HAEMOPHILUS INFLUENZAE TYPE B–NEISSERIA MENINGITIDIS SEROGROUPS C AND Y TETANUS TOXOID CONJUGATE VACCINE (HIBMENCY) WAS IMMUNOGENIC WITH AN ACCEPTABLE SAFETY PROFILE IN TWO PHASE 3 TRIALS

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BACKGROUND

- *Neisseria meningitidis* is an important cause of invasive disease in young children, with the highest incidence occurring in children <1 year of age in the US (5.38 cases annually per 100,000 population between 1998 and 2007, which equates to 14% of all cases over this time period).[1]
- 95% of cases in children aged below 1 year were caused by serogroups B, C and Y.[1]
- There is currently no licensed vaccine in the US for prevention of invasive meningococcal disease (IMD) for infants and toddlers <2 years of age.
- A novel, combined *Haemophilus influenzae* type b (Hib) and *N. meningitidis* serogroups C and Y-tetanus toxoid (TT)-conjugated vaccine (HibMenCY; GlaxoSmithKline Biologicals, Rixensart, Belgium) was immunogenic and had an acceptable safety profile in Phase II studies conducted in children <2 years of age.[2–4]
- Here we report the findings of two Phase III studies in which the immunogenicity and safety of a 4-dose series of HibMenCY was compared with licensed monovalent Hib vaccines when co-administered with routinely recommended vaccines.

METHODS

Study design

- Two Phase III, single-blind, randomized, controlled, multinational studies were conducted in the US, Australia and Mexico (NCT00289783 and NCT00345579).
- Infants were randomized (3:1) to receive three doses of either HibMenCY (polyribosylribitol phosphate [PRP] 2.5 µg conjugated to TT; MenC 5 µg conjugated to TT; MenY 5 µg conjugated to TT; HibMenCY group) or Hib-TT (PRP 10 µg conjugated to TT; *ActHIB®*, Sanofi Pasteur, Lyon, France; Hib group) at 2, 4 and 6 months of age. The vaccines were co-administered with diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated polio (DTaP–HepB–IPV; *Pediarix®*; GlaxoSmithKline Biologicals) and seven-valent CRM_{197}-conjugated pneumococcal vaccine (*Prevnar®*/*Prevenar®*; Pfizer Inc. New York, New York, US).
- At 12–15 months of age, infants received a fourth dose of either HibMenCY (HibMenCY group) or *PedvaxHIB®**(PRP 7.5 µg conjugated to 125 µg N. meningitidis outer membrane protein complex; Merck & Co. Inc., Whitehouse Station, NJ, US; Hib group), co-administered with routinely administered vaccines including: measles–mumps–rubella (MMR; M-M-R-II™; Merck & Co. Inc.), varicella (*Varivax®*; Merck & Co., Inc.) and *Prevnar®*/*Prevenar®*.

Immunogenicity assessments

- Immunogenicity was assessed 1 month after administration of dose 3, then prior to, and 42 days after, dose 4.
- Concentration of antibody against the Hib polysaccharide PRP was measured by enzyme-linked immunosorbent assay (ELISA), with standard assay cut-offs of 0.15 µg/mL and 1.0 µg/mL (considered to be predictive of short- and long-term protection, respectively).[5,6]
- Functional anti-MenC and anti-MenY antibodies were determined using a serum bactericidal assay using human complement (hSBA) with cut-offs of ≥1:4 and ≥1:8. Titers ≥1:4 have previously been associated with seroprotection against MenC.[7] By convention, the same threshold is used to define seroprotection against MenY.
- MenC- and MenY-specific antibody concentrations were measured using an ELISA, with a cut-off concentration of 0.3 µg/mL. Antibody concentrations ≥2.0 µg/mL were also assessed, and were based on the correlate of protection proposed for the meningococcal plain polysaccharide MenA and MenC vaccines.[8,9]

Safety

- Solicited local (pain, redness, swelling) and general (fever, drowsiness, irritability/fussiness, loss of appetite) symptoms were recorded for 4 days following each dose.
- Serious adverse events (SAEs), new onset chronic diseases (NOCDs) (e.g. diabetes type 1, asthma, allergies, autoimmune disorders), rashes and AEs resulting in emergency room (ER) visits were recorded from vaccination day at dose 1 until 6 months from the day of dose 4 (end of study).

Statistical methods

- The primary analysis of immunogenicity was performed only on the US According-To-Protocol (ATP) cohort for immunogenicity (NCT00289783).
- Non-inferiority of PRP immunogenicity of HibMenCY *vs* the licensed Hib vaccines post-dose 3 and post-dose 4 was demonstrated in the HibMenCY group if the lower limit (LL) of the 95% confidence intervals (CI) of the difference (HibMenCY group minus Hib group) in the percentage of infants with anti-PRP concentration ≥1.0 µg/mL was ≥ –10%.
- Immunogenicity of MenC and MenY was demonstrated if the LL of the 95% CI in the percentage of infants with bactericidal antibodies against MenC and MenY ≥1:8 was at least 90% post-dose 4, and if the LL of the 95% CI of the post-dose 4/pre-dose 4 geometric mean antibody titer (GMT) ratio dose was at least 2.
- Safety analyses were performed on the Total Vaccinated Cohort (TVC; NCT00289783) for solicited and unsolicited symptoms (only unsolicited specific AEs, defined as SAEs, NOCDs, rashes and AEs resulting in ER visits were collected for study NCT00345579), and on the pooled TVC (NCT00289783 and NCT00345579) for specific AEs.

* Immunogenicity data for administration of *ActHIB®* at 12–15 months are not included in the FDA-approved labelling information for *ActHIB®*.

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RESULTS

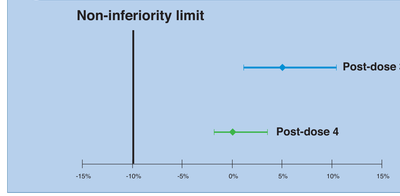
Demographics

- 8571 infants were enrolled in the two studies and included in the TVC for safety, 7712 were included in the fourth dose pooled TVC for safety. A total of 4180 infants were included in the primary TVC for solicited symptoms post-doses 1, 2 and 3, and 3692 in the fourth dose TVC for solicited symptoms post-dose 4.
- A total of 695 US infants met ATP criteria for immunogenicity after dose 3, and 521 met the ATP criteria after dose 4.
- The demographic profiles of the HibMenCY and Hib groups in the pooled TVC cohort were comparable. The mean age at the first vaccination visit was 61.0 (range 37–111 days) and 61.1 days (range 40–116 days) for the HibMenCY and Hib groups respectively. The distribution of males and females was also comparable between groups (males: 51.7% and 51.1% in HibMenCY and Hib groups, respectively). The predominant race was Hispanic (46.8% in the HibMenCY group and 46.3% in the Hib group), followed by Caucasian (43.5% in the HibMenCY group and 44.3% in the Hib group).

Immunogenicity

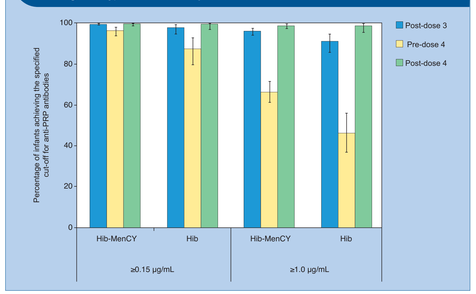
- Non-inferiority of HibMenCY for PRP immunogenicity compared with control was demonstrated at both time points (Figure 1).

Figure 1: Non-inferiority of PRP immunogenicity post-dose 3 and post-dose 4: difference between HibMenCY and Hib groups in the percentage of infants with anti-PRP ≥1 µg/mL (US ATP cohort for immunogenicity). Error bars represent 95% confidence intervals



- The percentages of subjects with anti-PRP antibody concentrations ≥0.15 µg/mL and ≥1.0 µg/mL post-dose 3 and pre-dose 4 were significantly higher in the HibMenCY group (Figure 2).

Figure 2: Percentage of infants with anti-PRP antibody concentrations above the specified cut-off post-dose 3, pre- and post-dose 4 (US ATP cohort for immunogenicity). Error bars represent 95% confidence intervals



- Anti-PRP geometric mean concentrations (GMCs) were significantly higher in the HibMenCY group post-dose 3, pre-dose 4 and post-dose 4.
- Over 95% of HibMenCY vaccinees achieved hSBA titers ≥1:4 and ≥1:8 against MenC (n=485) and MenY (n=463) after the third dose (Figures 3a and 3b).
- After the fourth dose, the percentage of HibMenCY vaccinees with hSBA titers ≥1:8 was 98.5% [95% CI: 96.5, 99.5] for MenC and 98.8% [95% CI: 97.0, 99.7] for MenY, satisfying the pre-specified immunogenicity criteria.
- Post-dose 4, GMTs in the HibMenCY group increased 12-fold against MenC and MenY with a LL of the 95% CI of 10 for both, satisfying the pre-specified immunogenicity criteria (Figure 4).
- After the fourth dose, anti-MenY polysaccharide ELISA data showed a positive anti-MenY response in the HibMenCY group (99.4% subjects ≥0.3 µg/mL; 97.3% ≥2.0 µg/mL), but not in the Hib control group (5.5% subjects ≥0.3 µg/mL; 3.7% ≥2.0 µg/mL), indicating that the increase in the control group hSBA-MenY titers between the third and fourth vaccinations was not due to anti-MenY polysaccharide-specific antibodies.
- Immunogenicity against MMR and varicella antigens was not affected by co-administration with HibMenCY (data not shown).

Safety

- Injection site pain, irritability and drowsiness were the most frequently reported solicited local and general symptoms in both groups during the 4-day (Days 0–3) follow-up period post-doses 1, 2, 3, and 4 (Table 1).
- Incidences of SAEs, NOCDs, rash and AEs resulting in ER visit from dose 1 until 6 months post-dose 4 were similar between the HibMenCY and Hib groups (Table 2).
- In the primary vaccination phase, two subjects (HibMenCY group) reported a vaccine-related SAE; both experienced pyrexia (fever >40°C) on the day of the first dose and recovered without sequelae. In the fourth dose phase, two subjects (HibMenCY group) reported SAEs (pyrexia and neutropenia, and idiopathic thrombocytopenic purpura [ITP]) that the investigator considered related to vaccination. The ITP was specifically thought to be related to the co-administered MMR vaccine. All events completely resolved ≤5 days after onset, except for the ITP which resolved 53 days after onset.

Figure 3: Percentage of infants with hSBA titers ≥1:4 and ≥1:8 to a) serogroup C (MenC) b) serogroup Y (MenY) in the HibMenCY and Hib control groups post-dose 3, pre- and post-dose 4 (US ATP cohort for immunogenicity). Error bars represent 95% confidence intervals

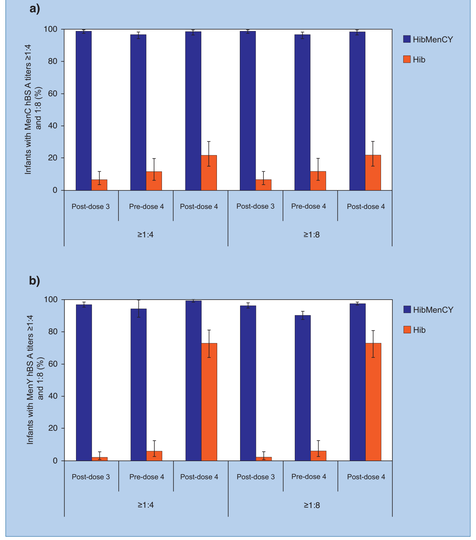


Figure 4: GMT post-dose 4 by pre-dose 4 ratio for serogroup C (MenC) and serogroup Y (MenY) (US ATP cohort for immunogenicity). Error bars represent 95% confidence intervals

Table 1: Percentage of subjects in the HibMenCY (A) and Hib (B) groups experiencing solicited and local general symptoms within the 4-day (Days 0–3) follow-up post-dose 1, 2, 3 and 4 (Total Vaccinated Cohort; NCT00289783)

A		HibMenCY							
Symptom	Category	Post-dose 1		Post-dose 2		Post-dose 3		Post-dose 4	
		N	%	N	%	N	%	N	%
Injection site pain	All	3056	48.9 [47.1, 50.7]	2901	46.5 [44.6, 48.3]	2738	42.3 [40.4, 44.2]	2528	52.2 [50.2, 54.1]
	Grade 3	3056	6.9 [6.0, 7.9]	2901	5.5 [4.7, 6.4]	2738	4.1 [3.4, 4.9]	2528	2.4 [1.8, 3.0]
Injection site redness	All	3056	22.0 [20.6, 23.5]	2901	31.1 [29.4, 32.8]	2738	35.4 [33.6, 37.3]	2528	48.0[46.0, 50.0]
	Grade 3	3056	0.1 [0.0, 0.3]	2901	0.2 [0.1, 0.4]	2738	0.1 [0.0, 0.3]	2528	2.5[2.0, 3.2]
Injection site swelling	All	3056	14.0 [12.8, 15.3]	2901	19.2 [17.8, 20.7]	2738	22.1 [20.5, 23.7]	2526	37.1[35.2, 39.0]
	Grade 3	3056	0.3 [0.2, 0.6]	2901	0.3 [0.1, 0.5]	2738	0.2 [0.1, 0.5]	2526	2.1[1.5, 2.7]
Drowsiness	All	3055	61.0 [59.3, 62.7]	2900	54.8 [52.9, 56.6]	2736	46.1 [44.2, 47.9]	2526	43.1[41.1, 45.0]
	Grade 3	3056	2.9 [2.3, 3.5]	2900	2.9 [2.3, 3.6]	2736	1.9 [1.4, 2.4]	2526	1.7[1.2, 2.2]
Fever	All	3056	22.5 [21.0, 24.0]	2900	27.7 [26.1, 29.4]	2736	22.3 [20.7, 23.9]	2527	13.5[12.2, 14.9]
	Grade 3	3056	0.0 [0.0, 0.2]	2900	0.1 [0.0, 0.2]	2736	0.2 [0.1, 0.5]	2527	0.2[0.0, 0.4]
Irritability	All	3055	70.6 [68.9, 72.2]	2900	71.5 [69.8, 73.2]	2736	64.7 [62.9, 66.5]	2526	58.7[56.7, 60.6]
	Grade 3	3056	4.1 [3.4, 4.9]	2900	5.2 [4.5, 6.1]	2736	3.6 [2.9, 4.3]	2526	3.1[2.4, 3.8]
Loss of appetite	All	3055	33.5 [31.8, 35.2]	2900	31.8 [30.1, 33.5]	2736	30.3 [28.5, 32.0]	2526	32.7[30.8, 34.5]
	Grade 3	3056	0.5 [0.3, 0.8]	2900	0.6 [0.4, 1.0]	2736	0.5 [0.3, 0.9]	2526	1.4[1.0, 2.0]
B		**Hib**							
Symptom	Category	Post-dose 1		Post-dose 2		Post-dose 3		Post-dose 4	
		N	%	N	%	N	%	N	%
Injection site pain	All	1008	60.9 [57.8, 63.9]	953	53.9 [50.7, 57.1]	904	51.2 [47.9, 54.5]	832	59.4 [55.9, 62.7]
	Grade 3	1008	13.2 [11.2, 15.4]	953	8.0 [6.3, 9.9]	904	5.1 [3.7, 6.7]	832	6.9 [5.2, 8.8]
Injection site redness	All	1008	29.2 [26.4, 32.1]	953	33.6 [30.6, 36.7]	904	40.2 [36.9, 43.4]	833	55.6 [52.1, 59.0]
	Grade 3	1008	1.5 [0.8, 2.4]	953	0.3 [0.1, 0.9]	904	0.4 [0.1, 1.1]	833	2.6 [1.7, 4.0]
Injection site swelling	All	1008	19.4 [17.0, 22.0]	953	19.9 [17.4, 22.6]	904	25.6 [22.7, 28.5]	832	40.1 [36.8, 43.6]
	Grade 3	1008	1.1 [0.5, 1.9]	953	0.2 [0.0, 0.8]	904	0.2 [0.0, 0.8]	832	2.8 [1.8, 4.1]
Drowsiness	All	1008	65.0 [61.9, 67.9]	952	58.0 [54.8, 61.1]	905	49.1 [45.8, 52.4]	830	45.9 [42.5, 49.4]
	Grade 3	1008	3.2 [2.2, 4.5]	952	3.0 [2.0, 4.3]	905	1.7 [0.9, 2.7]	830	1.6 [0.8, 2.7]
Fever	All	1008	22.6 [20.1, 25.3]	951	29.0 [26.2, 32.0]	905	22.8 [20.1, 25.6]	831	16.1 [13.7, 18.8]
	Grade 3	1008	0.0 [0.0, 0.4]	951	0.1 [0.0, 0.6]	905	0.2 [0.0, 0.8]	831	0.1 [0.0, 0.7]
Irritability	All	1008	77.6 [74.9, 80.1]	952	74.4 [71.5, 77.1]	905	66.3 [63.1, 69.4]	830	64.3 [61.0, 67.6]
	Grade 3	1008	7.7 [6.2, 9.6]	952	5.9 [4.5, 7.6]	905	4.6 [3.4, 6.2]	830	3.7 [2.6, 5.3]
Loss of appetite	All	1008	37.2 [34.2, 40.3]	952	33.3 [30.3, 36.4]	905	31.5 [28.5, 34.6]	830	34.6 [31.3, 37.9]
	Grade 3	1008	0.4 [0.1, 1.0]	952	0.8 [0.4, 1.6]	905	0.9 [0.4, 1.7]	830	1.8 [1.0, 3.0]

N, total number of subjects
Grade 3: pain, cried when limb was moved/spontaneously painful; redness/swelling, >30 mm diameter; drowsiness that prevented normal activity; fever, >40°C; irritability, crying that could not be comforted/prevented normal activity; loss of appetite, not eating at all
[], lower and upper limits of 95% confidence intervals

Table 2: Percentage of subjects in the HibMenCY and Hib groups with SAE, NOCD, rash and AEs resulting in ER visits from vaccination at dose 1 until 6 months post-dose 4 (end of the study) (Pooled Total Vaccinated Cohort; NCT00289783 and NCT00345579).

Symptom	HibMenCY N=6414		Hib N=2157	
	n	% [95% CI]	n	% [95% CI]
SAE	388	6.0 [5.5, 6.7]	130	6.0 [5.1, 7.1]
NOCD	341	5.3 [4.8, 5.9]	120	5.6 [4.6, 6.6]
Rash	1209	18.8 [17.9, 19.8]	416	19.3 [17.6, 21.0]
ER visit	613	9.6 [8.8, 10.3]	215	10.0 [8.7, 11.3]

N, total number of subjects; n, number of subjects reporting at least one symptom; SAE, serious adverse event; NOCD, new-onset chronic disease; ER, emergency room; CI, confidence interval

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CONCLUSIONS

- HibMenCY was non-inferior to licensed Hib vaccines in terms of the percentage of subjects achieving the long-term immunologic correlate of protection after dose 3 and dose 4. Anti-PRP GMCs were statistically significantly higher in the HibMenCY group than the licensed Hib vaccine group at all time points, suggesting that HibMenCY could be an important addition to the Hib vaccine supply in the US.
- HibMenCY was highly immunogenic against MenC and MenY in >95% of vaccinees as early as 1 month after dose 3, with primary immunogenicity endpoints being met post-dose 4.
- The increase in MenY hSBA titer in the Hib control group following dose 4 is not due to the inductions of anti-polysaccharide Y-specific IgG; these results are potentially related to immune responses induced by the meningococcal outer membrane proteins used as the carrier protein in the conjugate vaccine *PedvaxHIB®*, which may be cross-reactive with surface antigens on the MenY strain used in the GSK hSBA-MenY assay.
- HibMenCY had an acceptable safety profile in the pooled analysis of two large Phase III studies.
- HibMenCY could potentially protect children early in life against invasive Hib and *N. meningitidis* serogroups C and Y without the need for additional injections or medical visits.

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