anti-diphtheria antibody concentrations ≥ 0.016 IU/mL y Vero cell neutralisation test. One month after the third dose, all subjects had antibody concentrations ≥ assay cut-off values against PRP, diphtheria and poliovirus type 2. At the same time point, 99.4% of the subjects had antibody titres ≥ 8 against poliovirus types 1 and 3. At least one AE was reported for 10 subjects (4.5%). SAEs were reported in 4 subjects. One of these SAEs was considered by the investigator to be related to the study vaccination. No fatal SAEs were reported during the course of the study.

Publications: No publication

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