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Study No.: 213503/004 (DTPa-IPV-004)
Title: Randomised comparative clinical study to assess the immunogenicity and reactogenicity of SmithKline Beecham Biologicals' combined diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, co-administered with SmithKline Beecham Biologicals' Haemophilus influenzae type b conjugate vaccine, either in two concomitant injections into opposite limbs or mixed in one single injection, given to healthy infants as a primary vaccination course at the age of 2, 4 and 6 months. DTPa-IPV: GlaxoSmithKline (GSK) (previously SmithKline Beecham) Biologicals' combined diphtheria, tetanus, acellular pertussis, inactivated polio vaccine. Hib: GSK (previously SmithKline Beecham) Biologicals' <i>Haemophilus influenzae</i> type b tetanus conjugate vaccine.
Rationale: The aim of this study was to assess the immunogenicity and safety of DTPa-IPV and Hib vaccines, when administered either combined or separately in healthy children aged 2, 4 and 6 months. Note: The study included two phases: pilot phase and consistency phase.
Phase: Pilot phase: Phase II; Consistency phase: Phase III
Study Period: Pilot phase: 18 July 1994 to 10 April 1995 Consistency phase: 01 September 1994 to 26 May 1995.
Study Design: The pilot phase was an open randomised study with 2 study groups; the consistency phase was a double-blind, randomised study with 3 study groups.
Centres: 4 study centres in Canada.
Indication: Primary vaccination of healthy infants against diphtheria, tetanus, pertussis, poliomyelitis and Haemophilus <i>influenzae</i> type b diseases.
Treatment: <i>The study groups for the pilot phase were as follows:</i> <ul style="list-style-type: none"> • DTPa-IPV/Hib Group received intramuscular administration of the combined DTPa-IPV /Hib vaccine in the left anterolateral thigh. • DTPa-IPV + Hib Group received simultaneous intramuscular administration of DTPa-IPV vaccine in the left anterolateral thigh and Hib vaccine in the right anterolateral thigh. <i>The study groups for the consistency phase were as follows:</i> <ul style="list-style-type: none"> • DTPa-IPV/Hib Lot A Group: received intramuscular administration of the combined DTPa-IPV/Hib vaccine (Lot A) in the anterolateral thigh • DTPa-IPV/Hib Lot B Group: received intramuscular administration of the combined DTPa-IPV/Hib vaccine (Lot B) in the anterolateral thigh. • DTPa-IPV /Hib Lot C Group: received intramuscular administration of the combined DTPa-IPV/Hib vaccine (Lot C) in the anterolateral thigh.
Objectives: <ul style="list-style-type: none"> • <i>Pilot phase:</i> To assess the safety and immunogenicity of administration of DTPa-IPV and Hib vaccine when mixed in one single injection. • <i>Consistency phase:</i> To assess consistency in terms of immunogenicity between study groups receiving 3 lots of the DTPa-IPV vaccine mixed with 3 lots of Hib vaccine.
Primary Outcome/Efficacy Variable: <i>Immunogenicity</i> Before the three dose primary vaccination course and after the second and the third dose: <ul style="list-style-type: none"> • Anti-diphtheria and anti-tetanus toxoid antibody concentration ≥ 0.1 IU/mL and geometric mean concentrations (GMCs). • Anti-PRP antibody concentrations ≥ 0.15 μg/mL, ≥ 0.5 μg/mL and ≥ 1.0 μg/mL and GMTs

- Vaccine response to pertussis toxoid (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) concentrations ≥ 5 EL.U/mL and GMCs.

Vaccine response was defined as:

-For initially seronegative subjects (concentrations < 5 EL. U/mL), a post-vaccination antibody concentration equal to or above the assay cut-off.

-For initially seropositive subjects (concentrations ≥ 5 EL. U/mL), a post-vaccination antibody concentration at least twice the concentration present prior to vaccination.

- Vaccine response to polio virus type 1, type 2 and type 3 titres ≥ 8 and geometric mean titres (GMTs).

Vaccine response was defined as:

-For initially seronegative subjects, the appearance of antibody.

-For initially seropositive subjects, a maintenance of titres from pre to post vaccination.

Safety

- Occurrence and intensity of solicited local symptoms during the 4-day (Day 0-Day 3) follow-up period after booster vaccination.
- Occurrence, intensity and relationship of solicited general symptoms during the 4-day (Day 0-Day 3) follow-up period after booster vaccination.
- Occurrence and relationship of unsolicited symptoms post vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study period after vaccination

Secondary Outcome/Efficacy Variable(s): Not applicable.

Statistical Methods:

The analyses were performed on the Total Vaccinated Cohort and According-to-Protocol (ATP) cohort for immunogenicity

- The Total Vaccinated cohort included all vaccinated subjects.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study)

Analysis of Immunogenicity

The analysis was performed on the ATP cohort for immunogenicity

The percentages of subjects with antibody titers/concentrations above a specified level were calculated with 95% confidence interval (CI) per group for each vaccine antigen, as well as vaccine response rates to each of the pertussis and poliovirus antigens. GMTs/GMCs with 95% confidence interval (CI) were tabulated for all vaccine antigens. Antibody titres below the cut-off were given an arbitrary value of one-half the assay cut-off for GMT/GMC calculations.

Analysis of safety

The analysis was performed on the Total vaccinated cohort.

The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 0-3) solicited follow-up period was tabulated with 95% CI. The same tabulation was performed for Grade 3 symptoms and for solicited general symptoms with relation to vaccination.

The percentage of subjects with at least one report of unsolicited AE classified according to World Health Organization (WHO) preferred terms was tabulated. The occurrence of SAEs during the entire study period was tabulated according to the WHO preferred terms.

Study Population: Healthy subjects between 8 and 12 weeks of age at the time of first vaccination were included in the study. Written informed consent was obtained from the parents or guardians of all subjects.

Pilot Phase:

Number of subjects	DTPa-IPV/Hib Group	DTPa-IPV + Hib Group
Planned, N	Not available	Not available
Randomised, N (Total Vaccinated Cohort)	90	90
Completed, n (%)	86 (95.6)	88 (97.8)

Total Number Subjects Withdrawn, n (%)	4 (4.4)	2 (2.2)					
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)					
Withdrawn due to Lack of Efficacy, n (%)	Not Applicable	Not Applicable					
Withdrawn for other reasons, n (%)	4 (4.4)	2 (2.2)					
Demographics	DTPa-IPV/Hib Group	DTPa-IPV + Hib Group					
N (Total Vaccinated Cohort)	90	90					
Females: Males	45:45	45:45					
Mean Age, weeks (SD)	9.0 (0.93)	8.9 (0.90)					
White, n (%)	80 (8.89)	84 (93.3)					
Consistency phase:							
Number of subjects: Consistency Phase	DTPa-IPV /Hib Lot A Group	DTPa-IPV /Hib Lot B Group	DTPa-IPV/Hib Lot C Group				
Planned, N	90	90	90				
Randomised, N (Total Vaccinated Cohort)	90	89	89				
Completed, n (%)	90 (100)	84 (94.4)	87 (97.8)				
Total Number Subjects Withdrawn, n (%)	0 (0.0)	5 (5.6)	2 (2.2)				
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)				
Withdrawn due to Lack of Efficacy, n (%)	Not Applicable	Not Applicable	Not Applicable				
Withdrawn for other reasons, n (%)	0 (0.0)	5 (5.6)	2 (2.2)				
Demographics	DTPa-IPV /Hib Lot A Group	DTPa-IPV /Hib Lot B Group	DTPa-IPV/Hib Lot C Group				
N (Total Vaccinated Cohort)	90	89	89				
Females: Males	47:43	43:46	44:45				
Mean Age, weeks (SD)	8.86 (0.92)	8.84 (0.96)	8.80 (0.92)				
White, n (%)	85 (94.4)	85 (95.5)	83 (93.3)				
Primary Efficacy Results: Immune response to diphtheria toxoid (ATP cohort for immunogenicity) - Pilot phase							
Group	Timing	N	S+	%	GMC (IU/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	58	13	22.4	0.073	0.060	0.091
	PIII	79	79	100	1.817	1.460	2.263
DTPa-IPV + Hib	Pre	65	16	24.6	0.071	0.060	0.084
	PIII	78	75	96.2	1.552	1.222	1.971
<p>N = number of subjects tested S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 0.1 IU/mL % = percentage of subjects with concentrations ≥ 0.1 IU/mL 95% CI = 95% confidence interval; LL = lower limit, UL = upper limit Pre = pre-vaccination blood sample PIII = blood sample taken approximately one month after the third dose</p>							
Primary Efficacy Results: Immune response to diphtheria toxoid (ATP cohort for immunogenicity) - Consistency phase							
Group	Timing	N	S+	%	GMC (IU/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib Lot A	Pre	66	16	24.2	0.072	0.061	0.086
	PIII	79	77	97.5	2.125	1.669	2.707

DTPa-IPV/ Hib Lot B	Pre	69	21	30.4	0.082	0.068	0.099
	PIII	82	82	100	1.824	1.492	2.228
DTPa-IPV/ Hib Lot C	Pre	66	18	27.3	0.080	0.064	0.100
	PIII	77	77	100	2.001	1.641	2.440
All	Pre	201	55	27.4	0.078	0.070	0.087
	PIII	238	236	99.2	1.977	1.750	2.234

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 0.1 IU/mL

% = percentage of subjects with concentrations ≥ 0.1 IU/mL

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Immune response to tetanus toxoid (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMC (IU/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	59	51	86.4	0.314	0.241	0.408
	PIII	79	79	100	2.372	1.982	2.840
DTPa-IPV + Hib	Pre	64	53	82.8	0.330	0.250	0.436
	PIII	78	78	100	1.320	1.083	1.610

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 0.1 IU/mL

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

% = percentage of subjects with concentrations ≥ 0.1 IU/mL

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Immune response to tetanus toxoid (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMC (IU/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	64	55	85.9	0.333	0.253	0.437
	PIII	79	79	100	2.195	1.787	2.696
DTPa-IPV/ Hib Lot B	Pre	69	58	84.1	0.302	0.232	0.394
	PIII	82	82	100	2.412	2.072	2.808
DTPa-IPV/ Hib Lot C	Pre	66	54	81.8	0.305	0.232	0.400
	PIII	77	77	100	2.643	2.253	3.101
All	Pre	199	167	83.9	0.312	0.268	0.364
	PIII	238	238	100	2.408	2.180	2.659

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 0.1 IU/mL

% = percentage of subjects with concentrations ≥ 0.1 IU/mL

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results:

Distribution of anti-PRP concentrations (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	$\geq 0.15\mu\text{g/mL}$		$\geq 0.50\mu\text{g/mL}$		$\geq 1.0\mu\text{g/mL}$	
			n	%	n	%	n	%
			DTPa-IPV/Hib	Pre	68	30	44.1	11
PIII	83	80		96.4	68	81.9	55	66.3

DTPa-IPV + Hib	Pre	71	23	32.4	14	19.7	5	7.0
	PIII	81	77	95.1	70	86.4	62	76.5

N = number of subjects tested
n (%)= number (percentage) of subjects with antibody concentrations within the specified range
Pre = pre-vaccination blood sample
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: GMCs of anti-PRP antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	GMC ($\mu\text{g/mL}$)		
			Value	95% CI	
				LL	UL
DTPa-IPV/Hib	Pre	68	0.165	0.129	0.211
	PIII	83	1.571	1.175	2.099
DTPa-IPV + Hib	Pre	71	0.141	0.111	0.180
	PIII	81	3.222	2.229	4.658

N = number of subjects tested
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre = pre-vaccination blood sample
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Distribution of anti-PRP concentrations (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	$\geq 0.15\mu\text{g/mL}$		$\geq 0.50\mu\text{g/mL}$		$\geq 1.0\mu\text{g/mL}$	
			n	%	n	%	n	%
DTPa-IPV/Hib Lot A	Pre	70	15	21.4	7	10.0	4	5.7
	PIII	73	71	97.3	63	86.3	51	69.9
DTPa-IPV/Hib Lot B	Pre	71	23	32.4	12	16.9	7	9.9
	PIII	76	76	100	68	89.5	58	76.3
DTPa-IPV/Hib Lot C	Pre	64	20	31.3	5	7.8	1	1.6
	PIII	71	69	97.2	64	90.1	52	73.2
All	Pre	205	58	28.3	24	11.7	12	5.9
	PIII	220	216	98.2	195	88.6	161	73.2

N = number of subjects tested
n (%)= number (percentage) of subjects with antibody concentrations within the specified range
Pre = pre-vaccination blood sample
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: GMCs of anti-PRP antibody concentrations (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	GMC ($\mu\text{g/mL}$)		
			Value	95% CI	
				LL	UL
DTPa-IPV/Hib Lot A	Pre	70	0.115	0.092	0.145
	PIII	73	2.263	1.638	3.126
DTPa-IPV/Hib Lot B	Pre	71	0.144	0.112	0.187
	PIII	76	1.825	1.447	2.301
DTPa-IPV/Hib Lot C	Pre	64	0.120	0.098	0.147
	PIII	71	2.114	1.598	2.796
All	Pre	205	0.126	0.111	0.144
	PIII	220	2.055	1.752	2.410

N = number of subjects tested
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

Pre = pre-vaccination blood sample

P111 = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Vaccine response to pertussis antigens (ATP cohort for immunogenicity) - Pilot phase

Antibody	Pre-vaccination status	DTPa-IPV/Hib Group					DTPa-IPV + Hib Group				
		N	n	VR (%)	95% CI		N	n	VR (%)	95% CI	
					LL	UL				LL	UL
Anti-PT	S-	41	41	100	-	-	38	38	100	-	-
	S+	13	13	100	-	-	23	21	91.3	-	-
	Total	54	54	100	91.7	100	61	59	96.7	87.6	99.4
Anti-FHA	S-	12	12	100	-	-	24	24	100	-	-
	S+	41	40	97.6	-	-	34	34	100	-	-
	Total	53	52	98.1	88.6	99.9	58	58	100	92.3	100
Anti-PRN	S-	34	34	100	-	-	40	40	100	-	-
	S+	22	21	95.5	-	-	19	16	84.2	-	-
	Total	56	55	98.2	89.2	99.9	59	56	94.9	84.9	98.7

N = number of subjects tested

n = number of responders

S+ = number of subjects with antibody concentrations ≥ 5 EL.U/mL

S- = number of subjects with antibody concentrations < 5 EL.U/mL

VR (%) = Vaccine response

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

Vaccine response definition:

For initially seronegative subjects (antibody concentrations < 5 EL.U/mL) - a post-vaccination antibody concentration \geq assay cut-off.

For initially seropositive subjects (antibody concentrations ≥ 5 EL.U/mL) - a post-vaccination antibody concentration \geq pre-vaccination concentration.

Primary Efficacy Results: Vaccine response to pertussis antigens (ATP cohort for immunogenicity) - Consistency phase

Antibody	Pre-vaccination status	DTPa-IPV/Hib Lot A Group					DTPa-IPV/Hib Lot B Group				
		N	n	VR (%)	95% CI		N	n	VR (%)	95% CI	
					LL	UL				LL	UL
Anti-PT	S-	44	44	100	-	-	46	46	100	-	-
	S+	21	17	81.0	-	-	22	22	100	-	-
	Total	65	61	93.8	84.2	98.0	68	68	100	93.3	100
Anti-FHA	S-	13	13	100	-	-	17	17	100	-	-
	S+	31	31	100	-	-	29	29	100	-	-
	Total	44	44	100	90.0	100	46	46	100	90.4	100
Anti-PRN	S-	32	32	100	-	-	36	36	100	-	-
	S+	14	11	78.6	-	-	13	12	92.3	-	-
	Total	46	43	93.5	81.1	98.3	49	48	98.0	87.8	99.9

DTPa-IPV/Hib Lot C Group

Anti-PT	S-	47	47	100	-	-
	S+	15	15	100	-	-
	Total	62	62	100	92.7	100
Anti-FHA	S-	15	15	100	-	-
	S+	27	27	100	-	-
	Total	42	42	100	89.6	100
Anti-PRN	S-	36	36	100	-	-
	S+	9	9	100	-	-
	Total	45	45	100	90.2	100

N = number of subjects tested

n = number of responders

S+ = number of subjects with antibody concentrations ≥ 5 EL.U/mL

S- = number of subjects with antibody concentrations < 5 EL.U/mL

VR (%) = Vaccine response

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

Vaccine response definition:

- For initially seronegative subjects (antibody concentrations < 5 EL.U/mL) - a post-vaccination antibody concentration \geq assay cut-off.

- For initially seropositive subjects (antibody concentrations ≥ 5 EL.U/mL) - a post-vaccination antibody concentration \geq pre-vaccination concentration

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PT antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	58	13	22.4	3.2	2.8	3.6
	PII	7	7	100	21.5	12.9	35.9
	PIII	54	54	100	54.1	44.3	66.1
DTPa-IPV + Hib	Pre	65	23	35.4	4.1	3.4	4.9
	PII	9	9	100	24.1	15.4	37.6
	PIII	61	61	100	58.6	51.1	67.2

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 5 EL.U/mL

S- = number of subjects with concentrations < 5 EL.U/mL

% = percentage of subjects with concentrations ≥ 5 EL.U/mL

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

Pre = pre-vaccination blood sample

PII = blood sample taken approximately one month after the second dose

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PT antibody concentrations ((ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	67	22	32.8	4.3	3.4	5.4
	PIII	65	65	100	65.9	54.1	80.4
DTPa-IPV/ Hib Lot B	Pre	68	22	32.4	3.8	3.3	4.5
	PIII	68	68	100	65.7	56.9	75.9
DTPa-IPV/ Hib Lot C	Pre	65	16	24.6	3.4	2.9	3.9
	PIII	62	62	100	60.3	51.4	70.8
All	Pre	200	60	30.0	3.8	3.4	4.2
	PIII	195	195	100	64.0	58.1	70.4

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody concentrations ≥ 5 EL.U/mL

S- = number of subjects with concentrations < 5 EL.U/mL

% = percentage of subjects with concentrations ≥ 5 EL.U/mL

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMCs of anti-FHA antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	57	43	75.4	10.3	7.8	13.6
	PII	7	7	100	48.2	29.9	77.5
	PIII	53	53	100	181.4	152.2	216.2
DTPa-IPV + Hib	Pre	61	36	59.0	7.2	5.5	9.3
	PII	7	7	100	58.2	23.8	142.4
	PIII	58	58	100	193.5	166.7	224.7

N = number of subjects tested
S+ (%) = number (percentage) of subjects with antibody concentrations \geq 5 EL.U/mL
S- = number of subjects with concentrations < 5 EL.U/mL
% = percentage of subjects with concentrations \geq 5 EL.U/mL
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre = pre-vaccination blood sample
PII = blood sample taken approximately one month after the second dose
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMCs of anti-FHA antibody concentrations (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	63	46	73.0	9.2	7.0	12.0
	PIII	44	44	100	311.2	242.2	399.8
DTPa-IPV/ Hib Lot B	Pre	67	45	67.2	7.9	6.3	10.0
	PIII	46	46	100	249.3	216.5	287.0
DTPa-IPV/ Hib Lot C	Pre	61	37	60.7	7.3	5.7	9.3
	PIII	42	42	100	249.8	208.7	299.0
All	Pre	191	128	67.0	8.1	7.0	9.3
	PIII	132	132	100	268.6	240.4	300.1

N = number of subjects tested
S+ (%) = number (percentage) of subjects with antibody concentrations \geq 5 EL.U/mL
S- = number of subjects with concentrations < 5 EL.U/mL
% = percentage of subjects with concentrations \geq 5 EL.U/mL
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre = pre-vaccination blood sample
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PRN antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	59	23	39.0	4.7	3.7	6.0
	PII	7	6	85.7	38.4	8.9	166.5
	PIII	56	56	100	144.7	117.6	178.0
DTPa-IPV + Hib	Pre	63	20	31.7	4.3	3.4	5.3
	PII	7	7	100	64.7	26.6	157.4
	PIII	59	59	100	132.9	103.7	170.3

N = number of subjects tested
S+ (%) = number (percentage) of subjects with antibody concentrations \geq 5 EL.U/mL
S- = number of subjects with concentrations < 5 EL.U/mL
% = percentage of subjects with concentrations \geq 5 EL.U/mL
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

Pre = pre-vaccination blood sample

PII = blood sample taken approximately one month after the second dose

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMCs of anti-PRN antibody concentrations (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMC (EL.U/mL)		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	65	22	33.8	4.5	3.6	5.7
	PIII	46	46	100	161.8	121.3	215.7
DTPa-IPV/ Hib Lot B	Pre	70	23	32.9	4.8	3.7	6.3
	PIII	49	49	100	196.9	160.7	241.1
DTPa-IPV/ Hib Lot C	Pre	65	12	18.5	3.6	2.9	4.3
	PIII	45	45	100	153.9	122.0	194.1
All	Pre	200	57	28.5	4.3	3.7	4.9
	PIII	140	140	100	170.5	148.6	195.6

N = number of subjects tested

S+ (%) = number (percentage) with antibody concentrations \geq 5 EL.U/mL

S- = number of subjects with concentrations $<$ 5 EL.U/mL

% = percentage of subjects with concentrations \geq 5 EL.U/mL

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Immune response to poliovirus types 1, 2 and 3 antigens (ATP cohort for immunogenicity) - Pilot phase

Antibody	Pre-vaccination status	DTPa-IPV/Hib Group					DTPa-IPV + Hib Group				
		N	n	VR (%)	95% CI		N	n	VR (%)	95% CI	
					LL	UL				LL	UL
Anti-polio type 1	S-	14	14	100	-	-	20	20	100	-	-
	S+	57	47	82.5	-	-	52	44	84.6	-	-
	Total	71	61	85.9	75.2	92.7	72	64	88.9	78.7	94.7
Anti-polio type 2	S-	18	18	100	-	-	23	23	100	-	-
	S+	53	42	79.2	-	-	49	41	83.7	-	-
	Total	71	60	84.5	73.5	91.6	72	64	88.9	78.7	94.7
Anti-polio type 3	S-	30	30	100	-	-	32	32	100	-	-
	S+	41	38	92.7	-	-	40	36	90.0	-	-
	Total	71	68	95.8	87.3	98.9	72	68	94.4	85.7	98.2

N = number of subjects tested

n = number of responders

VR (%) = Vaccine response

S+ = antibody titer \geq 8 VN dil

S- = antibody titer $<$ 8 VN dil

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

Vaccine response definition:

For initially seronegative subjects (antibody titres $<$ 8 VN dil) - a post-vaccination antibody titre \geq assay cut-off.

For initially seropositive subjects (antibody titres \geq 8 VN dil) - a post-vaccination antibody titre \geq pre-vaccination titre.

Primary Efficacy Results: Immune response to poliovirus types 1, 2 and 3 antigens (ATP cohort for immunogenicity) - Consistency phase

Antibody	Pre-vaccination status	DTPa-IPV/ Hib Lot A Group					DTPa-IPV/ Hib Lot B Group				
		N	n	VR (%)	95% CI		N	n	VR (%)	95% CI	
					LL	UL				LL	UL

Anti-polio type 1	S-	12	12	100	-	-	7	7	100	-	-
	S+	40	36	90.0	-	-	39	34	87.2	-	-
	Total	52	48	92.3	80.6	97.5	46	41	89.1	75.6	95.9
Anti-polio type 2	S-	11	11	100	-	-	10	10	100	-	-
	S+	40	33	82.5	-	-	37	32	86.5	-	-
	Total	51	44	86.3	73.1	93.8	47	42	89.4	76.1	96.0
Anti-polio type 3	S-	22	22	100	-	-	17	17	100	-	-
	S+	30	29	96.7	-	-	31	27	87.1	-	-
	Total	52	51	98.1	88.4	99.9	48	44	91.7	79.1	97.3

DTPa-IPV/ Hib Lot C Group

Anti-polio type 1	S-	13	13	100	-	-
	S+	42	32	76.2	-	-
	Total	55	45	81.8	68.6	90.5
Anti-polio type 2	S-	10	10	100	-	-
	S+	44	39	88.6	-	-
	Total	54	49	90.7	78.9	96.5
Anti-polio type 3	S-	20	20	100	-	-
	S+	35	33	94.3	-	-
	Total	55	53	96.4	86.4	99.4

N = Number of subjects tested

n = number of responders

S+ = antibody titer \geq 8 VN dil

S- = antibody titer $<$ 8 VN dil

VR (%) = Vaccine response

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

Vaccine response definition:

For initially seronegative subjects (antibody titres $<$ 8 VN dil) - a post-vaccination antibody titre \geq assay cut-off.

For initially seropositive subjects (antibody titres \geq 8 VN dil) - a post-vaccination antibody titre \geq pre-vaccination titre.

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 1 antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	76	61	80.3	20.8	16.1	27.0
	PII	73	65	89.0	35.4	25.1	50.0
	PIII	71	69	97.2	156.2	114.7	212.7
DTPa-IPV/Hib	Pre	76	56	73.7	21.8	16.0	29.7
	PII	70	54	77.1	27.9	18.6	41.6
	PIII	72	72	100	173.7	130.0	232.0

N = number of subjects tested

S+ (%) = number (percentage) with antibody titres \geq 8 VN dil

S- = number of subjects with titres $<$ 8 VN dil

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

Pre = pre-vaccination blood sample

PII = blood sample taken approximately one month after the second dose

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 1 antibodies (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL

DTPa-IPV/ Hib Lot A	Pre	52	40	76.9	28.1	18.5	42.7
	PIII	52	52	100	284.9	202.2	401.3
DTPa-IPV/ Hib Lot B	Pre	48	41	85.4	30.9	20.7	46.0
	PIII	46	46	100	259.9	178.7	377.8
DTPa-IPV/ Hib Lot C	Pre	55	42	76.4	30.0	19.7	45.5
	PIII	55	55	100	225.4	152.6	332.9

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody titres \geq 8 VN dil

S- = number of subjects with titres < 8 VN dil

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 2 antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL
DTPa-IPV/Hib	Pre	76	58	76.3	18.3	13.7	24.4
	PII	73	52	71.2	28.2	18.7	42.6
	PIII	71	70	98.6	187.9	133.5	264.5
DTPa-IPV + Hib	Pre	76	53	69.7	15.3	11.6	20.2
	PII	70	50	71.4	28.6	19.6	41.7
	PIII	72	72	100	180.0	134.9	240.2

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody titres \geq 8 VN dil

S- = number of subjects with titres < 8 VN dil

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

Pre = pre-vaccination blood sample

PII = blood sample taken approximately one month after the second dose

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 2 antibodies (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	52	41	78.8	21.4	14.9	30.9
	PIII	51	51	100	247.1	161.8	377.4
DTPa-IPV/ Hib Lot B	Pre	48	38	79.2	23.6	15.9	35.1
	PIII	47	47	100	250.1	161.3	387.6
DTPa-IPV/ Hib Lot C	Pre	55	45	81.8	21.2	15.4	29.2
	PIII	54	53	98.1	225.1	144.0	352.0

N = number of subjects tested

S+ (%) = number (percentage) of subjects with antibody titres \geq 8 VN dil

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

Pre = pre-vaccination blood sample

PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 3 antibodies (ATP cohort for immunogenicity) - Pilot phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL

DTPa-IPV/Hib	Pre	76	44	57.9	11.5	8.7	15.0
	PII	73	65	89.0	78.8	52.3	118.8
	PIII	71	71	100	437.6	324.9	589.3
DTPa-IPV + Hib	Pre	76	43	56.6	12.4	8.9	17.2
	PII	70	65	92.9	103.7	69.1	155.8
	PIII	72	72	100	430.3	321.4	576.1

N = number of subjects tested
S+ (%) = number (percentage) of subjects with antibody titres \geq 8 VN dil
S- = number of subjects with titres < 8 VN dil
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre = pre-vaccination blood sample
PII = blood sample taken approximately one month after the second dose
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Seropositivity rates and GMTs of poliovirus type 3 antibodies (ATP cohort for immunogenicity) - Consistency phase

Group	Timing	N	S+	%	GMT		
					Value	95% CI	
						LL	UL
DTPa-IPV/ Hib Lot A	Pre	52	30	57.7	14.2	9.6	21.1
	PIII	52	52	100	924.6	649.9	1315.5
DTPa-IPV/ Hib Lot B	Pre	48	31	64.6	16.9	11.0	25.8
	PIII	48	48	100	644.6	434.6	956.1
DTPa-IPV/ Hib Lot C	Pre	55	35	63.6	15.1	10.7	21.5
	PIII	55	55	100	948.6	692.4	1299.8

N = number of subjects tested
S+ (%) = number (percentage) of subjects with antibody titres \geq 8 VN dil
S- = number of subjects with titres < 8 VN dil
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit
Pre = pre-vaccination blood sample
PIII = blood sample taken approximately one month after the third dose

Primary Efficacy Results: Incidence of solicited local symptoms and symptoms of highest intensity following vaccination (Total Vaccinated Cohort)-Pilot phase.

		DTPa-IPV/Hib Group			DTPa-IPV + Hib Group					
Side		Left			Left			Right		
Symptom	Intensity	N	n	%	N	n	%	N	n	%
Dose 1										
Pain	Any	90	10	11.1	90	9	10.0	90	6	6.7
	Grade 3	90	2	2.2	90	1	1.1	90	1	1.1
Redness	Any	90	13	14.4	90	8	8.9	90	4	4.4
	> 20 mm	90	2	2.2	90	0	0.0	90	0	0.0
Swelling	Any	90	12	13.3	90	9	10.0	90	5	5.6
	> 20 mm	90	3	3.3	90	0	0.0	90	0	0.0
Dose 2										
Pain	Any	88	4	4.5	89	9	10.1	89	5	5.6
	Grade 3	88	0	0.0	89	0	0.0	89	0	0.0
Redness	Any	88	13	14.8	89	11	12.4	89	6	6.7
	> 20 mm	88	0	0.0	89	0	0.0	89	0	0.0
Swelling	Any	88	7	8.0	89	11	12.4	89	2	2.2
	> 20 mm	88	0	0.0	89	0	0.0	89	0	0.0
Dose 3										
Pain	Any	86	6	7.0	88	9	10.2	88	6	6.8
	Grade 3	86	0	0.0	88	0	0.0	88	0	0.0

Redness	Any	86	9	10.5	88	10	11.4	88	1	1.1
	> 20 mm	86	0	0.0	88	1	1.1	88	0	0.0
Swelling	Any	86	7	8.1	88	10	11.4	88	2	2.3
	> 20 mm	86	0	0.0	88	1	1.1	88	0	0.0

N = total number of symptom sheets returned for a given vaccine dose

n (%) = total number (percentage) of reports of a given symptom

Any = occurrence of any solicited general symptom regardless of their intensity grade

Grade 3 pain = pain that prevented normal everyday activities

Primary Efficacy Results:

Incidence of solicited local symptoms and symptoms of highest intensity following vaccination (Total Vaccinated Cohort) - Consistency phase

Symptom	Intensity	DTPa-IPV/ Hib Lot A Group			DTPa-IPV/ Hib Lot B Group			DTPa-IPV/ Hib Lot C Group		
		N	n	%	N	n	%	N	n	%
Dose 1										
Pain	Any	87	26	29.9	88	12	13.6	87	13	14.9
	Grade 3	87	0	0.0	88	0	0.0	87	0	0.0
Redness	Any	87	14	16.1	88	12	13.6	87	14	16.1
	> 20 mm	87	1	1.1	88	0	0.0	87	0	0.0
Swelling	Any	87	17	19.5	88	19	21.6	87	18	20.7
	> 20 mm	87	3	3.4	88	0	0.0	87	1	1.1
Dose 2										
Pain	Any	87	9	10.3	85	8	9.4	87	9	10.3
	Grade 3	87	0	0.0	85	0	0.0	87	0	0.0
Redness	Any	87	12	13.8	85	14	16.5	87	15	17.2
	> 20 mm	87	1	1.1	85	0	0.0	87	0	0.0
Swelling	Any	87	11	12.6	85	9	10.6	87	10	11.5
	> 20 mm	87	0	0.0	85	0	0.0	87	0	0.0
Dose 3										
Pain	Any	87	5	5.7	84	8	9.5	85	7	8.2
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
Redness	Any	87	11	12.6	84	12	14.3	85	14	16.5
	> 20 mm	87	0	0.0	84	1	1.2	85	0	0.0
Swelling	Any	87	18	20.7	84	9	10.7	85	11	12.9
	> 20 mm	87	2	2.3	84	0	0.0	85	0	0.0

N = total number of symptom sheets returned for a given vaccine dose

n (%) = total number (percentage) of reports of a given symptom

Any = occurrence of any solicited general symptom regardless of their intensity grade.

Grade 3 pain = pain that prevented normal everyday activities

Primary Efficacy Results: Incidence of solicited general symptoms and symptoms of highest intensity following vaccination (Total Vaccinated Cohort) - Pilot phase

Symptom	Intensity / relationship	Group 1			Group 2		
		N	n	%	N	n	%
Dose 1							
Diarrhoea	Any	90	18	20.0	90	13	14.4
	Grade 3	90	0	0.0	90	0	0.0
	Related	90	0	0.0	90	0	0.0
Loss of appetite	Any	90	22	24.4	90	15	16.7
	Grade 3	90	0	0.0	90	0	0.0
	Related	90	0	0.0	90	0	0.0
Restlessness	Any	90	37	41.1	90	30	33.3
	Grade 3	90	1	1.1	90	1	1.1
	Related	90	4	4.4	90	2	2.2

Fever (rectally)	≥ 38.0°C	90	5	5.6	90	10	11.1
	> 39.5°C	90	0	0.0	90	0	0.0
	Related	90	1	1.1	90	2	2.2
Unusual crying	Any	90	15	16.7	90	17	18.9
	Grade 3	90	0	0.0	90	1	1.1
	Related	90	4	4.4	90	0	0.0
Vomiting	Any	90	7	7.8	90	10	11.1
	Grade 3	90	0	0.0	90	0	0.0
	Related	90	0	0.0	90	0	0.0
Dose 2							
Diarrhoea	Any	88	12	13.6	89	13	14.6
	Grade 3	88	0	0.0	89	0	0.0
	Related	88	0	0.0	89	0	0.0
Loss of appetite	Any	88	19	21.6	89	9	10.1
	Grade 3	88	1	1.1	89	0	0.0
	Related	88	0	0.0	89	0	0.0
Restlessness	Any	88	40	45.5	89	34	38.2
	Grade 3	88	1	1.1	89	0	0.0
	Related	88	1	1.1	89	0	0.0
Fever (rectally)	≥ 38.0°C	88	11	12.5	89	12	13.5
	> 39.5°C	88	0	0.0	89	0	0.0
	Related	88	1	1.1	89	3	3.4
Unusual crying	Any	88	20	22.7	89	16	18.0
	Grade 3	88	0	0.0	89	0	0.0
	Related	88	3	3.4	89	2	2.2
Vomiting	Any	88	11	12.5	89	12	13.5
	Grade 3	88	0	0.0	89	0	0.0
	Related	88	0	0.0	89	0	0.0
Dose 3							
Diarrhoea	Any	86	4	4.7	88	11	12.5
	Grade 3	86	0	0.0	88	0	0.0
	Related	86	0	0.0	88	0	0.0
Loss of appetite	Any	86	7	8.1	88	14	15.9
	Grade 3	86	0	0.0	88	0	0.0
	Related	86	0	0.0	88	0	0.0
Restlessness	Any	86	31	36.0	88	35	39.8
	Grade 3	86	1	1.2	88	0	0.0
	Related	86	0	0.0	88	0	0.0
Fever (rectally)	≥ 38.0°C	86	11	12.8	88	12	13.6
	> 39.5°C	86	0	0.0	88	1	0.0
	Related	86	3	3.5	88	1	1.1
Unusual crying	Any	86	8	9.3	88	9	10.2
	Grade 3	86	1	1.2	88	0	0.0
	Related	86	2	2.3	88	1	1.1
Vomiting	Any	86	4	4.7	88	8	9.1
	Grade 3	86	0	0.0	88	0	0.0
	Related	86	0	0.0	88	0	0.0
<p>N = total number of symptom sheets returned for a given vaccine dose n (%) = total number (percentage) of reports of a given symptom Any = occurrence of any solicited general symptom regardless of their intensity grade or relationship to study vaccination. Grade 3 symptoms = symptoms that prevented normal activities</p>							

Related = general symptom considered by the investigator to be possibly related to the study vaccination

Primary Efficacy Results: Incidence of solicited general symptoms and symptoms of highest intensity following vaccination (Total Vaccinated Cohort) - Consistency phase

Symptom	Intensity / relationship	DTPa-IPV/ Hib Lot A Group			DTPa-IPV/ Hib Lot B Group			DTPa-IPV/ Hib Lot C Group		
		N	n	%	N	n	%	N	n	%
Dose 1										
Diarrhoea	Any	87	15	17.2	88	13	14.8	87	18	20.7
	Grade 3	87	0	0.0	88	0	0.0	87	0	0.0
	Related	87	0	0.0	88	0	0.0	87	0	0.0
Loss of appetite	Any	87	21	24.1	88	18	20.5	87	22	25.3
	Grade 3	87	1	1.1	88	0	0.0	87	1	1.1
	Related	87	0	0.0	88	0	0.0	87	0	0.0
Restlessness	Any	87	43	49.4	88	33	37.5	87	36	41.4
	Grade 3	87	2	2.3	88	0	0.0	87	0	0.0
	Related	87	0	0.0	88	0	0.0	87	0	0.0
Fever (rectally)	≥ 38.0°C	87	6	6.9	88	3	3.4	87	6	6.9
	> 39.5°C	87	0	0.0	88	0	0.0	87	0	0.0
	Related	87	1	1.1	88	0	0.0	87	1	1.1
Unusual crying	Any	87	21	24.1	88	10	11.4	87	18	20.7
	Grade 3	87	0	0.0	88	0	0.0	87	0	0.0
	Related	87	3	3.4	88	1	1.1	87	3	3.4
Vomiting	Any	87	9	10.3	88	12	13.6	87	12	13.8
	Grade 3	87	0	0.0	88	0	0.0	87	0	0.0
	Related	87	0	0.0	88	0	0.0	87	0	0.0
Dose 2										
Diarrhoea	Any	87	11	12.6	85	6	7.1	87	9	10.3
	Grade 3	87	0	0.0	85	0	0.0	87	1	1.1
	Related	87	0	0.0	85	0	0.0	87	0	0.0
Loss of appetite	Any	87	14	16.1	85	17	20.0	87	14	16.1
	Grade 3	87	0	0.0	85	0	0.0	87	1	1.1
	Related	87	0	0.0	85	0	0.0	87	0	0.0
Restlessness	Any	87	40	46.0	85	40	47.1	87	37	42.5
	Grade 3	87	1	1.1	85	1	1.2	87	1	1.1
	Related	87	0	0.0	85	1	1.2	87	0	0.0
Fever (rectally)	≥ 38.0°C	87	10	11.5	85	9	10.6	87	13	14.9
	> 39.5°C	87	0	0.0	85	0	0.0	87	0	0.0
	Related	87	0	0.0	85	1	1.2	87	2	2.3
Unusual crying	Any	87	14	16.1	85	14	16.5	87	13	14.9
	Grade 3	87	0	0.0	85	0	0.0	87	0	0.0
	Related	87	1	1.1	85	2	2.4	87	0	0.0
Vomiting	Any	87	6	6.9	85	8	9.4	87	9	10.3
	Grade 3	87	0	0.0	85	0	0.0	87	0	0.0
	Related	87	0	0.0	85	0	0.0	87	0	0.0
Dose 3										
Diarrhoea	Any	87	10	11.5	84	9	10.7	85	11	12.9
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
	Related	87	0	0.0	84	0	0.0	85	0	0.0

Loss of appetite	Any	87	10	11.5	84	10	11.9	85	13	15.3
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
	Related	87	0	0.0	84	0	0.0	85	0	0.0
Restlessness	Any	87	29	33.3	84	34	40.5	85	30	35.3
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
	Related	87	0	0.0	84	0	0.0	85	0	0.0
Fever (rectally)	≥ 38.0°C	87	12	13.8	84	12	14.3	85	20	23.5
	> 39.5°C	87	0	0.0	84	2	2.4	85	0	0.0
	Related	87	0	0.0	84	1	1.2	85	0	0.0
Unusual crying	Any	87	2	2.3	84	11	13.1	85	9	10.6
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
	Related	87	0	0.0	84	0	0.0	85	0	0.0
Vomiting	Any	87	5	5.7	84	8	9.5	85	5	5.9
	Grade 3	87	0	0.0	84	0	0.0	85	0	0.0
	Related	87	0	0.0	84	0	0.0	85	0	0.0

N = total number of symptom sheets returned for a given vaccine dose

n (%) = total number (percentage) of reports of a given symptom

Any = occurrence of any solicited general symptom regardless of their intensity grade or relationship to vaccination.

Grade 3 symptoms = symptoms that prevented normal activities

Related = general symptom considered by the investigator to be possibly related to the study vaccination.

Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort) - Pilot phase

Most Frequent Adverse Events On-Therapy	DTPa-IPV/Hib Group N = 90	DTPa-IPV + Hib Group N = 90
Subjects with any AE(s), n (%)	78 (86.7)	82 (91.1)

Safety Results: Number (%) of subjects with unsolicited adverse events (Total Vaccinated Cohort) - Consistency phase

Most Frequent Adverse Events On-Therapy	DTPa-IPV/ Hib Lot A Group N = 90	DTPa-IPV/ Hib Lot B Group N = 89	DTPa-IPV/ Hib Lot C Group N = 89
Subjects with any AE(s), n (%)	81 (90.0)	81 (91.0)	82 (92.1)

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) ((Total Vaccinated Cohort) - Pilot phase

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

All SAEs	DTPa-IPV/Hib Group N = 90	DTPa-IPV + Hib Group N = 90
Subjects with any SAE(s), n (%) [related]	1 (1.1) [0]	4 (4.4) [0]
Gastro oesophageal reflux	1 (1.1) [0]	0 (0.0) [0]
Possible pertussis infection	0 (0.0) [0]	1 (1.1) [0]
Unilateral coronal synostosis	0 (0.0) [0]	1 (1.1) [0]
Urinary tract infection	0 (0.0) [0]	1 (1.1) [0]
Viral infection	0 (0.0) [0]	1 (1.1) [0]
Fatal SAEs	DTPa-IPV/Hib Group N = 90	DTPa-IPV + Hib Group N = 90
Subjects with fatal SAEs, n (%) [related]	0 (0.0) [0]	0 (0.0) [0]

Safety Results: Number (%) of subjects with Serious Adverse Events (SAEs) (Total Vaccinated Cohort) - Consistency phase

Serious adverse event, n (%) [n considered by the investigator to be related to study medication]			
All SAEs	DTPa-IPV/ Hib Lot A Group N = 90	DTPa-IPV/ Hib Lot B Group N = 89	DTPa-IPV/ Hib Lot C Group N = 89
Subjects with any SAE(s), n (%) [related]	1 (1.1) [0]	1 (1.1) [0]	4 (4.5) [0]
Cleft lip and nasal passage	0 (0.0) [0]	1 (1.1) [0]	0 (0.0) [0]
Croup	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Difficult to awake	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Drowsy	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Inguinal hernia repair	1 (1.1) [0]	0 (0.0) [0]	0 (0.0) [0]
Nasal stuffiness	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Overdose of Otrivin	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Restlessness	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Urinary tract infection	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Viral gastritis	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Vomiting	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Fatal SAEs	DTPa-IPV/ Hib Lot A Group N = 90	DTPa-IPV/ Hib Lot B Group N = 89	DTPa-IPV/ Hib Lot C Group N = 89
Subjects with fatal SAEs, n (%) [related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

In the pilot phase, at least one unsolicited AE was reported for 78 (86.7%) and 82 (91.1%) subjects in the DTPa-IPV/Hib and DTPa-IPV + Hib groups, respectively. For the remaining results on the pilot phase, please refer to the publication below.

In the consistency phase, one month after Dose 3, all subjects had anti-tetanus, anti-PT, anti-FHA, anti-PRN, and anti-poliovirus types 1 & 3 antibody titres \geq cut-off values; at least 97.5% and 98.1% of subjects had anti-diphtheria and anti-poliovirus type 2 antibody titres \geq cut-off values, respectively; 97.3%, 100%, and 97.2% of subjects had anti-PRP antibodies concentration \geq 0.15 g /mL in the DTPa-IPV+ Hib Lot A, DTPa-IPV+ Hib Lot B and DTPa-IPV + Hib Lot C groups, respectively. Across doses and groups, redness and restlessness were the most frequently reported solicited local and general symptoms during the 4-day follow-up period after vaccination. At least one unsolicited AE was reported for 81 (90.0%), 81 (91.0%) and 82 (92.1%) of the subjects from DTPa-IPV+ Hib Lot A, DTPa-IPV+ Hib Lot B and DTPa-IPV + Hib Lot C groups, respectively. During the entire study period, SAEs were reported for 1 (1.1%), 1 (1.1%) and 4 (4.5%) subjects from DTPa-IPV+ Hib Lot A, DTPa-IPV+ Hib Lot B and DTPa-IPV + Hib Lot C groups, respectively; none were considered by the investigator to be casually related to the study vaccination. No fatal SAEs were reported during the study.

Publications: Halperin SA et al. (1999) Safety and immunogenicity of Haemophilus influenzae-tetanus toxoid conjugate vaccine given separately or in combination with a three-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids and inactivated poliovirus vaccine for the first four doses. Clin Infect Dis. 28(5):995-1001.

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