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Study No.: 208140/032 (DTPa-HBV-032)
Title: Open clinical study of the immunogenicity and reactogenicity of SB Biologicals' DTPa-HBV vaccine, when co-administered with SB Biologicals' Hib vaccine in two concomitant injections into opposite limbs, as a primary vaccination course in healthy infants aged 2, 4 and 6 months, followed by a booster dose at 18 months of age. DTPa-HBV: GlaxoSmithKline Biologicals' (GSK) (formerly SmithKline Beecham [SB]) combined diphtheria, tetanus, acellular pertussis and hepatitis B vaccine. <i>Hiberix™</i> (Hib): GSK Biologicals' <i>Haemophilus influenzae</i> type b conjugate vaccine.
Rationale: The purpose of the study was to evaluate the immunogenicity and safety of DTPa-HBV vaccine when co-administered with Hib vaccine in 2 concomitant injections into opposite limbs as a primary vaccination course in healthy infants of age 2, 4 and 6 months, followed by a booster at 18 months of age.
Phase: IV
Study Period: 19 June 1997 to 28 May 1999
Study Design: Open, multicentric, single-group study
Centres: 3 centres, 2 in Argentina and 1 in Brazil
Indication: Immunization against diphtheria, tetanus, pertussis, hepatitis B and Hib diseases in the first year of life.
Treatment: The study group was as follows: <ul style="list-style-type: none"> DTPa-HBV + Hib Group: subjects received 3 primary doses of DTPa-HBV and Hib vaccines at 2 months interval followed by a booster vaccination at 18 months of age. The vaccines were administered intramuscularly into the anterolateral thigh, DTPa-HBV vaccine into the right thigh and Hib vaccine into the left thigh.
Objectives: To assess immune response to the Hib capsular polysaccharide polyribosylribitol-phosphate (PRP) antigen and hepatitis B surface antigen (HBsAg) after the third dose and after the booster dose.
Primary Outcome/Efficacy Variable: At the time of first dose and one month after the third dose of primary vaccination course and one month after the booster vaccination <ul style="list-style-type: none"> Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$. Anti-HBs antibody concentrations $\geq 10 \text{ mIU/mL}$.
Secondary Outcome/Efficacy Variable(s): <i>Immunogenicity:</i> At the time of first dose, one month after the third dose of primary vaccination course and one month after the booster vaccination <ul style="list-style-type: none"> Anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$. Anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA), and anti-pertactin (PRN) antibody concentrations $\geq 5 \text{ EL.U/mL}$. Vaccine response* to PT, FHA, PRN Anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/mL}$. Anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$. <i>*Vaccine response was defined as-</i> <ul style="list-style-type: none"> The appearance of antibodies (concentration $\geq 5 \text{ EL.U/mL}$) in initially seronegative subjects; Post-vaccination concentrations \geq pre-vaccination concentrations in initially seropositive subjects. Safety: <ul style="list-style-type: none"> Occurrence of solicited symptoms during the 4-day follow-up period after each vaccine dose. Occurrence of unsolicited symptoms occurring within 30 days after each vaccine dose. Occurrence of serious adverse events (SAEs) during the entire study period.
Statistical Methods: The analyses were performed on the Total Cohort and According-to-Protocol (ATP) cohort for analysis of safety. <ul style="list-style-type: none"> The Total Cohort included all vaccinated subjects with available data. The ATP cohort for analysis of safety included all subjects who received at least one dose of study vaccine, with sufficient data to perform an analysis of safety, with documented vaccination site and who had not received a vaccine not specified or forbidden in the study protocol.

Analysis of immunogenicity

The analysis was performed on the Total Cohort.

Seropositivity/seroprotection rates and geometric mean concentrations (GMCs) with 95% confidence intervals (CI) were calculated for antibodies against all vaccine antigen components at all blood sampling time points. Seropositivity was defined as antibody concentration \geq assay cut-off: anti-PRP (0.15 $\mu\text{g/mL}$), anti-HBs (10 mIU/mL), anti-tetanus (0.1 IU/mL), anti-diphtheria (0.1IU/mL) and anti-pertussis (5 EL.U/mL). In addition, anti-PRP antibody concentrations \geq 1.0 $\mu\text{g/mL}$ with 95% CI were calculated. Vaccine response, with 95% CI, was tabulated for each pertussis antigen. Antibody concentrations below cut-off level were given an arbitrary value of half the cut-off value for the purpose of GMC calculation.

Analysis of safety

The analysis was performed on the ATP cohort for analysis of safety.

The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (day 0-3) follow-up period after vaccination was tabulated with 95% CI. The same tabulation was performed for grade 3 symptoms and for general symptoms with relationship to vaccination. The percentage of subjects with at least one report of unsolicited AEs classified by the World Health Organization (WHO) preferred term and reported up to 31 days (day 0-30) after vaccination was tabulated. The occurrence of SAEs during the entire study period was tabulated according to WHO preferred terms.

Study Population: Healthy male and female subjects 6-10 weeks of age at the time of the first dose of the primary vaccination course were enrolled in the study. Written informed consent was obtained from the parents or guardians of the subjects.

Number of Subjects:	DTPa-HBV + Hib
Planned, N	240
Entered, N (Total Cohort)	199
Completed, n (%)	141 (70.9)
Total Number Subjects Withdrawn, n (%)	58 (29.1)
Withdrawn due to Adverse Events n (%)	0 (0.0)
Withdrawn due to Lack of Efficacy n (%)	Not Applicable
Withdrawn for other reasons n (%)	0 (0.0)
Demographics	DTPa-HBV + Hib
N (Total Cohort)	199
Females: Males	99:100
Mean Age, months (SD)	1.7 (0.48)
caucasian, n (%)	192 (96.5)

Primary Efficacy Results: Anti-PRP concentrations $\geq 0.15 \mu\text{g/mL}^*$ and $\geq 1.0 \mu\text{g/mL}$ (Total cohort)

Timing	N	$\geq 0.15 \mu\text{g/mL}^*$				$\geq 1.0 \mu\text{g/mL}$			
		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL
PRE	199	85	42.7	35.7	49.9	16	8.0	4.7	12.7
PIII-m5	178	177	99.4	96.9	100	172	96.6	92.8	98.8
PIII-m16	147	143	97.3	93.2	99.3	98	66.7	58.4	74.2
PIV-m17	141	141	100	97.4	100	141	100	97.4	100

N = number of subjects tested

n= number with concentrations within the specified range

Pre(m0): pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII(m5): post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII(m16): post vaccination blood sampling obtained at the time of the booster administration

PIV (m17): post-vaccination blood sampling obtained one month after booster administration

95% CI, LL and UL = 95% confidence intervals, lower and upper limit

*Primary outcome variable.

Primary Efficacy Results: Anti-PRP GMCs (Total cohort)

Timing	N	Value	GMC ($\mu\text{g/mL}$)	
			95% CI	
			LL	UL

PRE	199	0.165	0.141	0.192
PIII-m5	178	21.802	17.197	27.641
PIII-m16	147	2.007	1.579	2.551
PIV-m17	141	129.690	104.665	160.698

N = number of subjects tested

Pre(m0): pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII(m5): post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII(m16): post vaccination blood sampling obtained at the time of the booster administration

PIV (m17): post-vaccination blood sampling obtained one month after booster administration

95% CI, LL and UL = 95% confidence intervals, lower and upper limit

Primary Efficacy Results: Anti-HBs seropositivity (S+) rates (%) and GMCs (Total cohort)

Timing	N	Seropositivity				GMC (mIU/mL)		
		n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
PRE	199	7	3.5	1.4	7.1	5.5	5.1	6.0
PIII-m5	176	176	100	97.9	100	1505.8	1250.0	1814.0
PIII-m16	147	144	98.0	94.2	99.6	120.4	96.0	150.9
PIV-m17	141	141	100	97.4	100	6549.4	5185.6	8271.8

N = number of subjects tested

n = number of subjects with concentrations \geq assay cut-off of 10 mIU/mL

PRE: pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII-m5: post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII-m16: post vaccination blood sampling obtained at the time of the booster administration

PIV-m17: post-vaccination blood sampling obtained one month after booster administration

95% CI: 95% confidence intervals; LL and UL: lower and upper limits

Secondary Outcome Variable(s): Seropositivity (S+) rates (%) and GMCs of antibodies to pertussis antigens (Total cohort)

Antibody	Timing	N	Seropositivity				GMC (EL.U/mL)		
			n	%	95% CI		Value	95% CI	
					LL	UL		LL	UL
Anti-PT	PRE	199	76	38.2	31.4	45.3	4.4	3.9	4.9
	PIII-m5	178	178	100	97.9	100	61.6	55.8	68.0
	PIII-m16	147	87	59.2	50.8	67.2	5.3	4.7	5.9
	PIV-m17	141	141	100	97.4	100	107.7	94.9	122.2
Anti-FHA	PRE	197	174	88.3	83.0	92.5	16.0	14.0	18.4
	PIII-m5	174	174	100	97.9	100	291.2	261.7	324.0
	PIII-m16	145	144	99.3	96.2	100	39.9	34.2	46.5
	PIV-m17	141	141	100	97.4	100	776.0	698.8	861.9
Anti-PRN	PRE	199	60	30.2	23.9	37.0	4.0	3.6	4.4
	PIII-m5	177	177	100	97.9	100	191.1	171.0	213.6
	PIII-m16	147	139	94.6	89.6	97.6	17.3	14.9	20.1
	PIV-m17	141	141	100	97.4	100	599.0	521.3	688.3

N = number of subjects tested

n = number of subjects with concentrations \geq assay cut-off 5 EL.U/mL by ELISA

PRE: pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII-m5: post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII-m16: post vaccination blood sampling obtained at the time of the booster administration

PIV-m17: post-vaccination blood sampling obtained one month after booster administration

95% CI: 95% confidence intervals; LL and UL: lower and upper limits

Secondary Outcome Variable(s): Vaccine Response to the pertussis antigens (Total cohort)

Antibody	Timing	Prevacc. status	Number of subjects	Responders	Percentage of Responders	95% CI	
						LL	UL

Anti-PT	PIII-m5	S+	71	67	94.4	94.3	99.4
		S-	107	107	100		
		Total	178	174	97.8		
	PIV-m17	S+	81	81	100	97.4	100
		S-	60	60	100		
		Total	141	141	100		
Anti-FHA	PIII-m5	S+	157	155	98.7	95.9	99.9
		S-	15	15	100		
		Total	172	170	98.8		
	PIV-m17	S+	138	135	97.8	93.8	99.6
		S-	1	1	100		
		Total	139	136	97.8		
Anti-PRN	PIII-m5	S+	55	54	98.2	96.9	100
		S-	122	122	100		
		Total	177	176	99.4		
	PIV-m17	S+	133	133	100	97.4	100
		S-	8	8	100		
		Total	141	141	100		

S-: pre-vaccination antibody concentration < ELISA assay cut-off (5 EL.U/mL)

S+: pre-vaccination antibody concentration ≥ ELISA assay cut-off (5 EL.U/mL)

95% CI, Lower, Upper: Upper and Lower limits of 95% confidence interval

Vaccine response definition: the appearance of antibodies (concentration ≥ cut-off 5 ELU/mL) in initially seronegative subjects and/or a post-vaccination concentration greater than or equal to the pre-vaccination concentration in initially seropositive subjects

PIII-m5: post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIV-m17: post-vaccination blood sampling obtained one month after booster administration

Secondary Outcome Variable(s): Anti-diphtheria seropositivity (S+) rates (%) and GMCs in subjects in the Total cohort

Timing	N	Seropositivity				GMC (IU/mL)		
		n	%	95% CI		value	95% CI	
				LL	UL		LL	UL
PRE	199	106	53.3	46.1	60.4	0.189	0.154	0.232
PIII-m5	178	178	100	97.9	100	1.602	1.411	1.819
PIII-m16	147	53	36.1	28.3	44.4	0.081	0.072	0.090
PIV-m17	141	141	100	97.4	100	4.935	4.225	5.764

N = number of subjects tested

n = number of subjects with concentrations > assay cut off of 0.1 IU/mL by ELISA

PRE: pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII-m5: post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII-m16: post vaccination blood sampling obtained at the time of the booster administration

PIV-m17: post-vaccination blood sampling obtained one month after booster administration

95% CI: 95% confidence intervals; LL and UL: lower and upper limit

Secondary Outcome Variable(s): Anti-tetanus seropositivity (S+) rates (%) and GMCs (Total cohort)

Timing	N	Seropositivity				GMC (IU/mL)		
		n	%	95% CI		Value	95% CI	
				LL	UL		LL	UL
PRE	199	150	75.4	68.8	81.2	0.438	0.352	0.546
PIII-m5	178	178	100	97.9	100	3.448	3.050	3.898
PIII-m16	147	136	92.5	87.0	96.2	0.405	0.345	0.475
PIV-m17	141	141	100	97.4	100	13.836	12.069	15.862

N = number of subjects tested

n: number of subjects with concentrations ≥ assay cut-off of 0.1 IU/mL by ELISA

PRE: pre vaccination blood sampling obtained at the time of the first dose of the 3-dose course of study vaccination

PIII-m5: post vaccination blood sampling obtained one month after the 3rd dose of the 3-dose course of study vaccination

PIII-m16: post vaccination blood sampling obtained at the time of the booster administration

PIV-m17: post-vaccination blood sampling obtained one month after booster administration

95% CI: 95% confidence intervals; LL and UL: lower and upper limits									
Secondary Outcome Variable(s): Incidence of solicited local symptoms (ATP cohort for analysis of safety)									
	Type	Dose 1				Dose 2			
		n	%	LL	UL	n	%	LL	UL
-No Sheets-		189				186			
Pain at the injection site	Any	41	21.7	16.0	28.3	30	16.1	11.2	22.2
	Grade 3	1	0.5	0.0	2.9	0	0.0	0.0	2.0
Redness	Any	25	13.2	8.7	18.9	27	14.5	9.8	20.4
	> 20 mm	1	0.5	0.0	2.9	0	0.0	0.0	2.0
Swelling	Any	21	11.1	7.0	16.5	24	12.9	8.4	18.6
	> 20 mm	2	1.1	0.1	3.8	1	0.5	0.0	3.0
		Dose 3				Dose 4 (booster)			
		n	%	LL	UL	n	%	LL	UL
-No Sheets-		179				140			
Pain at the injection site	Any	19	10.6	6.5	16.1	48	34.3	26.5	42.8
	Grade 3	0	0.0	0.0	2.0	3	2.1	0.4	6.1
Redness	Any	25	14.0	9.2	19.9	38	27.1	20.0	35.3
	> 20 mm	0	0.0	0.0	2.0	2	1.4	0.2	5.1
Swelling	Any	30	16.8	11.6	23.1	34	24.3	17.4	32.2
	> 20 mm	1	0.6	0.0	3.1	4	2.9	0.8	7.2
		Across doses							
		n	%	LL	UL	n	%	LL	UL
-No Sheets-		190							
Pain at the injection site	Any	87		45.8		38.6		53.2	
	Grade 3	4		2.1		0.6		5.3	
Redness	Any	68		35.8		29.0		43.0	
	> 20 mm	3		1.6		0.3		4.5	
Swelling	Any	64		33.7		27.0		40.9	
	> 20 mm	6		3.2		1.2		6.7	
No sheets = total number of symptom sheets returned for a given vaccine dose									
n = number of reports of a given symptom									
Any = local symptom reported for any vaccination site. (For local symptoms following multiple injections, a symptom was counted once even if reported at multiple sites.)									
LL, UL = Upper and Lower limits of 95% confidence interval									
Across doses = total number (percentage) of subjects with at least one (type of) symptom									
Grade 3 pain: Cried when the limb was moved/spontaneously painful (prevented normal activity)									
Secondary Outcome Variable(s): Incidence of solicited general symptoms (ATP cohort for analysis of safety)									
		Dose 1				Dose 2			
		n	%	LL	UL	n	%	LL	UL
-No Sheets-		189				186			
Fever	Any	35	18.5	13.3	24.8	29	15.6	10.7	21.6
	Grade 3	0	0.0	0.0	1.9	3	1.6	0.3	4.6
	related	35	18.5	13.3	24.8	25	13.4	8.9	19.2
Fussiness	Any	68	36.0	29.1	43.3	51	27.4	21.1	34.4
	Grade 3	0	0.0	0.0	1.9	1	0.5	0.0	3.0
	related	57	30.2	23.7	37.2	47	25.3	19.2	32.1
		Dose 3				Dose 4 (Booster)			
		n	%	LL	UL	n	%	LL	UL
-No Sheets-		179				140			
Fever	Any	25	14.0	9.2	19.9	22	15.7	10.1	22.8
	Grade 3	0	0.0	0.0	2.0	0	0.0	0.0	2.6
	related	23	12.8	8.3	18.7	21	15.0	9.5	22.0
Fussiness	Any	42	23.5	17.5	30.4	46	32.9	25.2	41.3
	Grade 3	2	1.1	0.1	4.0	4	2.9	0.8	7.2
	related	42	23.5	17.5	30.4	46	32.9	25.2	41.3

		Across doses			
		n	%	LL	UL
-No Sheets-		190			
Fever	Any	79	41.6	34.5	48.9
	Grade 3	3	1.6	0.3	4.5
	related	76	40.0	33.0	47.3
Fussiness	Any	113	59.5	52.1	66.5
	Grade 3	7	3.7	1.5	7.4
	related	105	55.3	47.9	62.5

Across doses = total number (percentage) of subjects with at least one (type of) symptom

n = number of reports of a given symptom

Grade 3 fussiness: persistent crying, could not be comforted

LL, UL = Upper and Lower limits of 95% confidence interval

Safety results: Number (%) of subjects with unsolicited adverse events (ATP cohort for analysis of safety)

Most frequent* adverse events – On-Therapy (occurring within Day 0-30 following vaccination)	DTPa-HBV + Hib (N=190)
Subjects with any AE(s), n (%)	52 (27.4)
Otitis media	9 (4.74)
Rhinitis	9 (4.74)
Bronchitis	7 (3.68)
Pneumonia	7 (3.68)
Urticaria	6 (3.16)
Asthma	5 (2.63)
Pharyngitis	5 (2.63)
Abdominal pain	3 (1.58)
Diarrhoea	3 (1.58)
Vomiting	3 (1.58)
Other disorders	3 (1.58)

*:most frequent events: > 30 subjects per treatment group and <= 3 groups, display the most frequent 10 events in each group

Safety results: Number (%) of subjects with serious adverse events (ATP cohort for analysis of safety)

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

All SAEs	DTPa-HBV + Hib (N=190)
Subjects with any SAE(s), n (%) [n related]	1 (0.53)[0]
Meningitis	1 (0.53)[0]
Fatal SAEs	DTPa-HBV + Hib (N=190)
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0)[0]

Conclusion: Before the first dose, one month after Dose 3 and 1 month after booster vaccination, 42.7%, 99.4% and 100% of subjects had anti-PRP concentrations $\geq 0.15 \mu\text{g/mL}$ and 3.5%, 100% and 100% of subjects had anti-HBs concentrations $\geq 10\text{mIU/mL}$, respectively. Unsolicited AEs were reported in 52 (27.4%) subjects; 1 non-fatal SAE was reported for 1 subject, it was not considered by the investigator as related to the study vaccination.

Publications: None.

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