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Study No.: 103974 (Hib-MenC-TT-012)
Title: A phase III open (partially double-blind), controlled, multicentre, multicountry primary and booster vaccination study to demonstrate the non-inferiority of the meningococcal serogroup C immune response of GlaxoSmithKline (GSK) Biologicals' Hib-MenC vaccine co-administered with <i>Infanrix</i> -IPV versus a licensed meningococcal serogroup C vaccine co-administered with <i>Pediacel</i> when given according to a 2, 3, 4 month schedule and the immunogenicity of the Hib-MenC vaccine when given as a booster dose at 12-15 months of age.
Hib-MenC (<i>Menitorix</i>): GSK Biologicals' combined <i>Haemophilus influenzae</i> type b (Hib) and meningococcal serogroup C (MenC) tetanus toxoid conjugate vaccine. <i>Infanrix</i> -IPV: GSK Biologicals' combined diphtheria, tetanus, acellular pertussis, inactivated polio virus (DTPa-IPV) vaccine. <i>Pediacel</i> : Sanofi Pasteur's combined DTPa-IPV-Hib vaccine.
Rationale: The aim of this study was to demonstrate the non-inferiority of the MenC and Hib immune responses induced by Hib-MenC vaccine when given concomitantly with DTPa-IPV vaccine as 3 intramuscular doses to infants at 2, 3 and 4 months of age, compared to a licensed MenC conjugate vaccine† given concomitantly with DTPa-IPV-Hib.
† Meningitec: Wyeth's meningococcal serogroup C vaccine was used as control in this study (MenC). This study was conducted in 2 parts: the primary vaccination phase 103974 (HIB-MENC-TT-012) and the booster phase 104056 (HIB-MENC-TT-013 BST: 012). This CTRS report presents the results of the primary vaccination phase of the study. The results of the booster phase are presented in a separate document.
Phase: III
Study Period: 14 February 2005 to 05 September 2005
Study Design: Open (but double-blind with respect to the Hib-MenC lots), randomised (3:1), controlled multi-centre, multi-country study with 2 parallel groups.
Centres: 10 centres (1 in the UK and 9 in Poland)
Indication: Primary vaccination of healthy infants against <i>Haemophilus influenzae</i> type b and meningococcal serogroup C diseases.
Treatment: Study groups were as follows: <ul style="list-style-type: none"> HibMenC group: Hib-MenC (3 different lots pooled) + DTPa-IPV (3 different lots pooled). The subjects were further randomised (1:1:1) to one of 3 Hib-MenC and DTPa-IPV lot combinations (Groups HibMenC_A, HibMenC_B and HibMenC_C). Subjects who received one Hib-MenC lot were allocated to the same DTPa-IPV lot. LicMenC group: subjects received a licensed MenC vaccine + DTPa-IPV-Hib (as control) The vaccines were administered into the anterolateral thigh to ensure deep intramuscular injection, the DTPa-IPV vaccine left and meningococcal vaccines right.
Objectives: <p>The co-primary objectives of the primary vaccination phase were assessed in a sequential fashion i.e. a conclusion was drawn on the second objective only if the first objective had been demonstrated.</p> <ul style="list-style-type: none"> One month after the primary vaccination course, to demonstrate the non-inferiority of the meningococcal serogroup C immune response induced by Hib-MenC conjugate vaccine given concomitantly with DTPa-IPV compared to a licensed meningococcal serogroup C vaccine given concomitantly with DTPa-IPV-Hib when given as a 3-dose primary vaccination in infants at 2, 3 and 4 months of age. (Lower limit of the standardized asymptotic 95% CI on the difference between groups - Hib-MenC minus LicMenC - was to be above -5% for SBA-MenC $\geq 1:8$) One month after the primary vaccination course, to demonstrate the non-inferiority of the Hib immune response induced by Hib-MenC conjugate vaccine given concomitantly with DTPa-IPV compared to a licensed meningococcal serogroup C vaccine given concomitantly with DTPa-IPV-Hib when given as a 3-dose primary vaccination in infants at 2, 3 and 4 months of age. (Lower limit of the standardized asymptotic 95% CI on the difference between groups - Hib-MenC minus LicMenC - was to be above -5% for anti-PRP concentration $\geq 0.15 \mu\text{g/mL}$)
Primary Outcome/Efficacy Variable: One month after the third vaccine dose:

<ul style="list-style-type: none"> Percentage of subjects with Meningococcal C serum bactericidal assay (SBA-MenC) titres $\geq 1:8$ (seroprotection) Percentage of subjects with anti-polyribosylribitol phosphate (anti-PRP) antibody concentration $\geq 0.15\mu\text{g/mL}$ (seroprotection) 					
<p>Secondary Outcome/Efficacy Variable(s): <i>immunogenicity</i> One month after the third vaccine dose:</p> <ul style="list-style-type: none"> Percentage of subjects with SBA-MenC antibody titres $\geq 1:128$ Anti-polysaccharide C (anti-PSC) antibody concentrations $\geq 0.3\mu\text{g/mL}$ and $\geq 2.0\mu\text{g/mL}$, Anti-PRP antibody concentrations $\geq 1.0\mu\text{g/mL}$ Anti-tetanus and anti-diphtheria antibody concentrations $\geq 0.1\text{ IU/mL}$ (seroprotection) Anti-pertussis toxoid (anti-PT), anti-filamentous haemagglutinin (anti-FHA) and anti-pertactin (anti-PRN) antibody concentration $\geq 5\text{ EL.U/mL}$ (seropositivity) Anti-PT, anti-FHA and anti-PRN vaccine responses* Anti-poliovirus type 1, 2 and 3 antibody titres $\geq 1:8$ (seroprotection) Geometric mean concentrations (GMCs) for anti-PRP, anti-PSC, anti-tetanus, anti-diphtheria, anti-PT, anti-FHA and anti-PRN antibodies and geometric mean titres (GMTs) for SBA-MenC and anti-poliovirus types 1, 2 and 3 antibodies <p>* Vaccine response was defined as the appearance of antibodies in subjects that were seronegative before vaccination or at least maintenance of antibody concentration in those that were seropositive taking into consideration the decreasing maternal antibodies.</p> <p><i>Safety</i></p> <ul style="list-style-type: none"> Occurrence of local and general solicited symptoms during the 4-day (Day 0-3) follow-up period following the administration of each vaccine dose. Occurrence of unsolicited non-serious adverse events (AEs) within 31 days (Day 0-30) after each vaccination. Occurrence of any serious adverse events (SAEs) throughout the study. 					
<p>Statistical Methods: The analyses were performed on the Primary Total Vaccinated Cohort and the Primary According-To-Protocol (ATP) cohort for immunogenicity.</p> <ul style="list-style-type: none"> The Primary Total Vaccinated Cohort included all subjects with at least one vaccine administration documented. The Primary ATP cohort for immunogenicity included all subjects who had received at least one vaccination according to their random assignment, for whom the administration site of the study vaccine/comparator was known, who had not received a vaccine not specified or forbidden in the protocol, for whom the randomization code was not broken, who met all eligibility criteria defined in the protocol and for whom data concerning immunogenicity measures were available. <p><i>Analysis of immunogenicity</i> The analysis was performed on the Primary ATP cohort for immunogenicity.</p> <p><i>Inferential analysis</i> The difference between the pooled HibMenC group and the LicMenC group in terms of the percentages of subjects with SBA-MenC titres $\geq 1:8$ and with anti-PRP concentrations $\geq 0.15\mu\text{g/mL}$ was calculated with their 95% standardized asymptotic confidence interval (CI).</p> <p><i>Descriptive analysis</i> For each group, at each time point that a blood sampling was available for the applicable antigens, seropositivity / seroprotection rates with exact 95% CIs, GMCs/GMTs with 95% CIs and vaccine response rates (post-Dose 3) to pertussis antigens (PT, FHA and PRN) and their exact 95% CI were tabulated.</p> <p><i>Analysis of safety</i> The analysis was performed on the Primary Total Vaccinated Cohort. The incidence of each local (any and grade 3 symptoms) and general (any, grade 3 and related symptoms) solicited symptom reported during a 4-day (Day 0-3) follow-up period after each vaccination was tabulated together with their exact 95% CI. For each group, the number of subjects with unsolicited AEs within 31 days (Day 0-30) following vaccination was tabulated according to the Medical Dictionary for Regularity Activities (MedDRA) preferred terms. The incidence of subjects with SAEs during the primary vaccination phase was tabulated per group according to the MedDRA preferred terms.</p>					
<p>Study Population: Subjects were male or female infants between, and including, 6 to 12 weeks of age at the time of the first vaccination, born after a gestation period between 36 and 42 weeks. 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 or guardian of the subject prior to study entry. Vaccination with hepatitis B at birth and at 6 to 12 weeks (concomitantly with the first study vaccine) was accepted although not mandatory.</p>					
Number of subjects	HibMenC_A	HibMenC_B	HibMenC_C	HibMenC	LicMenC
Planned, N	125	125	125	375	125

Randomised, N (Primary Total Vaccinated Cohort)	125	125	125	375	125								
Completed, n (%)	124 (99.2)	123 (98.4)	124 (99.2)	371 (98.9)	124 (99.2)								
Total Number Subjects Withdrawn, n (%)	1 (0.8)	2 (1.6)	1 (0.8)	4 (1.1)	1 (0.8)								
Withdrawn due to Adverse Events, n (%)	0 (0.0)	1 (0.8)	1 (0.8)	2 (0.5)	1 (0.8)								
Withdrawn due to Lack of Efficacy, n (%)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable								
Withdrawn for other reasons, n (%)	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)	0 (0.0)								
Demographics	HibMenC_A	HibMenC_B	HibMenC_C	HibMenC	LicMenC								
N (Total Vaccinated Cohort)	125	125	125	375	125								
Females:Males	67:58	66:59	54:71	187:188	64:61								
Mean Age, weeks (SD)	8.0 (1.52)	7.9 (1.77)	7.8 (1.63)	7.9 (1.64)	8.3 (1.54)								
White/Caucasian, n (%)	121 (96.8)	117 (93.6)	120 (96.0)	358 (95.5)	125 (100)								
Primary Efficacy Results:													
Difference between the pooled HibMenC group and the control group in terms of percentages of subjects with SBA-MenC titre $\geq 1:8$, one month after the third dose (Primary ATP cohort for immunogenicity)													
HibMenC		LicMenC		Difference	%	95% CI							
N	%	N	%			LL	UL						
354	99.2	117	100	HibMenC - LicMenC	-0.85	-2.46*	2.34						
N = number of subjects with available results % = percentage of subjects with SBA-MenC titre $\geq 1:8$ 95% CI = 95% standardized asymptotic confidence interval; LL = lower limit, UL = upper limit *The first co-primary non-inferiority objective was met as the lower limit of the 95% standardized asymptotic CI for the difference between the pooled HibMenC group and the LicMenC group was above -5%.													
Primary Efficacy Results:													
Difference between the pooled HibMenC group and the control group in terms of percentages of subjects with anti-PRP antibody concentration $\geq 0.15 \mu\text{g/mL}$, one month after the third dose (Primary ATP cohort for immunogenicity)													
HibMenC		LicMenC		Difference	%	95% CI							
N	%	N	%			LL	UL						
357	100	117	92.3	HibMenC - LicMenC	7.69	4.10*	13.97						
N = number of subjects with available results % = percentage of subjects with SBA-MenC titre $\geq 1:8$ 95% CI = 95% standardized asymptotic confidence interval; LL = lower limit, UL = upper limit *The second co-primary non-inferiority objective was met as the lower limit of the 95% standardized asymptotic CI for the difference between the pooled HibMenC group and the LicMenC group was above -5%.													
Primary Efficacy Results:													
Percentage of subjects with SBA-MenC antibody titre $\geq 1:8$ or $\geq 1:128$ and GMTs (Primary ATP cohort for immunogenicity)													
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_A	PRE	118	13	11.0	6.0	18.1	4	3.4	0.9	8.5	5.4	4.5	6.4
	PIII(M3)*	119	116	97.5	92.8	99.5	107	89.9	83.0	94.7	520.8	408.3	664.3
HibMenC_B	PRE	115	9	7.8	3.6	14.3	4	3.5	1.0	8.7	5.3	4.3	6.4
	PIII(M3)*	119	119	100	96.9	100	113	95.0	89.3	98.1	601.4	504.6	716.8
HibMenC_C	PRE	118	9	7.6	3.5	14.0	3	2.5	0.5	7.3	5.0	4.2	5.9
	PIII(M3)*	116	116	100	96.9	100	109	94.0	88.0	97.5	627.9	508.4	775.4
Hib MenC	PRE	351	31	8.8	6.1	12.3	11	3.1	1.6	5.5	5.2	4.7	5.8
	PIII(M3)*	354	351	99.2	97.5	99.8	329	92.9	89.8	95.4	581.1	514.7	656.2
Lic MenC	PRE	108	8	7.4	3.3	14.1	1	0.9	0.0	5.1	4.7	4.2	5.3
	PIII(M3)*	117	117	100	96.9	100	116	99.1	95.3	100	1002.6	833.8	1205.6
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody titre \geq specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample PIII(M3) = post-Dose 3 blood sample at Month 3													

*Primary Efficacy Result													
Primary Efficacy Results:													
Seroprotection rates and GMCs for anti-PRP antibodies (Primary ATP cohort for immunogenicity)													
Group	Timing	N	≥ 0.15 µg/mL*				≥ 1 µg/mL				GMC (µg/mL)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC_A	PRE	120	47	39.2	30.4	48.5	13	10.8	5.9	17.8	0.156	0.127	0.192
	PIII(M3)*	120	120	100	97.0	100	116	96.7	91.7	99.1	13.979	11.497	16.998
HibMenC_B	PRE	117	46	39.3	30.4	48.8	5	4.3	1.4	9.7	0.138	0.117	0.163
	PIII(M3)*	119	119	100	96.9	100	115	96.6	91.6	99.1	11.522	9.407	14.111
HibMenC_C	PRE	118	56	47.5	38.2	56.9	14	11.9	6.6	19.1	0.188	0.152	0.232
	PIII(M3)*	118	118	100	96.9	100	116	98.3	94.0	99.8	14.471	11.915	17.576
HibMenC	PRE	355	149	42.0	36.8	47.3	32	9.0	6.2	12.5	0.159	0.142	0.178
	PIII(M3)*	357	357	100	99.0	100	347	97.2	94.9	98.6	13.257	11.835	14.850
LicMenC	PRE	111	45	40.5	31.3	50.3	14	12.6	7.1	20.3	0.167	0.134	0.208
	PIII(M3)*	117	108	92.3	85.9	96.4	83	70.9	61.8	79.0	2.403	1.747	3.305
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentration ≥ specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample PIII(M3) = post-Dose 3 blood sample at Month 3 *Primary Efficacy Result													
Secondary Outcome Variable(s):													
Seropositivity rates and GMCs for anti-PSC antibodies (Primary ATP cohort for immunogenicity)													
Group	Timing	N	≥ 0.3 µg/mL				≥ 2 µg/mL				GMC (µg/mL)		
			n	%	95% CI		n	%	95% CI		Value	95% CI	
					LL	UL			LL	UL		LL	UL
HibMenC_A	PRE	120	14	11.7	6.5	18.8	6	5.0	1.9	10.6	0.20	0.17	0.23
	PIII(M3)	119	119	100	96.9	100	117	98.3	94.1	99.8	9.37	8.22	10.68
HibMenC_B	PRE	117	18	15.4	9.4	23.2	7	6.0	2.4	11.9	0.21	0.18	0.25
	PIII(M3)	119	118	99.2	95.4	100	117	98.3	94.1	99.8	8.73	7.66	9.95
HibMenC_C	PRE	117	16	13.7	8.0	21.3	7	6.0	2.4	11.9	0.20	0.18	0.24
	PIII(M3)	118	118	100	96.9	100	117	99.2	95.4	100	9.25	8.14	10.51
HibMenC	PRE	354	48	13.6	10.2	17.6	20	5.6	3.5	8.6	0.20	0.19	0.22
	PIII(M3)	356	355	99.7	98.4	100	351	98.6	96.8	99.5	9.11	8.46	9.82
LicMenC	PRE	111	12	10.8	5.7	18.1	3	2.7	0.6	7.7	0.19	0.16	0.22
	PIII(M3)	114	114	100	96.8	100	114	100	96.8	100	12.92	11.43	14.61
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentration ≥ specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample PIII(M3) = post-Dose 3 blood sample at Month 3													
Secondary Outcome Variable(s):													
Seroprotection rates and GMCs for anti-diphtheria antibodies (Primary ATP cohort for immunogenicity)													
Group	Timing	N	≥ 0.1 IU/mL				GMC (IU/mL)						
			n	%	95% CI		Value	95% CI					
					LL	UL		LL	UL				
HibMenC	PRE	352	156	44.3	39.1	49.7	0.10	0.09	0.11				
	PIII(M3)	356	350	98.3	96.4	99.4	0.82	0.74	0.91				
LicMenC	PRE	110	41	37.3	28.2	47.0	0.09	0.08	0.11				
	PIII(M3)	117	117	100	96.9	100	1.76	1.49	2.08				
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentration ≥ specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample													

P111(M3) = post-Dose 3 blood sample at Month 3										
Secondary Outcome Variable(s):										
Seroprotection rates and GMCs for anti-tetanus antibodies (Primary ATP cohort for immunogenicity)										
Group	Timing	N	≥ 0.1 IU/mL				GMC (IU/mL)			
			n	%	95% CI		Value	95% CI		
					LL	UL		LL	UL	
HibMenC	PRE	353	312	88.4	84.6	91.5	0.37	0.33	0.41	
	P111(M3)	356	356	100	99.0	100	2.33	2.17	2.51	
LicMenC	PRE	110	94	85.5	77.5	91.5	0.31	0.25	0.37	
	P111(M3)	117	116	99.1	95.3	100	0.88	0.75	1.04	
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentration ≥ specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample P111(M3) = post-Dose 3 blood sample at Month 3										
Secondary Outcome Variable(s):										
Seropositivity rates and GMCs for anti-PT, anti-FHA, anti-PRN antibodies (Primary ATP cohort for immunogenicity)										
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	PRE	350	78	22.3	18.0	27.0	3.6	3.3	3.9
		P111(M3)	356	355	99.7	98.4	100	44.4	41.8	47.3
	LicMenC	PRE	108	30	27.8	19.6	37.2	3.7	3.3	4.3
		P111(M3)	116	116	100	96.9	100	35.0	31.8	38.6
Anti-FHA	HibMenC	PRE	353	279	79.0	74.4	83.2	11.2	10.0	12.5
		P111(M3)	356	355	99.7	98.4	100	151.8	141.2	163.2
	LicMenC	PRE	110	87	79.1	70.3	86.3	10.8	8.9	13.1
		P111(M3)	117	117	100	96.9	100	113.4	100.6	127.7
Anti-PRN	HibMenC	PRE	352	141	40.1	34.9	45.4	4.7	4.3	5.2
		P111(M3)	356	352	98.9	97.1	99.7	81.1	72.8	90.3
	LicMenC	PRE	110	34	30.9	22.4	40.4	4.0	3.4	4.7
		P111(M3)	117	113	96.6	91.5	99.1	37.4	30.7	45.6
N = number of subjects with available results n (%) = number (percentage) of subjects with antibody concentration ≥ specified cut-off value 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit PRE = pre-vaccination blood sample P111(M3) = post-Dose 3 blood sample at Month 3										
Secondary Outcome Variable(s):										
Vaccine response rates for anti-PT, anti-FHA, anti-PRN antibody one month after the third dose (Primary ATP cohort for immunogenicity)										
Antibody	Group	Pre-vaccination Status	N	Vaccine Responses						
				n	%	95% CI				
						LL	UL			
Anti-PT	HibMenC	S-	271	270	99.6	98.0	100			
		S+	78	65	83.3	73.2	90.8			
		Total	349	335	96.0	93.4	97.8			
	LicMenC	S-	77	77	100	95.3	100			
		S+	30	24	80.0	61.4	92.3			
		Total	107	101	94.4	88.2	97.9			
Anti-FHA	HibMenC	S-	74	73	98.6	92.7	100			
		S+	278	262	94.2	90.8	96.7			
		Total	352	335	95.2	92.4	97.2			
	LicMenC	S-	23	23	100	85.2	100			
		S+	87	83	95.4	88.6	98.7			
		Total	110	106	96.4	91.0	99.0			

Anti-PRN	HibMenC	S-	210	209	99.5	97.4	100
		S+	141	114	80.9	73.4	87.0
		Total	351	323	92.0	88.7	94.6
	LicMenC	S-	76	74	97.4	90.8	99.7
		S+	34	24	70.6	52.5	84.9
		Total	110	98	89.1	81.7	94.2

S-/+ = seronegative/positive prior to vaccination

Total = subjects either seropositive or seronegative at pre-vaccination

N = number of subjects with both pre- and post-vaccination results available

n (%) = number (percentage) of responders

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

Secondary Outcome Variable(s):

Seroprotection rates and GMTs for anti-poliovirus types 1, 2, and 3 antibodies (Primary ATP cohort for immunogenicity)

Antibody	Group	Timing	N	≥ 1:8				Value	GMT		
				n	%	95% CI			LL	UL	
						LL	UL				
Anti-poliovirus type 1	HibMenC	PRE	295	209	70.8	65.3	76.0	19.0	16.3	22.1	
		P111(M3)	319	318	99.7	98.3	100	185.1	163.8	209.1	
	LicMenC	PRE	100	63	63.0	52.8	72.4	15.1	11.7	19.5	
		P111(M3)	104	102	98.1	93.2	99.8	101.5	80.6	127.6	
Anti-poliovirus type 2	HibMenC	PRE	298	195	65.4	59.7	70.8	11.7	10.4	13.1	
		P111(M3)	313	309	98.7	96.8	99.7	118.5	102.6	136.8	
	LicMenC	PRE	98	54	55.1	44.7	65.2	10.9	8.7	13.7	
		P111(M3)	103	101	98.1	93.2	99.8	103.3	83.5	127.8	
Anti-poliovirus type 3	HibMenC	PRE	299	43	14.4	10.6	18.9	4.9	4.6	5.2	
		P111(M3)	298	295	99.0	97.1	99.8	434.1	376.4	500.7	
	LicMenC	PRE	100	18	18.0	11.0	26.9	5.0	4.5	5.7	
		P111(M3)	100	100	100	96.4	100	223.7	177.3	282.2	

N = number of subjects with available results

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

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

PRE = pre-vaccination blood sample

P111(M3) = post-Dose 3 blood sample at Month 3

Secondary Outcome Variable(s):

Number (percentage) of subjects with solicited local symptoms reported during the 4-day (Day 0-3) post-vaccination period following each dose and overall (Primary Total vaccinated cohort)

Symptom	Intensity	HibMenC_A				HibMenC_B				HibMenC_C			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
Dose 1													
		N=125				N=125				N=125			
Pain	Any	24	19.2	12.7	27.2	26	20.8	14.1	29.0	22	17.6	11.4	25.4
	Grade 3	2	1.6	0.2	5.7	0	0.0	0.0	2.9	1	0.8	0.0	4.4
Redness	Any	24	19.2	12.7	27.2	29	23.2	16.1	31.6	31	24.8	17.5	33.3
	> 30 mm	0	0.0	0.0	2.9	1	0.8	0.0	4.4	1	0.8	0.0	4.4
Swelling	Any	17	13.6	8.1	20.9	22	17.6	11.4	25.4	18	14.4	8.8	21.8
	> 30 mm	0	0.0	0.0	2.9	1	0.8	0.0	4.4	0	0.0	0.0	2.9
Dose 2													
		N=125				N=124				N=124			
Pain	Any	24	19.2	12.7	27.2	23	18.5	12.1	26.5	14	11.3	6.3	18.2
	Grade 3	1	0.8	0.0	4.4	1	0.8	0.0	4.4	1	0.8	0.0	4.4
Redness	Any	35	28.0	20.3	36.7	41	33.1	24.9	42.1	36	29.0	21.2	37.9
	> 30 mm	1	0.8	0.0	4.4	1	0.8	0.0	4.4	0	0.0	0.0	2.9
Swelling	Any	18	14.4	8.8	21.8	23	18.5	12.1	26.5	20	16.1	10.1	23.8
	> 30 mm	1	0.8	0.0	4.4	2	1.6	0.2	5.7	0	0.0	0.0	2.9

Dose 3													
		N=125				N=123				N=124			
Pain	Any	16	12.8	7.5	20.0	15	12.2	7.0	19.3	20	16.1	10.1	23.8
	Grade 3	0	0.0	0.0	2.9	2	1.6	0.2	5.8	1	0.8	0.0	4.4
Redness	Any	42	33.6	25.4	42.6	37	30.1	22.1	39.0	40	32.3	24.1	41.2
	> 30 mm	0	0.0	0.0	2.9	0	0.0	0.0	3.0	0	0.0	0.0	2.9
Swelling	Any	24	19.2	12.7	27.2	21	17.1	10.9	24.9	21	16.9	10.8	24.7
	> 30 mm	0	0.0	0.0	2.9	1	0.8	0.0	4.4	0	0.0	0.0	2.9
Across doses													
		N=125				N=125				N=125			
Pain	Any	42	33.6	25.4	42.6	47	37.6	29.1	46.7	36	28.8	21.1	37.6
	Grade 3	3	2.4	0.5	6.9	3	2.4	0.5	6.9	3	2.4	0.5	6.9
Redness	Any	55	44.0	35.1	53.2	59	47.2	38.2	56.3	57	45.6	36.7	54.7
	> 30 mm	1	0.8	0.0	4.4	2	1.6	0.2	5.7	1	0.8	0.0	4.4
Swelling	Any	40	32.0	23.9	40.9	40	32.0	23.9	40.9	38	30.4	22.5	39.3
	> 30 mm	1	0.8	0.0	4.4	4	3.2	0.9	8.0	0	0.0	0.0	2.9
Symptom	Intensity	HibMenC				LicMenC							
		n	%	95% CI		n	%	95% CI					
				LL	UL			LL	UL				
Dose 1													
		N=375				N=125							
Pain	Any	72	19.2	15.3	23.6	28	22.4	15.4	30.7				
	Grade 3	3	0.8	0.2	2.3	4	3.2	0.9	8.0				
Redness	Any	84	22.4	18.3	27.0	43	34.4	26.1	43.4				
	> 30 mm	2	0.5	0.1	1.9	6	4.8	1.8	10.2				
Swelling	Any	57	15.2	11.7	19.2	20	16.0	10.1	23.6				
	> 30 mm	1	0.3	0.0	1.5	5	4.0	1.3	9.1				
Dose 2													
		N=373				N=124							
Pain	Any	61	16.4	12.7	20.5	20	16.1	10.1	23.8				
	Grade 3	3	0.8	0.2	2.3	3	2.4	0.5	6.9				
Redness	Any	112	30.0	25.4	35.0	40	32.3	24.1	41.2				
	> 30 mm	2	0.5	0.1	1.9	3	2.4	0.5	6.9				
Swelling	Any	61	16.4	12.7	20.5	24	19.4	12.8	27.4				
	> 30 mm	3	0.8	0.2	2.3	2	1.6	0.2	5.7				
Dose 3													
		N=372				N=124							
Pain	Any	51	13.7	10.4	17.6	14	11.3	6.3	18.2				
	Grade 3	3	0.8	0.2	2.3	1	0.8	0.0	4.4				
Redness	Any	119	32.0	27.3	37.0	42	33.9	25.6	42.9				
	> 30 mm	0	0.0	0.0	1.0	1	0.8	0.0	4.4				
Swelling	Any	66	17.7	14.0	22.0	25	20.2	13.5	28.3				
	> 30 mm	1	0.3	0.0	1.5	2	1.6	0.2	5.7				
Across doses													
		N=375				N=125							
Pain	Any	125	33.3	28.6	38.4	41	32.8	24.7	41.8				
	Grade 3	9	2.4	1.1	4.5	7	5.6	2.3	11.2				
Redness	Any	171	45.6	40.5	50.8	66	52.8	43.7	61.8				
	> 30 mm	4	1.1	0.3	2.7	9	7.2	3.3	13.2				
Swelling	Any	118	31.5	26.8	36.4	39	31.2	23.2	40.1				
	> 30 mm	5	1.3	0.4	3.1	7	5.6	2.3	11.2				

N = number of subjects with an administered dose
n (%) = number (percentage) of subjects for whom the symptom was reported at least once
95%CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Any = incidence of a particular symptom regardless of grade													
Grade 3 pain = cried when limb was moved/ spontaneously painful													
Secondary Outcome Variable(s):													
Number (percentage) of subjects with solicited general symptoms reported during the 4-day (Day 0-3) post-vaccination period following each dose and overall (Primary Total vaccinated cohort)													
Symptom	Intensity/ relation- ship	HibMenC_A				HibMenC_B				HibMenC_C			
		n	%	95% CI		n	%	95% CI		n	%	95% CI	
				LL	UL			LL	UL			LL	UL
Dose 1													
		N=125				N=125				N=125			
Drowsiness	Any	61	48.8	39.8	57.9	51	40.8	32.1	49.9	62	49.6	40.5	58.7
	Grade 3	0	0.0	0.0	2.9	1	0.8	0.0	4.4	1	0.8	0.0	4.4
	Related	50	40.0	31.3	49.1	43	34.4	26.1	43.4	52	41.6	32.9	50.8
Fever (Rectally)	≥ 38°C	9	7.2	3.3	13.2	10	8.0	3.9	14.2	8	6.4	2.8	12.2
	> 40°C	0	0.0	0.0	2.9	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	7	5.6	2.3	11.2	10	8.0	3.9	14.2	6	4.8	1.8	10.2
Irritability	Any	60	48.0	39.0	57.1	60	48.0	39.0	57.1	58	46.4	37.4	55.5
	Grade 3	0	0.0	0.0	2.9	1	0.8	0.0	4.4	3	2.4	0.5	6.9
	Related	50	40.0	31.3	49.1	53	42.4	33.6	51.6	49	39.2	30.6	48.3
Loss of appetite	Any	27	21.6	14.7	29.8	20	16.0	10.1	23.6	22	17.6	11.4	25.4
	Grade 3	0	0.0	0.0	2.9	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	23	18.4	12.0	26.3	19	15.2	9.4	22.7	21	16.8	10.7	24.5
Dose 2													
		N=125				N=124				N=124			
Drowsiness	Any	35	28.0	20.3	36.7	39	31.5	23.4	40.4	54	43.5	34.7	52.7
	Grade 3	1	0.8	0.0	4.4	0	0.0	0.0	2.9	1	0.8	0.0	4.4
	Related	29	23.2	16.1	31.6	37	29.8	22.0	38.7	45	36.3	27.8	45.4
Fever (Rectally)	≥ 38°C	15	12.0	6.9	19.0	10	8.1	3.9	14.3	10	8.1	3.9	14.3
	> 40°C	0	0.0	0.0	2.9	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	10	8.0	3.9	14.2	8	6.5	2.8	12.3	6	4.8	1.8	10.2
Irritability	Any	60	48.0	39.0	57.1	64	51.6	42.5	60.7	57	46.0	37.0	55.1
	Grade 3	3	2.4	0.5	6.9	2	1.6	0.2	5.7	4	3.2	0.9	8.1
	Related	54	43.2	34.4	52.4	55	44.4	35.4	53.5	48	38.7	30.1	47.9
Loss of appetite	Any	33	26.4	18.9	35.0	25	20.2	13.5	28.3	27	21.8	14.9	30.1
	Grade 3	0	0.0	0.0	2.9	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	27	21.6	14.7	29.8	24	19.4	12.8	27.4	23	18.5	12.1	26.5
Dose 3													
		N=125				N=123				N=124			
Drowsiness	Any	19	15.2	9.4	22.7	35	28.5	20.7	37.3	37	29.8	22.0	38.7
	Grade 3	0	0.0	0.0	2.9	0	0.0	0.0	3.0	0	0.0	0.0	2.9
	Related	18	14.4	8.8	21.8	33	26.8	19.2	35.6	35	28.2	20.5	37.0
Fever (Rectally)	≥ 38°C	9	7.2	3.3	13.2	7	5.7	2.3	11.4	9	7.3	3.4	13.3
	> 40°C	0	0.0	0.0	2.9	0	0.0	0.0	3.0	0	0.0	0.0	2.9
	Related	7	5.6	2.3	11.2	7	5.7	2.3	11.4	6	4.8	1.8	10.2
Irritability	Any	47	37.6	29.1	46.7	46	37.4	28.8	46.6	53	42.7	33.9	51.9
	Grade 3	1	0.8	0.0	4.4	2	1.6	0.2	5.8	2	1.6	0.2	5.7
	Related	42	33.6	25.4	42.6	41	33.3	25.1	42.4	46	37.1	28.6	46.2
Loss of appetite	Any	12	9.6	5.1	16.2	16	13.0	7.6	20.3	25	20.2	13.5	28.3
	Grade 3	1	0.8	0.0	4.4	0	0.0	0.0	3.0	0	0.0	0.0	2.9
	Related	12	9.6	5.1	16.2	13	10.6	5.7	17.4	23	18.5	12.1	26.5
Across doses													
		N=125				N=125				N=125			
Drowsiness	Any	70	56.0	46.8	64.9	72	57.6	48.4	66.4	85	68.0	59.1	76.1
	Grade 3	1	0.8	0.0	4.4	1	0.8	0.0	4.4	2	1.6	0.2	5.7
	Related	62	49.6	40.5	58.7	66	52.8	43.7	61.8	76	60.8	51.7	69.4

Fever (Rectally)	≥ 38°C	30	24.0	16.8	32.5	23	18.4	12.0	26.3	22	17.6	11.4	25.4
	> 40°C	0	0.0	0.0	2.9	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	21	16.8	10.7	24.5	22	17.6	11.4	25.4	14	11.2	6.3	18.1
Irritability	Any	90	72.0	63.3	79.7	89	71.2	62.4	78.9	88	70.4	61.6	78.2
	Grade 3	4	3.2	0.9	8.0	5	4.0	1.3	9.1	8	6.4	2.8	12.2
	Related	85	68.0	59.1	76.1	81	64.8	55.8	73.1	81	64.8	55.8	73.1
Loss of appetite	Any	46	36.8	28.4	45.9	44	35.2	26.9	44.2	46	36.8	28.4	45.9
	Grade 3	1	0.8	0.0	4.4	0	0.0	0.0	2.9	0	0.0	0.0	2.9
	Related	39	31.2	23.2	40.1	40	32.0	23.9	40.9	42	33.6	25.4	42.6
Symptom	Intensity/ relationship	HibMenC				LicMenC							
		n	%	95% CI		n	%	95% CI					
				LL	UL			LL	UL				
Dose 1													
		N=375				N=125							
Drowsiness	Any	174	46.4	41.3	51.6	63	50.4	41.3	59.5				
	Grade 3	2	0.5	0.1	1.9	1	0.8	0.0	4.4				
	Related	145	38.7	33.7	43.8	55	44.0	35.1	53.2				
Fever (Rectally)	≥ 38°C	27	7.2	4.8	10.3	11	8.8	4.5	15.2				
	> 40°C	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	23	6.1	3.9	9.1	10	8.0	3.9	14.2				
Irritability	Any	178	47.5	42.3	52.7	70	56.0	46.8	64.9				
	Grade 3	4	1.1	0.3	2.7	3	2.4	0.5	6.9				
	Related	152	40.5	35.5	45.7	58	46.4	37.4	55.5				
Loss of appetite	Any	69	18.4	14.6	22.7	29	23.2	16.1	31.6				
	Grade 3	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	63	16.8	13.2	21.0	28	22.4	15.4	30.7				
Dose 2													
		N=373				N=124							
Drowsiness	Any	128	34.3	29.5	39.4	42	33.9	25.6	42.9				
	Grade 3	2	0.5	0.1	1.9	0	0.0	0.0	2.9				
	Related	111	29.8	25.2	34.7	34	27.4	19.8	36.2				
Fever (Rectally)	≥ 38°C	35	9.4	6.6	12.8	10	8.1	3.9	14.3				
	> 40°C	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	24	6.4	4.2	9.4	8	6.5	2.8	12.3				
Irritability	Any	181	48.5	43.3	53.7	58	46.8	37.8	55.9				
	Grade 3	9	2.4	1.1	4.5	2	1.6	0.2	5.7				
	Related	157	42.1	37.0	47.3	48	38.7	30.1	47.9				
Loss of appetite	Any	85	22.8	18.6	27.4	25	20.2	13.5	28.3				
	Grade 3	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	74	19.8	15.9	24.3	20	16.1	10.1	23.8				
Dose 3													
		N=372				N=124							
Drowsiness	Any	91	24.5	20.2	29.2	34	27.4	19.8	36.2				
	Grade 3	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	86	23.1	18.9	27.7	30	24.2	17.0	32.7				
Fever (Rectally)	≥ 38°C	25	6.7	4.4	9.8	8	6.5	2.8	12.3				
	> 40°C	0	0.0	0.0	1.0	0	0.0	0.0	2.9				
	Related	20	5.4	3.3	8.2	7	5.6	2.3	11.3				
Irritability	Any	146	39.2	34.3	44.4	47	37.9	29.3	47.1				
	Grade 3	5	1.3	0.4	3.1	2	1.6	0.2	5.7				
	Related	129	34.7	29.8	39.8	42	33.9	25.6	42.9				
Loss of appetite	Any	53	14.2	10.9	18.2	12	9.7	5.1	16.3				
	Grade 3	1	0.3	0.0	1.5	0	0.0	0.0	2.9				
	Related	48	12.9	9.7	16.7	11	8.9	4.5	15.3				

Across doses									
		N=375				N=125			
Drowsiness	Any	227	60.5	55.4	65.5	81	64.8	55.8	73.1
	Grade 3	4	1.1	0.3	2.7	1	0.8	0.0	4.4
	Related	204	54.4	49.2	59.5	72	57.6	48.4	66.4
Fever (Rectally)	≥ 38°C	75	20.0	16.1	24.4	24	19.2	12.7	27.2
	> 40°C	0	0.0	0.0	1.0	0	0.0	0.0	2.9
	Related	57	15.2	11.7	19.2	20	16.0	10.1	23.6
Irritability	Any	267	71.2	66.3	75.7	95	76.0	67.5	83.2
	Grade 3	17	4.5	2.7	7.2	7	5.6	2.3	11.2
	Related	247	65.9	60.8	70.7	80	64.0	54.9	72.4
Loss of appetite	Any	136	36.3	31.4	41.4	45	36.0	27.6	45.1
	Grade 3	1	0.3	0.0	1.5	0	0.0	0.0	2.9
	Related	121	32.3	27.6	37.3	42	33.6	25.4	42.6

N = number of subjects with an administered dose

n (%) = number (percentage) of subjects for whom the symptom was reported at least once

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

Any = incidence of a particular symptom regardless of grade or relationship to study vaccination

Grade 3 drowsiness = symptom that prevented normal activity

Grade 3 irritability: crying that could not be comforted/ prevented normal activity

Grade 3 loss of appetite = not eating at all

Related: symptoms considered by the investigator to have a causal relationship to study vaccination

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

Most frequent adverse events - On-Therapy (occurring within Day 0-30 following vaccination)	HibMenC_A N = 125	HibMenC_B N = 125	HibMenC_C N = 125	HibMenC N=375	LicMenC N = 125
Subjects with any AE(s), n (%)	72 (57.6)	60 (48.0)	72 (57.6)	204 (54.4)	67 (53.6)
Nasopharyngitis	13 (10.4)	8 (6.4)	7 (5.6)	28 (7.5)	6 (4.8)
Teething	10 (8.0)	9 (7.2)	8 (6.4)	27 (7.2)	8 (6.4)
Rhinitis	10 (8.0)	7 (5.6)	7 (5.6)	24 (6.4)	10 (8.0)
Diarrhoea	5 (4.0)	5 (4.0)	9 (7.2)	19 (5.1)	4 (3.2)
Upper respiratory tract infection	3 (2.4)	7 (5.6)	8 (6.4)	18 (4.8)	4 (3.2)
Dermatitis allergic	6 (4.8)	2 (1.6)	6 (4.8)	14 (3.7)	4 (3.2)
Cough	5 (4.0)	4 (3.2)	2 (1.6)	11 (2.9)	2 (1.6)
Rash	2 (1.6)	3 (2.4)	2 (1.6)	7 (1.9)	6 (4.8)
Eczema	1 (0.8)	5 (4.0)	0 (0.0)	6 (1.6)	2 (1.6)

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

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

All SAEs	HibMenC_A N = 125	HibMenC_B N = 125	HibMenC_C N = 125	HibMenC N=375	LicMenC N = 125
Subjects with any SAE(s), n (%) [n related]	7 (5.6) [0]	4 (3.2) [0]	3 (2.4) [0]	14 (3.7) [0]	6 (4.8) [0]
Bronchitis	2 (1.6) [0]	0 (0.0) [0]	0 (0.0) [0]	2 (0.5) [0]	0 (0.0) [0]
Otitis media	0 (0.0) [0]	1 (0.8) [0]	1 (0.8) [0]	2 (0.5) [0]	0 (0.0) [0]
Anaemia	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	1 (0.8) [0]
Gastroesophageal reflux disease	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]	1 (0.3) [0]	1 (0.8) [0]
Laryngitis	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	1 (0.8) [0]
Pneumonia	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	1 (0.8) [0]
Bronchopneumonia	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Dermatitis allergic	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Enterocolitis	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Gastroenteritis	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Inguinal hernia, obstructive	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Nasopharyngitis	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Rash	0 (0.0) [0]	1 (0.8) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Sepsis	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]	1 (0.3) [0]	0 (0.0) [0]

Urinary tract infection	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Varicella	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]	1 (0.3) [0]	0 (0.0) [0]
Viral infection	1 (0.8) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.3) [0]	0 (0.0) [0]
Constipation	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Cow's milk intolerance	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Meningitis meningococcal	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Pyrexia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Thymus enlargement	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Viraemia	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	1 (0.8) [0]
Fatal SAEs	HibMenC_A	HibMenC_B	HibMenC_C	HibMenC	LicMenC
	N = 125	N = 125	N = 125	N=375	N = 125
Subjects with fatal SAE(s), n (%) [n related]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]	0 (0.0) [0]

Conclusion: Please refer to publication below.

Publications:

Peer review publications:

Pace D. et al (2007) An alternative primary infant immunisation schedule for Infants using a new combination Hib-MenC-TT vaccine. *Pediatr Infect Dis J*, 26(11):1057-1059.

Abstracts and posters :

D. Pace et al. Immunogenicity, Safety and Reactogenicity of a Combined Haemophilus influenzae type b and Neisseria meningitidis serogroup C-tetanus toxoid conjugate vaccine in Infants - 24th Annual Meeting ESPID, Basel, Switzerland, 03-05 May 2006.

D. Pace et al. Comparison of immunogenicity and reactogenicity of two diphtheria, tetanus, acellular pertussis and polio immunisation schedules in infants - 25th Annual Meeting ESPID, Porto, Portugal, 02-04 May 2007.

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