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Study No.: 213503/049 (DTPa-IPV-049)
Title: An open, multicentre, phase IV booster vaccination study to assess the immunogenicity and reactogenicity of GSK Biologicals' combined Infanrix TM IPV+Hib (DTPa-IPV/Hib) vaccine in healthy children aged 17 to 20 months who completed a three-dose primary vaccination course. DTPa-HBV-IPV/Hib: Diphtheria, tetanus, acellular pertussis, hepatitis B recombinant, inactivated poliomyelitis and <i>Haemophilus influenzae</i> type b vaccine. DTPa-IPV/Hib: Diphtheria, tetanus, acellular pertussis, inactivated poliovirus and <i>Haemophilus influenzae</i> type b vaccine.
Rationale: The study provided data on the persistence of antibodies in children fully vaccinated with a meningococcal C (MenC) conjugate vaccine and DTPa-HBV-IPV/Hib vaccine and on the response of these children to a booster dose of DTPa-IPV/Hib vaccine in the second year of life. The safety of the booster vaccination was also assessed.
Phase: IV
Study Period: 08 November 2002 to 09 June 2003
Study Design: Open, multicentre, single group booster study
Centres: Seventeen centres in Spain.
Indication: Immunization against diphtheria, tetanus, acellular pertussis, hepatitis B, poliomyelitis and <i>Haemophilus influenzae</i> type b diseases of healthy children.
Treatment: The study groups in the primary study were as follows: <ul style="list-style-type: none"> • Co-administration group: primed with DTPa-HBV-IPV/Hib vaccine and a MenC conjugate vaccine as concomitant injections at 2, 4 and 6 months of age. • Separate administration group: primed with DTPa-HBV-IPV/Hib vaccine at 2, 4 and 6 months of age and a MenC conjugate vaccine at 3, 5 and 7 months of age. In the present study, all subjects received a single booster dose of DTPa-IPV/Hib vaccine at 17 to 20 months of age.
Objectives: <ul style="list-style-type: none"> • To evaluate non-inferiority in terms of antibody response to polyribosyl-ribitol-phosphate (PRP) vaccine antigen of DTPa-IPV/Hib vaccine administered as a booster in children primed with DTPa-HBV-IPV/Hib vaccine, co-administered with a MenC conjugate vaccine at the same visit, as compared to children primed with the same vaccines administered at different visits.
Primary Outcome/Efficacy Variable: Anti-PRP antibody concentrations $\geq 1 \mu\text{g/mL}$ one month after the administration of the booster dose of DTPa-IPV/Hib.
Secondary Outcome/Efficacy Variable(s): <i>Antibody persistence before the booster dose:</i> <ul style="list-style-type: none"> • Seroprotection against MenC defined as serum bactericidal activity against <i>Neisseria meningitidis</i> serogroup C (SBA-MenC) titer $\geq 1:8$ • Seroprotection against hepatitis B surface antigen (HBsAg) defined as anti-HBs antibody concentrations $\geq 10 \text{ mIU/mL}$ • Anti-polysaccharide C (PSC) antibody concentration, SBA-MenC antibody titer • Anti-PSC antibody concentration $\geq 0.3 \mu\text{g/mL}$ • Anti-HBs antibody concentrations <i>Antibody persistence before the booster dose and immunogenicity one month after the booster dose:</i> <ul style="list-style-type: none"> • Seroprotection status defined as: <ul style="list-style-type: none"> – Anti-PRP antibody concentration $\geq 0.15 \mu\text{g/mL}$

- Anti-PRP antibody concentration $\geq 1 \mu\text{g/mL}$
- Anti-diphtheria toxoid antibody concentrations $\geq 0.1 \text{ IU/mL}$
- Anti-tetanus toxoid antibody concentrations $\geq 0.1 \text{ IU/mL}$
- Anti-polio type 1, 2 and 3 antibody titres ≥ 8
- Anti-*Pertussis* toxoid (PT), filamentous hem agglutinin (FHA) and pertactin (PRN) antibody concentrations $\geq 5 \text{ EL.U/mL}$

Immunogenicity after immunization:

- Vaccine response to PT, FHA and PRN, defined as appearance of antibodies in subjects who were initially seronegative (i.e. with concentrations $< 5 \text{ EL.U/mL}$) or at least two-fold increase of pre-vaccination antibody titers after the booster dose in subjects who were initially seropositive (i.e. with concentrations $\geq 5 \text{ EL.U/mL}$).

Safety:

- Occurrence of solicited local and general symptoms within 4 days (Day 0-3) after the booster dose of DTPa-IPV/Hib vaccine.
- Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0-30) after the booster dose of DTPa-IPV/Hib vaccine.
- Occurrence of serious adverse events (SAEs) throughout the entire study up to and including 31 days (Day 0-30) after the booster dose of DTPa-IPV/Hib vaccine.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort, the According-To-Protocol (ATP) cohort for antibody persistence and the ATP cohort for immunogenicity.

- The Total Vaccinated cohort included all subjects who received the booster vaccine dose.
- The ATP cohort for antibody persistence included all subjects who received the primary vaccination course and for whom immunogenicity data were available at pre-booster vaccination.
- 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.

Analysis of immunogenicity:

The analysis of antibody persistence was performed on the ATP cohort for antibody persistence.

The analysis of immune response to the booster was performed on the ATP cohort for immunogenicity.

Geometric Mean Concentrations (GMCs) or Geometric Mean Titre (GMTs) and seroprotection or seropositivity rates for antibodies against all vaccine antigens were summarized before and after the booster vaccine dose with 95% Confidence Interval (CI).

Vaccine response to PT, FHA and PRN was calculated one month after the administration of the booster vaccine dose with exact 95% CI.

Evaluation of the comparability between the 2 groups after booster vaccination was exploratory. The asymptotic standardized 95% CIs on the difference in seroprotection rates for anti-PRP (rate in the Separate administration group minus rate in the Co-administration group) one month after booster administration was computed.

Analysis of safety:

The analysis of safety was performed on the Total Vaccinated cohort.

The percentage of subjects with solicited local and general symptoms reported during the 4-day (Day 0-3) follow-up period was summarized after the booster vaccination for each group with exact 95% CI.

The percentage of subjects with unsolicited AEs reported within 31 days (Day 0-30) following the booster vaccination was tabulated according to the World Health Organization (WHO) preferred term for each group.

The occurrence of SAEs was tabulated according to the WHO preferred term for each group during the entire study period.

Study Population: Male or female infants between, and including, 17 to 20 months of age at the

time of the booster vaccination, free of obvious health problems as established by medical history and clinical examination before entering into the study. All subjects completed the three-dose primary vaccination course. Written informed consent was obtained from the parent/ guardian of the subject prior to study entry.

Number of subjects		Co-administration	Separate administration										
Planned, N		458											
Entered, N (Total Vaccinated Cohort)		175	169										
Completed, n (%)		174 (99.4)	169 (100)										
Total Number Subjects Withdrawn, n (%)		1 (0.6)	0 (0.0)										
Withdrawn due to Adverse Events, n (%)		1 (0.6)	0 (0.0)										
Withdrawn due to Lack of Efficacy, n (%)		Not applicable	Not applicable										
Withdrawn for other reasons, n (%)		0 (0.0)	0 (0.0)										
Demographics		Co-administration	Separate administration										
N (Total Vaccinated Cohort)		175	169										
Females:Males		101:74	86:83										
Mean Age, months (SD)		17.6 (0.71)	17.7 (0.81)										
White/caucasian, n (%)		175 (100)	167 (98.8)										
Primary Efficacy Results:													
Differences in seroprotection rates for anti-PRP antibodies between the two groups one month post booster (ATP cohort for immunogenicity)													
Antibody	Cut-off value	Co-administration group		Separate administration group		Difference							
		N	%	N	%	%	95% CI						
							LL	UL					
Anti-PRP	≥ 1 µg/ml	160	100	155	98.71	-1.29	-4.58	1.07					
N: Number of subjects with available results %: percentage of subjects with antibody concentrations ≥ 1 µg/mL Difference: Difference between the 2 groups in percentage of seroprotected subjects (Separate administration group minus Co-administration group) 95% CI: 95% confidence interval; LL: Lower Limit; UL: Upper Limit													
Primary Efficacy Results:													
Seroprotection rates and GMCs for anti-PRP antibodies at pre- and post-booster vaccination (ATP cohort for immunogenicity)													
Group	Timing	N	≥ 0.15 g/ mL				≥ 1 g/mL				GMC		
			n	%	95% CI		n	%	95% CI		g/mL	95% CI	
					LL	UL			LL	UL		LL	UL
Co-administration	Pre	149	120	80.5	73.3	86.6	40	26.8	19.9	34.7	0.455	0.372	0.557
	Post	160	160	100	97.7	100	160	100*	97.7	100	49.401	40.717	59.937
Separate administration	Pre	143	119	83.2	76.1	88.9	46	32.2	24.6	40.5	0.527	0.417	0.664
	Post	155	155	100	97.6	100	153	98.7*	95.4	99.8	33.767	27.534	41.412
N: number of subjects with available results n(%): number(percentage) of subjects with antibody concentrations ≥ the specified cut-off 95% CI: 95% confidence interval; LL: lower limit; UL: upper limit Pre: pre-booster vaccination Post: post-booster vaccination *Primary efficacy results													
Secondary Outcome Variable(s):													
Seropositivity rates and GMTs for SBA-MenC antibodies before the booster vaccination (ATP cohort for antibody persistence)													

Group	N	≥ 8 dilution				GMT		
		n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
Co-administration	151	88	58.3	50.0	66.2	28.1	20.8	38.0
Separate administration	152	128	84.2	77.4	89.6	143.5	106.7	192.9

N: number of subjects with available results

n(%): number(percentage) of subjects with antibody titre ≥ the specified cut-off

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

Secondary Outcome Variable(s):

Seroprotection rates and GMCs for anti-HBs antibodies before the booster vaccination (ATP cohort for antibody persistence)

Group	N	≥ 10 mIU/mL				GMC		
		n	%	95% CI		mIU/mL	95% CI	
				LL	UL		L	LL
Co-administration	158	137	86.7	80.4	91.6	107.9	83.3	139.8
Separate administration	151	137	90.7	84.9	94.8	109.1	84.9	140.2

N: number of subjects with available results

n(%): number(percentage) of subjects with antibody concentration ≥ the specified cut-off

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

Secondary Outcome Variable(s):

Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies at pre and post-booster vaccination (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 0.1 IU/mL				GMC		
				n	%	95% CI		IU/mL	95% CI	
						LL	UL		L	LL
Anti-diphtheria	Co-administration	Pre	147	123	83.7	76.7	89.3	0.257	0.217	0.305
		Post	159	159	100	97.7	100	10.735	9.632	11.963
	Separate administration	Pre	140	138	98.6	94.9	99.8	0.649	0.561	0.751
		Post	155	155	100	97.6	100	15.584	13.828	17.563
Anti-tetanus	Co-administration	Pre	147	142	96.6	92.2	98.9	0.373	0.327	0.424
		Post	159	159	100	97.7	100	9.048	8.014	10.215
	Separate administration	Pre	140	136	97.1	92.8	99.2	0.370	0.322	0.424
		Post	155	155	100	97.6	100	6.388	5.611	7.272

N: number of subjects with available results

n(%): number(percentage) of subjects with antibody concentration ≥ the specified cut-off

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

Pre: pre-booster vaccination

Post: post-booster vaccination

Secondary Outcome Variable (s):

Seroprotection rates and GMTs for anti-polio 1, 2 and 3 antibodies at pre and post-booster vaccination (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 8				GMT		
				n	%	95% CI		Value	95% CI	
						LL	UL		LL	UL

Anti-poliovirus type 1	Co-administration	Pre	142	140	98.6	95.0	99.8	140.8	112.1	176.9
		Post	152	152	100	97.6	100	2193.0	1863.2	2581.1
	Separate administration	Pre	135	132	97.8	93.6	99.5	107.3	86.0	133.8
		Post	148	148	100	97.5	100	1593.7	1357.1	1871.6
Anti-poliovirus type 2	Co-administration	Pre	141	138	97.9	93.9	99.6	136.9	107.9	173.7
		Post	150	150	100	97.6	100	2357.9	2044.9	2718.7
	Separate administration	Pre	134	131	97.8	93.6	99.5	93.4	73.6	118.6
		Post	146	146	100	97.5	100	1793.0	1515.8	2120.9
Anti-poliovirus type 3	Co-administration	Pre	140	140	100	97.4	100	257.3	203.1	325.9
		Post	141	141	100	97.4	100	3823.7	3310.2	4416.7
	Separate administration	Pre	135	132	97.8	93.6	99.5	118.7	95.1	148.3
		Post	144	144	100	97.5	100	2470.8	2109.3	2894.3

N: number of subjects with available results

n(%): number(percentage) of subjects with antibody titre \geq the specified cut-off

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

Pre: pre-booster vaccination

Post: post-booster vaccination

Secondary Outcome Variable(s):

Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies at pre- and post-booster vaccination (ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 5 EL.U/mL				GMC		
				n	%	95% CI		EL.U/mL	95% CI	
						LL	UL		L	LL
Anti-PT	Co-administration	Pre	129	56	43.4	34.7	52.4	4.8	4.2	5.6
		Post	158	158	100	97.7	100	136.2	118.2	156.9
	Separate administration	Pre	126	55	43.7	34.8	52.8	5.2	4.4	6.3
		Post	155	155	100	97.6	100	100.4	87.8	114.7
Anti-FHA	Co-administration	Pre	149	148	99.3	96.3	100	26.5	23.0	30.5
		Post	159	159	100	97.7	100	655.4	583.0	736.7
	Separate administration	Pre	143	142	99.3	96.2	100	30.7	26.0	36.4
		Post	155	155	100	97.6	100	462.7	409.0	523.4
Anti-PRN	Co-administration	Pre	147	129	87.8	81.3	92.6	14.2	11.9	16.9
		Post	159	159	100	97.7	100	390.6	331.3	460.5
	Separate administration	Pre	140	127	90.7	84.6	95.0	16.1	13.4	19.3
		Post	155	154	99.4	96.5	100	336.2	287.1	393.7

N: number of subjects with available results

Pain	Any	83	47.4	39.8	55.1	77	45.6	37.9	53.4
	Grade 3	9	5.1	2.4	9.5	4	2.4	0.6	5.9
Redness	Any	87	49.7	42.1	57.4	86	50.9	43.1	58.6
	> 20 mm	41	23.4	17.4	30.4	44	26.0	19.6	33.3
Swelling	Any	68	38.9	31.6	46.5	73	43.2	35.6	51.0
	> 20 mm	26	14.9	9.9	21.0	28	16.6	11.3	23.0

N: number of subjects with at least one solicited local symptoms sheet completed
n(%): number(percentage) of subjects with a specific symptom
Any: incidence of a particular solicited local symptom regardless of intensity
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):

Number and percentage of subjects with solicited general symptoms during the 4-day period (Day 0-3) following the administration of the booster dose (Total Vaccinated cohort)

Symptom	Intensity	Co-administration (N = 175)				Separate administration (N = 169)			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
Drowsiness	Any	29	16.6	11.4	22.9	26	15.4	10.3	21.7
	Grade 3	0	0.0	0.0	2.1	0	0.0	0.0	2.2
	Related	19	10.9	6.7	16.4	25	14.8	9.8	21.1
Irritability	Any	62	35.4	28.4	43.0	42	24.9	18.5	32.1
	Grade 3	1	0.6	0.0	3.1	0	0.0	0.0	2.2
	Related	54	30.9	24.1	38.3	39	23.1	17.0	30.2
Loss of appetite	Any	43	24.6	18.4	31.6	32	18.9	13.3	25.7
	Grade 3	4	2.3	0.6	5.7	1	0.6	0.0	3.3
	Related	35	20.0	14.3	26.7	30	17.8	12.3	24.4
Fever (rectal)	≥ 38°C	29	16.6	11.4	22.9	28	16.6	11.3	23.0
	> 39.5°C	3	1.7	0.4	4.9	2	1.2	0.1	4.2
	Related	24	13.7	9.0	19.7	27	16.0	10.8	22.4

N: number of subjects with at least one solicited general symptoms sheet completed
n(%): number(percentage) of subjects with a specific solicited general symptom
Any: incidence of a particular solicited general symptom regardless of intensity and relationship to vaccination
Grade 3 drowsiness: drowsiness that prevented normal activity
Grade 3 irritability: crying that could not be comforted/prevented normal activity
Grade 3 loss of appetite: not eating at all
Related: solicited symptom considered by the investigator to have a causal relationship to study vaccination
95% CI: exact 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)	Co- administration N = 175	Separate administration N = 169
Subjects with any AE(s), n (%)	87 (49.7)	68 (40.2)
Upper respiratory tract infection	23 (13.1)	26 (15.4)
Otitis media	14 (8.0)	10 (5.9)
Gastroenteritis	15 (8.6)	8 (4.7)
Bronchitis	10 (5.7)	8 (4.7)
Pharyngitis	12 (6.9)	4 (2.4)
Infection viral	7 (4.0)	6 (3.6)

Conjunctivitis	4 (2.3)	5 (3.0)
Pneumonia	5 (2.9)	3 (1.8)
Rash erythematous	3 (1.7)	2 (1.2)
Bronchospasm	1 (0.6)	3 (1.8)
Dermatitis	2 (1.1)	2 (1.2)
Injection site mass	3 (1.7)	1 (0.6)
Fever	1 (0.6)	2 (1.2)
Injection site reaction	1 (0.6)	2 (1.2)
Safety Results: Number (%) of subjects with SAEs (Total Vaccinated cohort)		
SAE, n (%) [n considered by the investigator to be related to study medication]		
All SAEs	Co-administration N = 175	Separate administration N = 169
Subjects with any SAE(s), n (%) [n related]	2 (1.1) [1]	0 (0.0) [0]
Gastroenteritis	1 (0.6) [0]	0 (0.0) [0]
Injection site reaction	1 (0.6) [1]	0 (0.0) [0]
Fatal SAEs	Co-administration N = 175	Separate administration N = 169
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: See publication below

Publications:

Tejedor et al. Diphtheria-tetanus acellular pertussis hepatitis B-inactivated polio virus-haemophilus influenzae type B (DTPa-HBV-IPV/Hib) vaccine co-administered with meningococcal group C conjugate (Men C) antibody persistence at 18 months of age and response to a DTPa-IPV/HIB booster. Presented at the International Congress of Pediatrics (ICP) 15-20 August 2004, Cancun Mexico.

Tejedor JC, Omeñaca F, García-Sicilia J, Esporrín C, Molina V, Marés J, Muro M, Sanjuan P, Méndez M, Teixidor R, Enrubia M, García-Corbeira P, Boceta R, Jacquet JM, Schuerman L. Antibody persistence after primary vaccination with a hexavalent DTPa-HBV-IPV/Hib vaccine co-administered with a MenC-CRM₁₉₇ vaccine and response to a DTPa-IPV/Hib booster at 18 months of age *Ped Infect Dis J.* 2006; 25(10):943-945.

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