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Study No.: 347414/029
Title: A multinational, randomised, controlled, open, phase II clinical study to evaluate the safety and immunogenicity of GSK Biologicals' investigational vaccination regimen administered as a booster dose to healthy children 12 to 15 months old, previously vaccinated in infancy with the investigational vaccination regimen in a primary study.
Rationale: The purpose of the study was to assess: <ul style="list-style-type: none"> • The safety and immunogenicity of the investigational vaccination regimen administered as a booster dose to healthy children between 12 and 15 months of age. • The persistence of antibodies against the antigens contained in the administered vaccines, prior to booster vaccination 6 to 10 months after completion of primary vaccination. • The safety and the immunogenicity of the MMR vaccine when administered concomitantly with the investigational vaccination regimen, compared with that of the co-administration of MMR and Hib vaccines. Hib: GSK Biologicals' <i>Haemophilus influenzae</i> type b vaccine; MMR: GSK Biologicals' Measles-Mumps-Rubella vaccine.
Phase: II
Study Period: 16 August 2001 to 09 January 2002
Study Design: Open, randomised study with 4 groups (4:1:1:1). Data from the group receiving the currently registered vaccine are presented. Data from the investigational vaccination regimen, which is not yet approved or marketed, are not reported at this time.
Centres: 1 centre in Argentina and 1 in Costa Rica.
Indication: Booster vaccination against <i>Haemophilus influenzae</i> type b in healthy children aged 12 to 15 months.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> • 3 groups received an investigational vaccination regimen. • 1 control group (MMR + Hib) received one dose of Hib vaccine co-administered with MMR; Meningococcal conjugate C vaccine was offered free of charge at the end of the study.
Objectives: To assess the safety of the investigational vaccination regimen when administered, either alone or concomitantly with the MMR vaccine, as a booster dose at 12-15 months of age.
Primary Outcome/Efficacy Variable: <i>Only outcome variables related to the licensed vaccines are presented.</i> Hib and MMR <ul style="list-style-type: none"> • Occurrence of each solicited symptom within 8 days (Day 0 - Day 7) after the administration of the booster dose. • Occurrence of unsolicited adverse events (AEs) within 31 days (Day 0 - Day 30) after the administration of the booster dose. • Occurrence of any serious adverse event (SAE) within 31 days (Day 0 - Day 30) after the administration of the booster dose. • Occurrence of any late SAEs occurring from 1 month up to 6 months after the administration of the booster dose. MMR <ul style="list-style-type: none"> • Occurrence of specific solicited general AEs (fever, rash/exanthema, parotid/salivary gland swelling, suspected signs of meningism) within 31 days* (Day 0 – Day 30) after the administration of the booster dose. *Analyzed only within 8 days.
Secondary Outcome/Efficacy Variable(s): <i>Only outcome variables related to the licensed vaccines are presented</i> *Prior to (i.e. 6 to 10 months after completion of the primary course) and 1 month after booster vaccination: Hib antigen <ul style="list-style-type: none"> • Anti- polyribosyl-ribitol-phosphate (PRP) antibody concentrations. • Seroprotection rate: <ul style="list-style-type: none"> – anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$, $\geq 1.0 \mu\text{g/mL}$. *Prior to and 30 days after MMR vaccination: MMR antigens <ul style="list-style-type: none"> • Anti-measles, anti-mumps and anti-rubella antibody concentrations. • Seroconversion* rates for measles, mumps and rubella:

*appearance of antibody concentrations above or equal to the cut-off value in subjects seronegative for the antigen before vaccination (seronegative subjects are subjects with concentration strictly below the cut-off value, except for rubella, where seroconversion is defined as concentrations ≥ 10 IU/ml when concentration < 4 IU/ml (seronegative) before vaccination).

Cut-off values for seroconversion:

- measles ≥ 150 mLU/mL,
- mumps ≥ 231 U/mL,
- rubella ≥ 10 IU/mL.

*Prior to booster vaccination:

DTPw-HBV antigens

- Anti-diphtheria and anti-tetanus toxoids, anti-*Bordetella Pertussis* toxoid (BPT), anti-hepatitis B (HBs) antibody concentrations
- Seroprotection rates for diphtheria, tetanus and hepatitis B defined as:
 - anti-diphtheria toxoid antibody concentrations ≥ 0.1 IU/mL,
 - anti-tetanus toxoid antibody concentrations ≥ 0.1 IU/mL,
 - anti-HBs antibody concentrations ≥ 10 mIU/mL.
- Seropositivity rates:
 - anti-BPT antibody concentrations ≥ 15 EL.U/mL.

*Only results for post booster dose were analyzed and presented in the report.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort.

- The Total Vaccinated cohort included all subjects who received the booster dose.

Analysis of immunogenicity:

The analysis of immunogenicity was performed on the Total Vaccinated cohort on the subjects for whom immunogenicity data were available.

Geometric Mean Concentrations (GMCs) and seropositivity (percentage of subjects with antibody concentrations equal to or above the assay cut-off) or seroprotection rates (percentage of subjects with antibody concentrations or antibody titers equal to or above a protective level) for all antibodies were calculated one month after the administration of the booster dose with 95% Confidence Intervals (CI).

Seroconversion rate for anti-measles, anti-mumps and anti-rubella antibodies were calculated one month after the booster dose with exact 95% CI.

Analysis of safety:

The analysis of safety was performed on the Total Vaccinated cohort on the subjects for whom safety data were available. For the solicited symptoms, the percentage of subjects for whom the symptom was reported during the 8-day (Day 0 – 7) follow-up period was summarised with exact 95% CI. The percentage of subjects for whom unsolicited AEs were reported within 31 days (Day 0 – 30) following booster dose administration was tabulated according to the World Health Organisation (WHO) preferred term. The occurrence of SAEs up to 6 months after the administration of the booster dose was tabulated according to the WHO preferred term.

Study Population: Male or female infants between 12 and 15 months of age at the time of booster vaccination, vaccinated in the primary study and free of obvious health problems as established by medical history and clinical examination before entering into the study. Written informed consent was obtained from a parent or guardian of each subject prior to study entry.

Number of subjects	MMR + Hib
Planned, N	61
Entered, N (Total Vaccinated cohort)	47
Completed, n (%)	47 (100)
Total Number Subjects Withdrawn, n (%)	0 (0.0)
Withdrawn due to AEs, n (%)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)
Demographics	MMR + Hib
N (Total Vaccinated cohort)	47
Females:Males	20:27
Mean Age, months (SD)	13.3 (0.73)
White/Caucasian, n (%)	47 (100)

Primary Efficacy Results:
 Percentage of subjects for whom solicited local symptoms were reported within the 8-day (Day 0 - 7) follow-up period after the booster dose (Total Vaccinated cohort)

Symptoms	Intensity	n	%	95% CI	
				LL	UL
N = 46					
MMR+Hib					
Pain	Any	16	34.8	21.4	50.2
	Grade 3	2	4.3	0.5	14.8
Rash (Local)	Any	0	0.0	0.0	7.7
	Grade 3*	-	-	-	-
Redness	Any	15	32.6	19.5	48.0
	> 30 mm	0	0.0	0.0	7.7
Swelling	Any	8	17.4	7.8	31.4
	> 30 mm	1	2.2	0.1	11.5

N: number of subjects with a symptom sheet completed
 n (%): number (percentage) of subjects for whom a specific symptom was reported
 Any: incidence of a particular symptom regardless of grade
 Grade 3 Pain: cried when limb was moved / spontaneously painful
 95% CI: exact 95% Confidence Interval; LL: lower limit, UL: upper limit
 * No information about intensity was collected for rash

Primary Efficacy Results
 Percentage of subjects for whom solicited general symptoms were reported within the 8-day (Day 0 – 7) follow-up period after the booster dose (Total Vaccinated cohort)

Symptoms	Intensity/ Relationship	n	%	95% CI	
				LL	UL
N = 46					
MMR+Hib					
Drowsiness	Any	2	4.3	0.5	14.8
	Grade 3	0	0.0	0.0	7.7
	Related	2	4.3	0.5	14.8
Irritability	Any	18	39.1	25.1	54.6
	Grade 3	0	0.0	0.0	7.7
	Related	14	30.4	17.7	45.8
Loss of Appetite	Any	15	32.6	19.5	48.0
	Grade 3	1	2.2	0.1	11.5
	Related	13	28.3	16.0	43.5
Meningism*	Any	0	0.0	0.0	7.7
	Grade 3	0	0.0	0.0	7.7
	Related	0	0.0	0.0	7.7
Parotid/salivary gland Swelling	Any	0	0.0	0.0	7.7
	Grade 3	-	-	-	-
	Related	0	0.0	0.0	7.7
Rash ** (generalised)	Any	0	0.0	0.0	7.7
	Grade 3	0	0.0	0.0	7.7
	Related	0	0.0	0.0	7.7
Fever (Rectal)	≥ 38.0°C	16	34.8	21.4	50.2
	> 40.0°C	1	2.2	0.1	11.5
	Related	12	26.1	14.3	41.1

N: number of subjects with a symptom sheet completed
 n (%): number (percentage) of subjects for whom a specific symptom was reported
 Any: incidence of a particular symptom regardless of grade and relationship to vaccination
 Grade 3: symptom which prevented normal everyday activities
 Grade 3 irritability: crying that could not be comforted
 Grade 3 loss of appetite: not eating at all
 Related: symptoms considered by the investigator to have a causal relationship to study vaccination

<p>95% CI: exact 95% Confidence Interval; LL: lower limit, UL: upper limit * suspected signs of meningism ** No information about intensity was collected for rash 95% CI: exact 95% Confidence Interval; LL: lower limit, UL: upper limit</p>											
<p>Secondary Outcome Variable (s): GMCs and seroprotection rate for anti-PRP antibodies one month after the booster dose (Total Vaccinated cohort)</p>											
N	≥ 0.15 µg/mL				≥ 1 µg/mL				GMC		
	N	%	95% CI		n	%	95% CI		Value	95% CI	
			LL	UL			LL	UL		LL	UL
37	37	100	90.5	100	37	100	90.5	100	53.627	37.118	77.477
<p>N = number of subjects with available results n(%) = number (percentage) of subjects with specified antibody concentrations 95% CI = 95% Confidence Interval; LL: lower limit; UP: upper limit</p>											
<p>Secondary Outcome Variables: Seroconversion rate and GMCs for anti-measles, anti-mumps and anti-rubella antibodies one month after the booster dose (Total Vaccinated cohort)</p>											
Antibody	N	Seroconversion rate				GMC					
		n	%	95% CI		Value	95% CI				
				LL	UL		LL	UL			
Anti-measles (< 150 mIU/mL)	40	40	100	91.2	100	4423.4	3779.8	5176.4			
Anti-mumps (≥ 231 U/mL)	43	38	88.4	74.9	96.1	1021.9	728.5	1433.6			
Anti-rubella (< 4 IU/mL)	43	43	100	91.8	100	66.9	53.5	83.7			
<p>N = number of subjects with available results Seroconversion rate was defined as the appearance of antibody concentrations ≥ cut-off values in subjects who were initially seronegative n(%) = number (percentage) of subjects with specified antibody concentrations 95% CI = 95% Confidence Interval; LL: lower limit; UP: upper limit</p>											
<p>Secondary Outcome Variables: Seroprotection rate and GMCs for anti-diphtheria and anti-tetanus antibodies one month after the booster dose (Total Vaccinated cohort)</p>											
Antibody	N	≥ 0.1 IU/mL				GMC					
		n	%	95% CI		Value	95% CI				
				LL	UL		LL	UL			
Anti-Diphtheria	37	23	62.2	44.8	77.5	0.13	0.10	0.17			
Anti-Tetanus	37	37	100	90.5	100	3.27	2.37	4.52			
<p>N = number of subjects with available results n(%) = number (percentage) of subjects with specified antibody concentrations 95% CI = 95% Confidence Interval; LL: lower limit; UP: upper limit</p>											
<p>Secondary Outcome Variables: Seroprotection rate and GMCs for anti-HBs antibodies one month after the booster dose (Total Vaccinated cohort)</p>											
N	≥ 10 mIU/mL				GMC						
	n	%	95% CI		Value	95% CI					
			LL	UL		LL	UL				
37	36	97.3	85.8	99.9	157.3	107.5	230.3				
<p>N = number of subjects with available results n(%) = number (percentage) of subjects with specified antibody concentrations 95% CI = 95% Confidence Interval; LL: lower limit; UP: upper limit</p>											
<p>Secondary Outcome Variables: Seropositivity rate and GMCs for anti-BPT antibodies one month after the booster dose (Total Vaccinated cohort)</p>											
N	≥ 15 EL.U/mL				GMC						
	n	%	95% CI		Value	95% CI					
			LL	UL		LL	UL				
39	25	64.1	47.2	78.8	19.0	14.5	24.8				
<p>N = number of subjects with available results n(%) = number (percentage) of subjects with specified antibody concentrations 95% CI = 95% Confidence Interval; LL: lower limit; UP: upper limit</p>											

Safety Results: Number (%) of subjects with unsolicited AEs (Total Vaccinated cohort)	
Most Frequent AEs - On-Therapy (occurring within day 0-30 following vaccination)	MMR + Hib N = 47
Subjects with any AE(s), n(%)	25 (53.2)
Upper respiratory tract infection	6 (12.8)
Pharyngitis	4 (8.5)
Diarrhoea	3 (6.4)
Rhinitis	3 (6.4)
Fever	2 (4.3)
Otitis media	2 (4.3)
Asthma	1 (2.1)
Bronchitis	1 (2.1)
Bronchospasm	1 (2.1)
Dermatitis	1 (2.1)
Gastroenteritis	1 (2.1)
Laryngitis	1 (2.1)
Moniliasis	1 (2.1)
Otitis externa	1 (2.1)
Pneumonia	1 (2.1)
Vomiting	1 (2.1)
Safety Results: Number (%) of subjects with SAEs reported up to Day 30 after vaccination (Day 0 - 30) (Total Vaccinated cohort)	
SAE, n (%) [n considered by the investigator to be related to study medication]	
All SAEs	MMR + Hib N = 47
Subjects with any SAE(s), n (%) [n related]	1 (2.1) [0]
Pneumonia	1 (2.1) [0]
Fatal SAEs	MMR + HiB N = 47
Subjects with any fatal SAE(s)	0 (0.0) [0]
Primary Efficacy Results: Number (%) of subjects with late SAEs reported from Day 31 after vaccination up to Month 6 (Total Vaccinated cohort)	
SAE, n (%) [n considered by the investigator to be related to study medication]	
All SAEs	MMR + Hib N = 47
Subjects with any SAE(s), n (%) [n related]	0 (0.0) [0]
Fatal SAEs	MMR + HiB N = 47
Subjects with any fatal SAE(s)	0 (0.0) [0]

Conclusion:

Pain was the most frequently reported solicited local symptom (34.8%) during the 8-day follow-up period. Irritability was the most frequently reported solicited general symptom (39.1%) during the 8-day follow-up period. One month after the booster dose, all subjects had anti-PRP, anti-measles, anti-rubella and anti-tetanus antibody concentrations \geq the cut-off values; 88.4% 62.2%, 97.3% and 64.1% of the subjects had concentrations \geq the cut-off values for anti-mumps, anti-diphtheria, anti-HBs and anti-BPT antibodies, respectively. The percentage of subjects for whom at least one unsolicited AE was reported during the 31-day follow-up after vaccination was 53.2%, upper respiratory tract infection being the most frequent (12.8%). One case of non-vaccine related SAE, namely pneumonia, was reported. No fatal SAE was reported during the study period.

Publications: No Publication

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