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Study No.: 102547 (Hib-MenC-TT-010)
Title: A Phase III open, multicentre, booster vaccination study to assess the immunogenicity, safety and reactogenicity of a booster dose of GlaxoSmithKline (GSK) Biologicals' <i>Haemophilus influenzae</i> type b-meningococcal serogroup C conjugate vaccine (Hib-MenC) compared to a booster dose of <i>Infanrix hexa</i> (combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio-Hib vaccine) when given to 14-month-old subjects who were primed in study 217744/097 (DTPa-HBV-IPV-097). <i>Infanrix™ hexa</i> : GlaxoSmithKline Biologicals' combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio and <i>Haemophilus influenzae</i> type b vaccine (DTPa-HBV-IPV/Hib).
Rationale: The purpose of this study was to assess the immunogenicity and safety of a booster dose of a Hib-MenC conjugate vaccine in subjects primed with either Hib-MenC co-administered with DTPa-HBV/IPV vaccine or with a licensed MenC-TT vaccine* co-administered with Hib vaccine reconstituted with a DTPa containing vaccine, compared to a booster dose of DTPa-HBV-IPV/Hib vaccine in subjects primed with a licensed MenC-CRM ₁₉₇ vaccine co-administered with DTPa-HBV-IPV/Hib. *MenC-TT vaccine: Neis vac-C from Baxter; ** MenC-CRM ₁₉₇ vaccine: Meningitec from Wyeth.
Phase: III.
Study Period: 08 November 2004 until 17 March 2005.
Study Design: Open (double-blind for Hib-MenC lots) multicentre study with 3 parallel groups.
Centres: Sixteen centres in Spain.
Indication: Booster vaccination against Hib and MenC diseases.
Treatment: The study groups were as follows: <ul style="list-style-type: none"> • HibMenC group: primed with Hib-MenC (co-administered with DTPa-HBV/IPV), boosted with Hib-MenC. • MenCTT group: primed with MenC-TT vaccine (co-administered with DTPa-(HBV)-IPV/Hib), boosted with Hib-MenC. • MenCCRM group: primed with MenC-CRM₁₉₇ vaccine (co-administered with DTPa-HBV-IPV/Hib), boosted with DTPa-HBV-IPV/Hib. <p>To analyse the post-booster data, subjects boosted with Hib-MenC were pooled across primary vaccination schedules into HibCPoo group (Hib-MenC and MenCTT groups). Vaccines were administered intramuscularly in the left upper thigh.</p>
Objectives: <ul style="list-style-type: none"> • To evaluate the non-inferiority in terms of the percentage of subjects with anti-polyribosylribitol phosphate (anti-PRP) antibody concentrations $\geq 1.0 \mu\text{g/mL}$ induced by a booster dose of a Hib-MenC vaccine after a primary vaccination with either Hib-MenC or a licensed MenC-TT vaccine versus a booster dose of DTPa-HBV-IPV/Hib after primary vaccination with a licensed MenC-CRM₁₉₇ vaccine (control group) when given to toddlers aged 14 months. • To evaluate the immunogenicity in terms of the percentage of subjects with serum bactericidal assay/activity against <i>N. meningitidis</i> serogroup C (SBA-MenC) titres $\geq 1:128$ induced by a booster dose of a Hib-MenC vaccine in toddlers aged 14 months who had been primed with either Hib-MenC or a licensed MenC-TT vaccine.
Primary Outcome/Efficacy Variable(s): One month after the booster vaccination: <ul style="list-style-type: none"> • In all subjects: anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$, • In subjects boosted with the Hib-MenC vaccine: SBA-MenC titres $\geq 1:128$.
Secondary Outcome Variable(s): <i>Immunogenicity:</i> Prior to the booster vaccination: <i>In all subjects</i> <ul style="list-style-type: none"> • Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$ and $\geq 1.0 \mu\text{g/mL}$, • SBA-MenC titres $\geq 1:8$ and $\geq 1:128$, • Anti-polysaccharide C (anti-PSC) antibody concentrations $\geq 0.3 \mu\text{g/mL}$ and $\geq 2.0 \mu\text{g/mL}$, • Anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$, • Geometric Mean Concentrations (GMCs) for anti-PRP and anti-tetanus antibodies. <i>In a subset of 50% of subjects</i> <ul style="list-style-type: none"> • Anti-diphtheria antibody concentrations $\geq 0.1 \text{ IU/mL}$ by ELISA or $\geq 0.016 \text{ IU/mL}$ by Vero-cell neutralisation test (if anti-diphtheria antibody concentrations $< 0.1 \text{ IU/mL}$ by ELISA), • Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentrations $\geq 5 \text{ EL.U/mL}$, • Anti-hepatitis B surface antigen (anti-HBs) antibody concentrations $\geq 10 \text{ mIU/mL}$,

- Anti-poliovirus type 1, 2 & 3 titres ≥ 8 .
- GMCs or Geometric Mean Titres (GMTs) for, SBA-MenC, anti-PSC, anti-diphtheria, anti-PT, anti-FHA, anti-PRN, anti-HBs antibodies and anti-poliovirus types 1, 2 & 3.

One month after the booster vaccination:

In all subjects

- Anti-PRP antibody concentrations $\geq 0.15 \mu\text{g/mL}$,
- SBA-MenC titres $\geq 1:8$,
- Anti-PSC antibody concentrations $\geq 0.3 \mu\text{g/mL}$ and $\geq 2.0 \mu\text{g/mL}$,
- Anti-tetanus antibody concentrations $\geq 0.1 \text{ IU/mL}$,
- GMCs or GMTs for anti-PRP, SBA-MenC, anti-PSC and anti-tetanus antibodies.

Safety:

- Occurrence of solicited local and general symptoms during the 4-day (Day 0-3) follow-up period,
- Occurrence of unsolicited adverse events (AEs) during the 31-day (Day 0-30) follow-up period,
- Occurrence of serious adverse events (SAEs) over the full course of the study.

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 dose.
- The ATP cohort for the antibody persistence included all subjects who received the 3 primary vaccine doses and the booster vaccine dose and who did not receive a vaccine forbidden as per protocol.
- 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 and the analysis of antibody response were based on the ATP cohort for antibody persistence and the ATP cohort for immunogenicity, respectively.

For each group, GMCs or GMTs and seroconversion/seroprotection/seropositivity rates for all antibodies were calculated one month after the primary vaccination course and before the booster vaccine dose with their 95% confidence intervals (CIs). For each group, GMCs or GMTs and seroconversion/seroprotection/seropositivity rates for anti-PRN, SBA-MenC, anti-PSC and anti-tetanus antibodies were calculated at pre- and post-booster vaccination with their 95% CI.

With respect to the co-primary study objectives, non-inferiority was concluded if the upper limit of the standardised asymptotic 95% CI on the difference in the percentage of subjects with anti-PRP antibody concentrations $\geq 1.0 \mu\text{g/mL}$ post-booster between the MenCCRM control group and the HibCPoo groups was below the non-inferiority limit of 5%. If the first co-primary objective was met, then the second co-primary objective (immunogenicity in terms of the percentage of subjects with a SBA-MenC titre $\geq 1:128$ induced by a booster dose of Hib-MenC vaccine primed with either Hib-MenC or MenC-TT) was demonstrated if the lower limit of the exact 95% CI on the percentage of subjects with a SBA-MenC titre $\geq 1:128$ in the HibCPoo group was above 90%.

Analysis of Safety:

The analysis of safety was performed on the Total Vaccinated Cohort. For each solicited local and general symptom, the percentage of subjects with the symptom reported within the 4 days (Day 0-3) following vaccination and its exact 95% CI was summarised by vaccine group. The same tabulation was performed for grade 3 symptoms and for solicited general symptoms with a reasonable possibility of being related to vaccination. The percentage of subjects with unsolicited adverse events (AEs) reported within 31 days (Day 0-30) following vaccination was summarised by vaccine group according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The occurrence of serious adverse events (SAEs) during the entire study period was tabulated according to the MedDRA preferred term.

Study Population: Healthy male or female subjects between, and including, 13 and 14 months of age at the time of booster vaccination, who had participated in the primary vaccination study. Subjects were free of obvious health problems as established by medical history and clinical examination before entering into the study. Written informed consent was obtained from the parent(s) or guardian(s) of the subjects prior to study entry.

Number of subjects	HibMenC	MenCTT	HibCPoo	MenCCRM
Planned, N	117	234	351	117
Randomised, N (Total Vaccinated Cohort)	87	178	265	93
Completed, n (%)	87 (100)	178 (100)	265 (100)	92 (98.9)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable
Withdrawn for other reasons, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Demographics	HibMenC	MenCTT	HibCPoo	MenCCRM
N (Total Vaccinated Cohort)	87	178	265	93
Females:Males	45:42	83:95	128:137	49:44
Mean Age, months (SD)	13.3 (0.50)	13.4 (0.54)	13.4 (0.53)	13.3 (0.49)
White/Caucasian, n (%)	71 (81.6)	162 (91.0)	233 (87.9)	83 (89.2)

Primary Efficacy Results: Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for immunogenicity).													
Group	Timing	N	≥ 0.15 µg/mL				≥ 1.0 µg/mL				GMC (µg/mL)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PRE	80	77	96.3	89.4	99.2	40	50.0	38.6	61.4	0.966	0.739	1.265
	PI(M1)	81	81	100	95.5	100	81	100*	95.5	100	63.848	49.349	82.608
MenCTT	PRE	167	160	95.8	91.6	98.3	75	44.9	37.2	52.8	0.918	0.767	1.098
	PI(M1)	165	165	100	97.8	100	163	98.8*	95.7	99.9	77.154	62.866	94.690
HibCPoo	PRE	247	237	96.0	92.7	98.0	115	46.6	40.2	53.0	0.934	0.805	1.083
	PI(M1)	246	246	100	98.5	100	244	99.2*	97.1	99.9	72.492	61.725	85.138
MenCCRM	PRE	84	73	86.9	77.8	93.3	31	36.9	26.6	48.1	0.633	0.482	0.832
	PI(M1)	86	86	100	95.8	100	86	100*	95.8	100	52.400	40.363	68.027
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentrations ≥ specified cut-off 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Pre-booster dose PI(M1) = Post-booster dose (Month 1) * primary efficacy results													
Primary Efficacy Results: Difference in the percentage of subjects with anti-PRP concentrations ≥ 1.0 µg/mL, one month after the booster dose (ATP cohort for immunogenicity).													
≥ 1.0 µg/mL						Difference		%		95 % CI			
Group 1	N	%	Group 2	N	%					LL		UL	
HibCPoo	246	99.2	MenCCRM	86	100	MenCCRM - HibCPoo		0.81		-3.47		2.92*	
N = number of subjects with available results % = percentage of subjects with anti-PRP concentrations ≥ 1.0 µg/mL 95% CI = 95% Standardised asymptotic confidence interval; LL = Lower Limit, UL = Upper Limit * As the UL of the standardised asymptotic 95%CI was below 5%, non-inferiority was shown.													
Primary Efficacy Results: Seroprotection rates and GMCs for SBA-MenC antibodies (ATP cohort for immunogenicity).													
Group	Timing	N	≥ 1:8				≥ 1:128				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PRE	78	75	96.2	89.2	99.2	66	84.6	74.7	91.8	365.2	267.0	499.6
	PI(M1)	81	81	100	95.5	100	81	100*	95.5	100	5266.2	4265.6	6501.3
MenCTT	PRE	160	145	90.6	85.0	94.7	96	60.0	52.0	67.7	130.2	102.4	165.5
	PI(M1)	167	166	99.4	96.7	100	166	99.4*	96.7	100	11710.5	9441.5	14524.8
HibCPoo	PRE	238	220	92.4	88.3	95.5	162	68.1	61.7	73.9	182.5	149.5	222.9
	PI(M1)	248	247	99.6	97.8	100	247	99.6*	97.8^	100	9020.2	7637.2	10653.5
MenCCRM	PRE	78	67	85.9	76.2	92.7	44	56.4	44.7	67.6	122.1	80.7	184.8
	PI(M1)	84	65	77.4	67.0	85.8	47	56.0*	44.7	66.8	94.1	59.6	148.7
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody titres ≥ specified cut-off 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = Pre-booster dose PI(M1) = Post-booster dose (Month 1) * Primary efficacy results ^ The second co-primary objective was reached as the lower limit of the exact 95% CI for the percentage of subjects with SBA-Men titers ≥ 1:128 post-booster in the HibCPoo group (boosted with Hib-MenC) was above 90%.													
Secondary Outcome Variables: Seroprotection rates and GMCs for anti-PRP antibodies (ATP cohort for antibody persistence).													
Group*	Timing	N	≥ 0.15 µg/mL				≥ 1.0 µg/mL				GMC (µg/mL)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PIII(M7)	84	84	100	95.7	100	82	97.6	91.7	99.7	13.069	10.536	16.212
	PRE	83	80	96.4	89.8	99.2	41	49.4	38.2	60.6	0.963	0.742	1.251
MenCTT	PIII(M7)	176	176	100	97.9	100	163	92.6	87.7	96.0	7.113	5.970	8.474
	PRE	178	171	96.1	92.1	98.4	80	44.9	37.5	52.6	0.908	0.764	1.079
MenCCRM	PIII(M7)	90	89	98.9	94.0	100	75	83.3	74.0	90.4	4.302	3.183	5.814
	PRE	88	76	86.4	77.4	92.8	32	36.4	26.4	47.3	0.617	0.473	0.806
N = number of subjects with available results													

<p>n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PIII(M7) = Post Dose 3, Month 7, i.e. one month after primary vaccination course PRE = Pre-booster dose * Results were not available for the HibCPoo group.</p>													
Secondary Outcome Variable(s): Seroprotection rates and GMTs for SBA-MenC antibodies (ATP cohort for antibody persistence).													
Group*	Timing	N	$\geq 1:8$				$\geq 1:128$				GMT		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PIII(M7)	84	84	100	95.7	100	83	98.8	93.5	100	2697.9	2207.6	3297.0
	PRE	81	78	96.3	89.6	99.2	68	84.0	74.1	91.2	366.1	270.1	496.2
MenCTT	PII(M6)	174	174	100	97.9	100	170	97.7	94.2	99.4	1419.0	1205.3	1670.6
	PRE	169	153	90.5	85.1	94.5	101	59.8	52.0	67.2	131.0	103.5	165.6
MenCCRM	PIII(M7)	90	89	98.9	94.0	100	88	97.8	92.2	99.7	1871.6	1465.1	2390.9
	PRE	82	70	85.4	75.8	92.2	46	56.1	44.7	67.0	120.5	80.2	180.9
<p>N = number of subjects with available results n (%) = number (percentage) of subjects with antibody titres \geq specified cut-off 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PII (M6) = Post Dose 2, Month 6 PIII(M7) = Post Dose 3, Month 7, i.e. one month after primary vaccination course PRE = Pre-booster dose * Results were not available for the HibCPoo group.</p>													
Secondary Outcome Variable(s): Seropositivity rates and GMCs for anti-PSC antibodies (ATP cohort for antibody persistence).													
Group*	Timing	N	$\geq 0.3 \mu\text{g/mL}$				$\geq 2.0 \mu\text{g/mL}$				GMC ($\mu\text{g/mL}$)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PIII(M7)	76	76	100	95.3	100	76	100	95.3	100	22.08	19.02	25.62
	PRE	83	78	94.0	86.5	98.0	20	24.1	15.4	34.7	1.05	0.88	1.26
MenCTT	PII(M6)	173	173	100	97.9	100	167	96.5	92.6	98.7	10.43	9.33	11.67
	PRE	174	120	69.0	61.5	75.7	9	5.2	2.4	9.6	0.47	0.41	0.54
MenCCRM	PIII(M7)	86	86	100	95.8	100	86	100	95.8	100	24.78	21.16	29.01
	PRE	87	80	92.0	84.1	96.7	43	49.4	38.5	60.4	1.53	1.21	1.93
<p>N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PII (M6) = Post Dose 2, Month 6 PIII(M7) = Post dose 3, Month 7, i.e. one month after primary vaccination course PRE = Pre-booster dose * Results were not available for the HibCPoo group.</p>													
Secondary Outcome Variable(s): Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies (ATP cohort for antibody persistence).													
Antibody	Group*	Timing	N	$\geq 0.1 \text{ IU/mL}$				GMC (IU/mL)					
				n	%	95% CI		Value	95% CI				
						LL	UL		LL	UL			
Anti-diphtheria [^]	HibMenC	PIII(M7)	84	83	98.8	93.5	100	2.860	2.328	3.513			
		PRE	39	38	97.4	86.5	99.9	0.899	0.637	1.267			
	MenCTT	PIII(M7)	176	175	99.4	96.9	100	2.155	1.888	2.461			
		PRE	86	83	96.5	90.1	99.3	0.555	0.441	0.698			
	MenCCRM	PIII(M7)	90	90	100	96.0	100	3.495	2.999	4.074			
		PRE	44	44	100	92.0	100	0.732	0.556	0.963			
Anti-tetanus	HibMenC	PIII(M7)	84	84	100	95.7	100	4.220	3.742	4.759			
		PRE	83	82	98.8	93.5	100	0.659	0.573	0.759			
	MenCTT	PIII(M7)	176	176	100	97.9	100	4.446	3.997	4.946			
		PRE	178	174	97.8	94.3	99.4	0.626	0.549	0.713			
	MenCCRM	PIII(M7)	90	90	100	96.0	100	2.721	2.292	3.231			
		PRE	88	81	92.0	84.3	96.7	0.331	0.274	0.401			
<p>N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off</p>													

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 PIII(M7) = Post dose 3, Month 7, i.e. one month after primary vaccination course
 PRE = Pre-booster dose
 * Results were not available for the HibCPoo group.
 ^ Four subjects with anti-diphtheria concentrations <0.1 IU/mL in the groups primed with Hib-MenC (1 subject) or MenC-TT (3 subjects) were also tested with the Vero-cell neutralization test at the pre-booster time point. For the 3 subjects in the MenC-TT primed group the results of the Vero-cell neutralization test were ≥ 0.016 IU/mL.

Secondary Outcome Variable(s): Seropositivity rates and GMCs for anti-PT, anti-FHA and anti-PRN antibodies (ATP cohort for antibody persistence).

Antibody	Group*	Timing	N	≥ 5 EL.U/mL				GMC (EL.U/mL)			
				n	%	95% CI		Value	95% CI		
						LL	UL		LL	UL	
Anti-PT	HibMenC	PIII(M7)	84	84	100	95.7	100	59.9	52.6	68.2	
		PRE	37	30	81.1	64.8	92.0	8.9	6.8	11.7	
	MenCTT	PIII(M7)	176	176	100	97.9	100	56.1	51.6	61.0	
		PRE	84	58	69.0	58.0	78.7	7.6	6.3	9.1	
	MenCCRM	PIII(M7)	90	90	100	96.0	100	60.6	53.9	68.2	
		PRE	44	31	70.5	54.8	83.2	7.5	5.8	9.7	
Anti-FHA	HibMenC	PIII(M7)	84	84	100	95.7	100	303.8	265.6	347.6	
		PRE	39	39	100	91.0	100	56.3	45.0	70.5	
	MenCTT	PIII(M7)	176	176	100	97.9	100	282.9	256.4	312.2	
		PRE	86	85	98.8	93.7	100	57.2	46.6	70.3	
	MenCCRM	PIII(M7)	90	90	100	96.0	100	313.0	277.2	353.4	
		PRE	44	44	100	92.0	100	52.4	41.4	66.3	
Anti-PRN	HibMenC	PIII(M7)	84	84	100	95.7	100	187.6	160.9	218.7	
		PRE	39	37	94.9	82.7	99.4	24.6	18.7	32.4	
	MenCTT	PIII(M7)	176	176	100	97.9	100	160.5	143.3	179.8	
		PRE	86	81	94.2	87.0	98.1	25.0	20.2	31.0	
	MenCCRM	PIII(M7)	90	90	100	96.0	100	152.3	132.1	175.5	
		PRE	44	41	93.2	81.3	98.6	18.4	14.2	23.8	

N = number of subjects with available results
 n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off
 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 PIII(M7) = Post dose 3, Month 7, i.e. one month after primary vaccination course
 PRE = Pre-booster dose
 * Results were not available for the HibCPoo group.

Secondary Outcome Variable(s): Seroprotection rates and GMCs for anti-HBs antibodies (ATP cohort for antibody persistence).

Group*	Timing	N	≥ 10 mIU/mL				GMC (mIU/mL)			
			n	%	95% CI		Value	95% CI		
					LL	UL		LL	UL	
HibMenC	PIII(M7)	84	83	98.8	93.5	100	697.6	509.2	955.7	
	PRE	39	39	100	91.0	100	135.2	90.8	201.4	
MenCTT	PIII(M7)	175	173	98.9	95.9	99.9	916.5	746.6	1125.1	
	PRE	85	83	97.6	91.8	99.7	206.0	150.4	282.2	
MenCCRM	PIII(M7)	89	85	95.5	88.9	98.8	579.2	410.4	817.3	
	PRE	42	37	88.1	74.4	96.0	108.0	66.1	176.4	

N = number of subjects with available results
 n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off
 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
 PIII(M7) = Post dose 3, Month 7, i.e. one month after primary vaccination course
 PRE = Pre-booster dose
 * Results were not available for the HibCPoo group.

Secondary Outcome Variable(s): Seroprotection rates and GMTs for anti-poliovirus types 1, 2 & 3 (ATP cohort for antibody persistence).

Antibody	Group*	Timing	N	$\geq 1:8$				GMT			
				n	%	95% CI		Value	95% CI		
						LL	UL		LL	UL	
Anti-poliovirus	HibMenC	PIII(M7)	74	74	100	95.1	100	744.8	560.0	990.7	
		PRE	36	32	88.9	73.9	96.9	142.6	80.6	252.2	

type 1	MenCTT	PIII(M7)	158	158	100	97.7	100	728.9	614.2	864.9
		PRE	79	79	100	95.4	100	207.4	153.4	280.4
	MenCCRM	PIII(M7)	76	76	100	95.3	100	800.4	598.6	1070.4
		PRE	41	38	92.7	80.1	98.5	170.9	98.1	297.5
Anti-poliovirus type 2	HibMenC	PIII(M7)	63	63	100	94.3	100	384.7	269.9	548.3
		PRE	37	34	91.9	78.1	98.3	109.2	64.2	185.9
	MenCTT	PIII(M7)	153	153	100	97.6	100	433.7	344.1	546.7
		PRE	76	71	93.4	85.3	97.8	130.3	91.3	185.8
	MenCCRM	PIII(M7)	74	73	98.6	92.7	100	505.2	372.8	684.5
		PRE	41	38	92.7	80.1	98.5	110.1	70.7	171.4
Anti-poliovirus type 3	HibMenC	PIII(M7)	72	72	100	95.0	100	1497.7	1183.3	1895.7
		PRE	37	37	100	90.5	100	345.5	230.9	517.1
	MenCTT	PIII(M7)	156	156	100	97.7	100	1217.6	1016.3	1458.9
		PRE	78	78	100	95.4	100	432.6	310.4	603.0
	MenCCRM	PIII(M7)	69	69	100	94.8	100	1448.1	1108.6	1891.5
		PRE	41	40	97.6	87.1	99.9	341.1	218.8	531.8

N = number of subjects with available results

n (%) = number (percentage) of subjects with antibody titres \geq specified cut-off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PIII(M7) = Post dose 3, Month 7, i.e. one month after primary vaccination course

PRE = Pre-booster dose

* Results were not available for the HibCPoo group.

Secondary Outcome Variable(s): Seropositivity rates and GMCs for anti-PSC antibodies (ATP cohort for immunogenicity).

Group	Timing	N	$\geq 0.3 \mu\text{g/mL}$				$\geq 2.0 \mu\text{g/mL}$				GMC ($\mu\text{g/mL}$)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC	PRE	80	75	93.8	86.0	97.9	20	25.0	16.0	35.9	1.05	0.87	1.28
	PI(M1)	81	81	100	95.5	100	76	93.8	86.2	98.0	7.23	6.02	8.69
MenCTT	PRE	164	111	67.7	59.9	74.8	8	4.9	2.1	9.4	0.46	0.40	0.53
	PI(M1)	163	162	99.4	96.6	100	153	93.9	89.0	97.0	10.07	8.50	11.92
HibCPoo	PRE	244	186	76.2	70.4	81.4	28	11.5	7.8	16.2	0.60	0.53	0.69
	PI(M1)	244	243	99.6	97.7	100	229	93.9	90.1	96.5	9.02	7.93	10.26
MenCCRM	PRE	83	76	91.6	83.4	96.5	42	50.6	39.4	61.8	1.54	1.22	1.96
	PI(M1)	84	78	92.9	85.1	97.3	31	36.9	26.6	48.1	1.30	1.03	1.63

N = number of subjects with available results

n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-booster dose

PI(M1) = Post-booster dose (Month 1)

Secondary Outcome Variable(s): Seroprotection rates and GMCs for anti-tetanus antibodies (ATP cohort for immunogenicity).

Group	Timing	N	$\geq 0.1 \text{ IU/mL}$				GMC (IU/mL)			
			n	%	95% CI		Value	95% CI		
					LL	UL		LL	UL	
HibMenC	PRE	80	79	98.8	93.2	100	0.645	0.560	0.744	
	PI(M1)	81	81	100	95.5	100	5.483	4.687	6.415	
MenCTT	PRE	167	163	97.6	94.0	99.3	0.615	0.536	0.706	
	PI(M1)	165	165	100	97.8	100	7.030	5.927	8.338	
HibCPoo	PRE	247	242	98.0	95.3	99.3	0.625	0.564	0.693	
	PI(M1)	246	246	100	98.5	100	6.478	5.712	7.346	
MenCCRM	PRE	84	77	91.7	83.6	96.6	0.333	0.273	0.406	
	PI(M1)	85	85	100	95.8	100	4.398	3.603	5.368	

N = number of subjects with available results

n (%) = number (percentage) of subjects with antibody concentrations \geq specified cut-off

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = Pre-booster dose

PI(M1) = Post-booster dose (Month 1)

Secondary Outcome Variable(s): Number and percentage of subjects with solicited local symptoms within the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort).

Symptom	Intensity	HibMenC (N = 87)				MenCTT (N = 178)			
		n	%	95 % CI		n	%	95 % CI	
				LL	UL			LL	UL
Pain	Any	19	21.8	13.7	32.0	39	21.9	16.1	28.7
	Grade 3	0	0.0	0.0	4.2	2	1.1	0.1	4.0
Redness	Any	34	39.1	28.8	50.1	69	38.8	31.6	46.3
	> 30 mm	5	5.7	1.9	12.9	10	5.6	2.7	10.1
Swelling	Any	19	21.8	13.7	32.0	55	30.9	24.2	38.2
	> 30 mm	2	2.3	0.3	8.1	3	1.7	0.3	4.8
		HibCPoo (N = 265)				MenCCRM (N = 93)			
Pain	Any	58	21.9	17.1	27.4	39	41.9	31.8	52.6
	Grade 3	2	0.8	0.1	2.7	2	2.2	0.3	7.6
Redness	Any	103	38.9	33.0	45.0	46	49.5	38.9	60.0
	> 30 mm	15	5.7	3.2	9.2	21	22.6	14.6	32.4
Swelling	Any	74	27.9	22.6	33.7	32	34.4	24.9	45.0
	> 30 mm	5	1.9	0.6	4.3	4	4.3	1.2	10.6

N = number of subjects with the booster administered dose
n (%) = number (percentage) of subjects for whom a specified symptom was reported at least once
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

Secondary Outcome Variable(s): Number and percentage of subjects with solicited general symptoms within the 4-day (Day 0-3) follow-up period (Total Vaccinated Cohort).

Symptom	Intensity/ Relationship	HibMenC (N = 87)				MenCTT (N = 178)			
		n	%	95 % CI		n	%	95 % CI	
				LL	UL			LL	UL
Drowsiness	Any	19	21.8	13.7	32.0	28	15.7	10.7	21.9
	Grade 3	0	0.0	0.0	4.2	0	0.0	0.0	2.1
	Related	17	19.5	11.8	29.4	20	11.2	7.0	16.8
Fever	≥ 38°C	14	16.1	9.1	25.5	26	14.6	9.8	20.7
	> 40.0°C	1	1.1	0.0	6.2	0	0.0	0.0	2.1
	Related	12	13.8	7.3	22.9	17	9.6	5.7	14.9
Irritability	Any	21	24.1	15.6	34.5	39	21.9	16.1	28.7
	Grade 3	1	1.1	0.0	6.2	1	0.6	0.0	3.1
	Related	17	19.5	11.8	29.4	32	18.0	12.6	24.4
Loss of appetite	Any	16	18.4	10.9	28.1	31	17.4	12.2	23.8
	Grade 3	2	2.3	0.3	8.1	2	1.1	0.1	4.0
	Related	13	14.9	8.2	24.2	22	12.4	7.9	18.1
		HibCPoo (N = 265)				MenCCRM (N = 93)			
Drowsiness	Any	47	17.7	13.3	22.9	25	26.9	18.2	37.1
	Grade 3	0	0.0	0.0	1.4	1	1.1	0.0	5.8
	Related	37	14.0	10.0	18.7	21	22.6	14.6	32.4
Fever (rectal)	≥ 38°C	40	15.1	11.0	20.0	25	26.9	18.2	37.1
	> 40.0°C	1	0.4	0.0	2.1	0	0.0	0.0	3.9
	Related	29	10.9	7.5	15.3	21	22.6	14.6	32.4
Irritability	Any	60	22.6	17.7	28.2	35	37.6	27.8	48.3
	Grade 3	2	0.8	0.1	2.7	1	1.1	0.0	5.8
	Related	49	18.5	14.0	23.7	32	34.4	24.9	45.0
Loss of appetite	Any	47	17.7	13.3	22.9	21	22.6	14.6	32.4
	Grade 3	4	1.5	0.4	3.8	0	0.0	0.0	3.9
	Related	35	13.2	9.4	17.9	20	21.5	13.7	31.2

N = number of subjects with the booster administered dose
n (%) = number (percentage) of subjects for whom a specified symptom was reported at least once
Any = Incidence of a particular solicited symptom regardless of grade or relationship to study vaccination.
Grade 3 drowsiness = Drowsiness that prevented normal everyday activities
Grade 3 irritability = Crying that could not be comforted
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 (Total Vaccinated Cohort).

Most frequent adverse events - On-Therapy (occurring within Day 0-30 following booster vaccination)	HibMenC N = 87	MenCTT N = 178	HibCPoo N = 265	MenCCRM N = 93
Subjects with any AE(s), n (%)	19 (21.8)	55 (30.9)	74 (27.9)	29 (31.2)
Upper respiratory tract infection	1 (1.1)	14 (7.9)	15 (5.7)	8 (8.6)
Gastroenteritis	4 (4.6)	8 (4.5)	12 (4.5)	5 (5.4)
Ear infection	2 (2.3)	6 (3.4)	8 (3.0)	2 (2.2)
Pyrexia	1 (1.1)	5 (2.8)	6 (2.3)	0 (0.0)
Rhinitis	2 (2.3)	3 (1.7)	5 (1.9)	1 (1.1)
Tonsillitis	2 (2.3)	3 (1.7)	5 (1.9)	1 (1.1)
Injection site nodule	1 (1.1)	1 (0.6)	2 (0.8)	5 (5.4)
Pharyngitis	0 (0.0)	4 (2.2)	4 (1.5)	0 (0.0)
Rash	2 (2.3)	2 (1.1)	4 (1.5)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.6)	1 (0.4)	3 (3.2)
Conjunctivitis	0 (0.0)	1 (0.6)	1 (0.4)	2 (2.2)
Injection site haemorrhage	0 (0.0)	1 (0.6)	1 (0.4)	2 (2.2)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Safety Results: Number (%) of subjects with serious adverse events (Total Vaccinated Cohort).				
Serious adverse event, n (%) [n considered by the investigator to be related to study medication]				
All SAEs	HibMenC N = 87	MenCTT N = 178	HibCPoo N = 265	MenCCRM N = 93
Subjects with any SAE(s), n (%) [n related]	1 (1.1) [0]	1 (0.6) [0]	2 (0.8) [0]	2 (2.2) [0]
Pneumonia	1 (1.1) [0]	1 (0.6) [0]	2 (0.8) [0]	0 (0.0) [0]
Gastroenteritis	1 (1.1) [0]	0 (0.0) [0]	1 (0.4) [0]	1 (1.1) [0]
Ear infection	1 (1.1) [0]	0 (0.0) [0]	1 (0.4) [0]	0 (0.0) [0]
Intussusception	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (1.1) [0]
Fatal SAEs	HibMenC	MenCTT	HibCPoo	MenCCRM
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion:

Please refer to the publication below.

Publications:

Tejedor JC et al. (2008) Immunogenicity and Reactogenicity of a Booster Dose of a Novel Combined Haemophilus influenzae Type b-Neisseria meningitidis Serogroup C-Tetanus Toxoid Conjugate Vaccine Given to Toddlers of 13–14 Months of Age With Antibody Persistence Up to 31 Months of Age. *Pediatr Infect Dis J.* 27(7): 579–588.

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