International Journal of Infectious Diseases 28 (2014) 204–210

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Immunogenicity and safety of a novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) in healthy Korean adolescents and adults

Hoan Jong Lee [a,b,*], Moon-Hyun Chung [c], Woo Joo Kim [d], Young Jin Hong [c], Kyong Min Choi [e], Jina Lee [f,1], Chi Eun Oh [g], Jo Anne Welsch [h], Kyung-Hyo Kim [i], Ki Bae Hong [a], Alemnew F. Dagnew [h], Hans Bock [h], Peter M. Dull [h], Tatjana Odrljin [h]

[a] Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-769, Korea
[b] Seoul National University College of Medicine, Seoul, Korea
[c] Inha University Hospital, Incheon, Korea
[d] Korea University Guro Hospital, Seoul, Korea
[e] Myongji Hospital, Kwandong University College of Medicine, Koyang, Korea
[f] Seoul National University Bundang Hospital, Seongnam, Korea
[g] Kosin University College of Medicine, Busan, Korea
[h] Novartis Vaccines and Diagnostics, Cambridge, Massachusetts, USA
[i] Ewha Womans University School of Medicine, Seoul, Korea

ARTICLE INFO

Article history:
Received 3 March 2014
Received in revised form 2 June 2014
Accepted 9 June 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Neisseria meningitidis
Conjugate vaccines
Quadrivalent meningococcal vaccine
Korea

SUMMARY

Objectives: This phase III placebo-controlled study evaluated the immunogenicity and safety of MenACWY-CRM vaccination in healthy Korean adolescents and adults.
Methods: Serum bactericidal activity with human complement (hSBA) was measured before and 1 month after vaccination against all four meningococcal serogroups. The IgG concentration specific for serogroup W capsular polysaccharide was measured in a subset of subjects in a post-hoc analysis. Adverse reactions were monitored throughout the study.
Results: Four hundred and fifty subjects were randomized 2:1 to receive MenACWY-CRM (N = 297) or a saline placebo (N = 153). MenACWY-CRM induced a good immune response against all four serogroups, with seroprotection rates (hSBA titers ≥8) of 79%, 99%, 98%, and 94% for serogroups A, C, W, and Y, respectively. Seroresponse rates were high for serogroups A, C, and Y, i.e. 76%, 86%, and 69%, respectively; the rate for serogroup W was 28%. MenACWY-CRM vaccine induced serum bactericidal antibodies against all four serogroups in a majority of subjects regardless of their baseline hSBA titers. MenACWY-CRM was generally well tolerated with most reactions being transient and mild to moderate in severity.
Conclusions: Findings of this first study of a quadrivalent meningococcal polysaccharide conjugate vaccine in Korean adults and adolescents demonstrated that a single dose of MenACWY-CRM was well tolerated and immunogenic, as indicated by the percentages of subjects with hSBA titers ≥8 (79%, 99%, 98%, and 94% of subjects) and geometric mean titers (48, 231, 147, and 107) against serogroups A, C, W, and Y, respectively, at 1 month post-vaccination.

* Corresponding author. Tel.: +82 2 2072 3633; fax: +82 2 745 4703.
E-mail address: hoanlee@snu.ac.kr (H.J. Lee).
[1] Asan Medical Center, University of Ulsan, Seoul, Korea.

http://dx.doi.org/10.1016/j.ijid.2014.06.008

1. Introduction

Neisseria meningitidis (N. meningitidis) is a leading cause of bacterial meningitis and sepsis worldwide, capable of causing outbreaks and epidemics of invasive disease.[1,2] Permanent disability or death can occur within hours of symptom onset and morbidity and mortality rates are high even among the patients who receive early antibiotic treatment.[3,4] Approximately 500 000 cases of meningococcal disease occur annually worldwide with a case-fatality rate of ≥10%.[5] Although the highest rates of meningococcal disease are in infants <1 year of age, a second peak occurs in adolescence.[6,7]

Based on antigenic differences in their capsular polysaccharide, at least 12 immunologically distinct serogroups of *N. meningitidis* have been identified.[8] However, >90% of disease is caused by serogroups A, B, C, W, and Y.[9] Serogroups B, C and Y cause much of the meningococcal disease in the USA, Europe, and Australia, whereas serogroup A, C, and W disease is more common in Asia and Africa.[9,10]

MenACWY-CRM (Menveo®; Novartis Vaccines and Diagnostics), a quadrivalent polysaccharide–CRM_{197} conjugate vaccine containing meningococcal serogroups A, C, W, and Y, has been approved for licensure in more than 50 countries including the USA[11] (in individuals 2 months to 55 years of age) and those of the European Union[12] (in subjects 11 years and older).

Previous phase II and III clinical trials have demonstrated MenACWY-CRM to be highly immunogenic and well tolerated in infants,[13,14] children,[15] adolescents,[16–18] and adults.[18–20]

In Korea, meningococcal disease is a notifiable disease. In a recent report, 401 cases of bacterial meningitis were observed in 17 university hospitals in Korea between 1996 and 2005. *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *N. meningitidis* were the major etiologic agents of bacterial meningitis in Korean children >3 months of age. *N. meningitidis* was responsible for 4.5% of all cases, with a case-fatality rate of 16.7%.[21] At the time this study was conducted, there were no vaccines licensed in Korea for the control of meningococcal disease.

This study was designed to evaluate the immunogenicity and safety of a single dose of MenACWY-CRM in healthy adolescents and adults 11–55 years of age in Korea.

2. Materials and methods

2.1. Study design

This multicenter, observer-blind, placebo-controlled phase III study was conducted at eight centers in Korea from December 2010 to March 2011 (ClinicalTrials.gov identifier NCT01274897). The study was undertaken in accordance with Good Clinical Practice and the Declaration of Helsinki. The ethics review committee of each participating center approved the protocol, and written informed consent was obtained from every participant, or legal guardians where appropriate, prior to enrolment.

2.2. Study subjects

A total of 450 participants were randomized 2:1 to receive one dose of MenACWY-CRM (N = 297) or saline placebo (N = 153). Eligible study participants were healthy subjects of either sex between 11 and 55 years of age. Subjects were excluded if they had a history of a previous or suspected disease caused by *N. meningitidis* or had received any meningococcal vaccine, had a serious acute, chronic, or progressive disease, were pregnant, or had received any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment.

2.3. Vaccine

Each 0.5-mL dose of MenACWY-CRM was composed of 10 μg of MenA oligosaccharide and 5 μg each of oligosaccharides from MenC, MenW, and MenY conjugated to CRM_{197}. The vaccine was prepared by extemporaneous mixing of the lyophilized MenA component with the liquid MenCWY component immediately before intramuscular injection in the deltoid area of the non-dominant arm. Each 0.5-mL dose of saline placebo contained 4.5 mg sodium chloride in water for injection.

2.4. Immunogenicity

Blood samples were obtained for immunogenicity testing on Day 1 (pre-vaccination) and Day 29 (1 month post-vaccination).

2.5. Serum bactericidal assay

Functional bactericidal antibodies were measured in pre- and post-vaccination serum (in the same assays) using human complement (hSBA) in the laboratories of Novartis Vaccines (Marburg, Germany), as described previously.[14] The strains used for measurement of anti-capsular bactericidal responses of serogroups A, C, W, and Y are presented in Table 1.

2.6. ELISA

The antibody concentration specific to serogroup W capsular polysaccharide was assessed by enzyme-linked immunosorbent assay (ELISA) in pre- and post-vaccination serum samples from a subset of subjects (MenACWY-CRM group, N = 50; placebo group, N = 20) in a post-hoc analysis. ELISA testing was performed at the Health Protection Agency, Manchester, UK, as described previously.[22]

2.7. Safety

The safety and tolerability of MenACWY-CRM was assessed in all subjects. Solicited local and systemic reactions were self-recorded on diary cards for 7 days post-vaccination. All medically attended adverse events (AEs) or serious AEs (SAEs) were monitored for 29 days post-vaccination.

2.8. Statistical analysis

The primary immunogenicity objective was to assess the immunogenicity of MenACWY-CRM as measured by the seroresponse rate at 1 month post-vaccination (Day 29). A conditional definition of seroresponse was used, in which seroresponse was defined as a post-vaccination hSBA titer ≥8 for subjects who were seronegative at baseline (hSBA titers <4), whereas for subjects who were seropositive at baseline (hSBA titers ≥4), seroresponse was defined as a ≥4-fold increase over baseline hSBA titer. The primary

Table 1
Strains used for measurement of anticapsular bactericidal responses of serogroups A, C, W, and Y

Strain	Target antigen	Phenotype	Clonal complex (ST)
240070	W	W:NT:P1.18-1,3	22 (184)
C11	C	C:16:P1.7-1,1	NA (345)
F8238	A	A:4,21:P1.20,9	5 (5)
860800	Y	Y:NT:P1.5	167 (29)

objective was considered met if the lower limit of the two-sided 95% Clopper–Pearson confidence interval (LL 95% CI) for the overall seroresponse rate was ≥50% for all four serogroups.

Secondary objectives included immunogenicity assessment as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA titers ≥8 at 1 month post-vaccination, per serogroup. In a post-hoc analysis, antibodies against serogroup W polysaccharide were measured by ELISA and expressed as IgG antibody geometric mean concentrations (GMCs). An IgG concentration ≥2.0 μg/mL was used as the cut-off. This level has been proposed for serogroups A and C and thus was applied in this analysis, although protection is not presumed since the correlate has not been established for MenW.[23–26] Pearson's correlation coefficients were used to assess the relationship between hSBA titers and concentration of antibodies determined by ELISA.

Sample size calculations were based on previous Novartis studies[17,20] conducted in the same age group, in which seroresponse rates of 71%, 72%, 67%, and 64% were observed for serogroups A, C, W, and Y, respectively. Assuming similar results, the power to detect a seroresponse rate ≥50% given 240 evaluable subjects would be ≥99% for each of the four serogroups, for an overall power of 96%. GMTs were computed by exponentiating (base 10) the least square means of the logarithmically transformed (base 10) titers, and their 95% CIs were obtained from a two-way analysis of variance with factors for vaccine group and center. The percentage of subjects with hSBA titers ≥8 and associated 95% CIs were computed for each vaccine group, using normal approximation where appropriate. Safety data were expressed as the number or percentage of subjects with AEs in each group.

All statistical analyses were performed using SAS® version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Subjects

A total of 450 healthy subjects were enrolled, 297 of whom received a dose of MenACWY-CRM and 153 of whom received the saline placebo (Figure 1). The mean age was 19.5 years (MenACWY-CRM, 19.6 years (mean) ± 9.2 (standard deviation); placebo, 19.3 years ± 8.9); all were of Asian origin and 52% were male. Height (164 cm ± 10.0; 163.9 cm ± 8.9) and weight (58.0 kg ± 12.7; 58.8 kg ± 12.9) were similar between the MenACWY-CRM and placebo groups, respectively. All enrolled subjects completed the study.

3.2. Immunogenicity

The immunogenicity analysis was based on the per-protocol (PP) population, which included all subjects who received an appropriately timed vaccine dose and provided appropriately timed evaluable serum samples (MenACWY-CRM, N = 296; placebo, N = 152).

The majority of MenACWY-CRM group subjects achieved seroresponse against serogroups A (76%), C (86%), and Y (69%), while the rate for serogroup W was 28% (Figure 2). The LL 95% CIs for these seroresponse rates were 71%, 82%, 23%, and 63% for serogroups A, C, W, and Y, respectively. As the LL 95% CI for the seroresponse rate against serogroup W was <50%, the primary objective was not met.

Among MenACWY-CRM vaccine recipients who were seronegative at baseline, high seroresponse rates were achieved: 76% (95% CI 70–81%) for serogroup A, 96% (95% CI 91–99%) for serogroup C, 84% (95% CI 67–95) for serogroup W, and 89% (95% CI 82–94%) for serogroup Y. Comparatively few subjects were

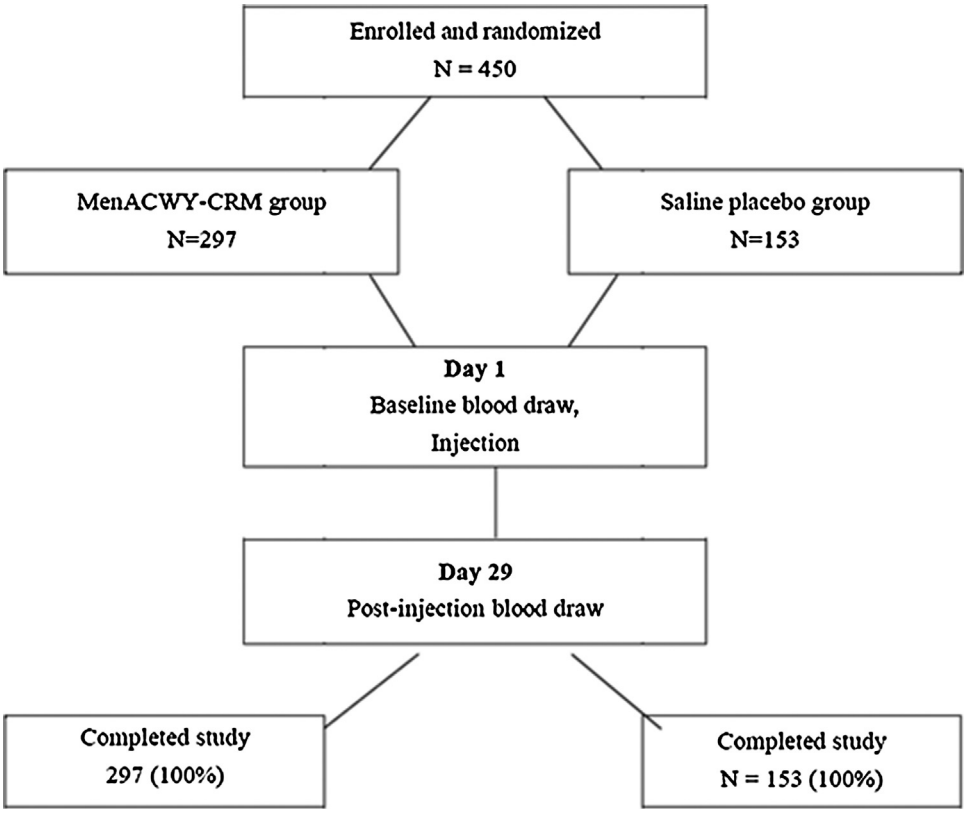

Figure 1. Participant flow chart.

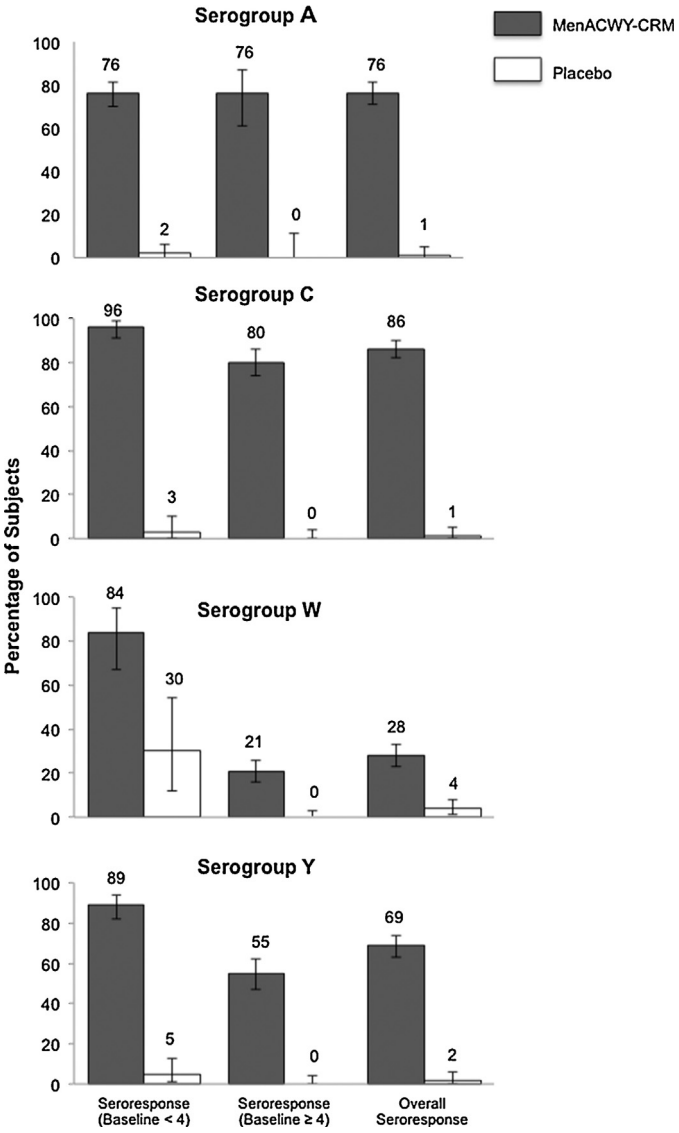

Figure 2. Seroresponse rates per serogroup and per vaccine group at 1 month post-vaccination (Day 29): overall seroresponse rates and seroresponse rates in subsets of subjects who were seronegative at baseline and seropositive at baseline. Overall seroresponse: post-vaccination hSBA titers ≥8 for subjects who were seronegative (hSBA titers <4) at baseline; ≥4-fold increase over pre-vaccination titers for subjects who were seropositive (hSBA titers ≥4) at baseline. hSBA, serum bactericidal activity assay using human complement.

seropositive (hSBA titers ≥4) for serogroup A at baseline (MenACWY-CRM, 17%; placebo, 21%), but high percentages of subjects were baseline seropositive for serogroups C (62%, 55%), W (89%, 87%), and Y (60%, 59%) in the MenACWY-CRM and placebo groups, respectively.

Baseline GMTs were comparable between the groups for serogroups A (2.7, 2.9), C (7.8, 5.9), and Y (9.0, 8.8), respectively, however the GMTs were higher against serogroup W (51, 48). In the placebo group, GMTs did not differ significantly between Days 1 and 29 for any serogroup. In contrast, an increase in GMTs was observed in the MenACWY-CRM group at 29 days post-vaccination, with 18-, 29-, 2.9-, and 12-fold increases over baseline with GMTs of 48, 231, 147, and 107 for serogroups A, C, W, and Y, respectively (Figure 3A). The percentages of subjects with hSBA titers ≥8 at baseline were relatively high for serogroups C (49%; 39%), W (89%; 87%), and Y (54%; 53%) and low for serogroup A (13%; 15%) in the MenACWY-CRM and placebo groups, respectively. After MenACWY-CRM vaccination, these rates increased to 79%, 99%, 98%, and 94% for serogroups A, C, W, and Y, respectively (Figure 3B), but there was no increase for any serogroup in the placebo group.

Responses to serogroup W at baseline and 1 month post-vaccination are shown in the reverse cumulative distribution of hSBA titers (Figure 4). The curve for the MenACWY-CRM group at 1 month post-vaccination is further to the right, illustrating a pre- to post-vaccination increase in the MenACWY-CRM group but not the placebo group.

In order to explore the specificity of bactericidal antibodies against the serogroup W capsule, post-hoc testing of sera from 50 MenACWY-CRM subjects (40 baseline seropositive and 10 baseline seronegative) and 20 placebo group subjects (16 baseline seropositive and four baseline seronegative) was performed by serogroup W specific IgG ELISA. Pre-vaccination ELISA GMCs against serogroup W capsule were 0.37 μg/mL and 0.14 μg/mL in the MenACWY-CRM and placebo groups, respectively. One month post-vaccination, GMCs against serogroup W had risen to 20 μg/mL in the MenACWY-CRM group but remained low in the placebo group (0.23 μg/mL) (Table 2). Using the ≥2.0 μg/mL cut-off, 94% of MenACWY-CRM recipients and 0% of placebo group subjects showed elevated responses at 1 month post-vaccination (Table 2). Also, there was a negligible correlation ($r = 0.19$; $p = 0.12$) between pre-vaccination hSBA titers and pre-vaccination serogroup W polysaccharide-specific IgG concentrations (ELISA), whereas there was a significant post-vaccination correlation between hSBA titers and IgG concentrations in MenACWY-CRM group subjects ($r = 0.52$; $p < 0.001$).

3.3. Safety

All enrolled subjects (450) were included in the safety analysis. MenACWY-CRM vaccination was generally well tolerated. The percentage of subjects reporting solicited local reactions within 7 days of vaccination was higher in the MenACWY-CRM group (28%) than in the placebo group (9%), whereas the percentage of subjects reporting systemic reactions was similar in both groups (28%). MenACWY-CRM vaccination was associated with more reports of transient, mild to moderate injection site pain (23% vs. 8%) than placebo injections. The most common systemic reaction was myalgia, reported by 15% and 8% in the MenACWY-CRM and placebo groups, respectively, and none were severe. Fever (≥38 °C) was reported by 1% of subjects in each group and none had a temperature ≥40 °C (Table 3).

Unsolicited AEs during Days 1–29 were reported in 12% of subjects in the MenACWY-CRM group and 7% in the placebo group; 4% of subjects in the MenACWY-CRM group and 1% in the placebo group reported unsolicited AEs that were possibly or probably related to vaccination. The most commonly reported AE was injection site pruritus, reported by three subjects (1%) after MenACWY-CRM vaccination. There were no SAEs, deaths, or premature withdrawals reported during the study.

4. Discussion

This study was the first evaluation of the immunogenicity and tolerability of MenACWY-CRM in healthy Korean adolescents and adults. MenACWY-CRM vaccination induced an immune response against all four serogroups, as evidenced by the percentages of subjects with hSBA titers ≥8 (79%, 99%, 98%, and 94% for serogroups A, C, W, and Y, respectively) and increases in the ratio of hSBA GMTs against the four serogroups (2.9- to 29-fold increases). This immune response is similar to that measured in subjects 11–55 years of age in two pivotal clinical studies used for licensure in Europe and the rest of the world.[17,20]

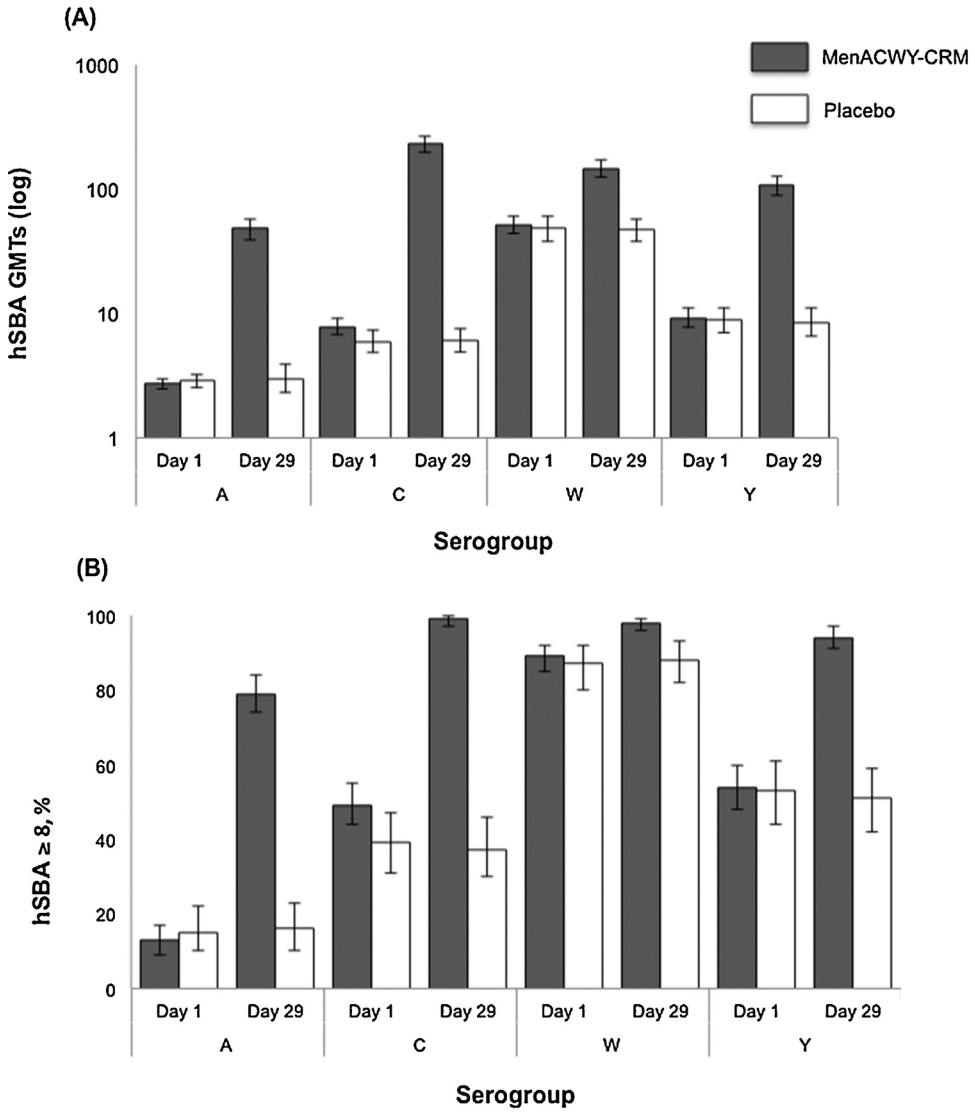

Figure 3. (A) hSBA GMTs at baseline (Day 1) and at 1 month post-vaccination (Day 29), and (B) percentages of subjects with hSBA titers ≥8 at baseline and at 1 month post-vaccination in the MenACWY-CRM and placebo groups. hSBA, serum bactericidal activity assay using human complement; GMT, geometric mean titer.

Immunogenicity as measured by seroresponse was predefined in this study as contingent upon pre-vaccination hSBA titers: for baseline seronegative subjects (hSBA titers <4), seroresponse was defined as post-vaccination hSBA titers ≥8, and for baseline seropositive subjects (hSBA titers ≥4), as a ≥4-fold increase over pre-vaccination titers. Seroresponse rates against serogroups A, C, and Y (and associated LL 95% CIs) were somewhat higher in the present study in comparison with the previous MenACWY-CRM studies conducted in the same age range.[17,20] However the seroresponse rate for serogroup W was lower in the present study; 28% of subjects achieved seroresponse for serogroup W at 1 month post-vaccination. Seroresponse is defined by the pre-vaccination antibody levels, and in this study, pre-vaccination hSBA was particularly striking for serogroup W, with 88% of the subjects baseline seropositive, much higher than in previous studies. Focusing on those subjects who were baseline seronegative for serogroup W, 84% achieved seroresponse for serogroup W and the LL 95% CI was 67%, which would have satisfied the predefined criteria. Also, the percentage of subjects with hSBA titers ≥8 for serogroup W at 1 month post-vaccination was significantly higher in MenACWY-CRM recipients than in the placebo group (as evidenced by non-overlapping CIs) (Figure 2). Figure 4 clearly illustrates the immunogenicity of MenACWY-CRM against the serogroup W strain despite the high baseline titers and corresponding low seroresponse. Thus the observed levels of pre-vaccination serogroup W hSBA titers in this study were analyzed further for specificity and warrant further discussion.

The serum bactericidal assay measures cumulative killing of all bactericidal antibodies in the vaccine recipient's serum against the test strain and is not specific for anti-capsular antibodies. Therefore, bactericidal antibodies against other non-capsular antigens contained in the outer membrane of any bacteria that cross-react with any of the proteins on this W strain or cross-reactive capsular polysaccharides could be responsible for the measured pre-vaccination hSBA titers. Because ELISA measures only anti-capsular polysaccharide antibodies, a comparison of hSBA and ELISA results can help determine the extent to which baseline hSBA titers reflect anti-capsular antibodies. We found a weak, non-significant correlation between serogroup W hSBA titers and serogroup W ELISA IgG concentrations for pre-vaccination samples ($r = 0.19$; $p = 0.12$). There was a significant correlation between hSBA titers and ELISA IgG concentrations in post-vaccination samples of subjects vaccinated with MenACWY-CRM ($r = 0.52$; $p < 0.001$). Similar correlations in post-vaccination

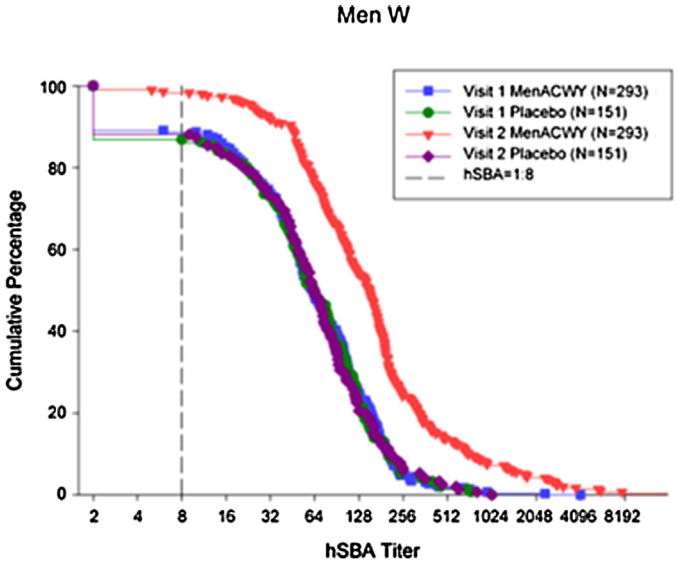

Figure 4. Reverse cumulative distribution of hSBA titers against serogroup W at baseline (Day 1) and at 1 month post-vaccination (Day 29) in the MenACWY-CRM group and placebo group. Day 1: MenACWY-CRM, blue squares; placebo, green circles. Day 29: MenACWY-CRM, red triangles; placebo, purple diamonds; hSBA 1:8 for reference, black dashed line.

Table 3
Numbers (%) of subjects with local and systemic reactions during the 7 days after vaccination

		MenACWY-CRM (N = 297)	Placebo (N = 153)
Local reactions			
Pain	Any	69 (23)	12 (8)
	Severe	0	0
Erythema (mm)	Any	30 (10)	3 (2)
	>100 mm	8 (3)	0
Induration (mm)	Any	30 (10)	0
	>100 mm	4 (1)	0
Systemic reactions			
Chills	Any	17 (6)	7 (5)
	Severe	0	0
Nausea	Any	22 (7)	10 (7)
	Severe	1 (<1)	0
Myalgia	Any	45 (15)	13 (8)
	Severe	0	0
Arthralgia	Any	6 (2)	4 (3)
	Severe	0	0
Headache	Any	39 (13)	25 (16)
	Severe	1 (<1)	0
Rash	Any	1 (<1)	0
	Severe	0	0
Fever (≥38 °C)	Yes	3 (1)	1 (1)
Other			
Axillary temperature	<38.0 °C	294 (99)	152 (99)
	≥40 °C	0	0
Use of analgesic or antipyretic	Yes	7 (2)	3 (2)

sera were demonstrated in a previous study.[27] In that study, no correlation was found between serogroup C hSBA and serogroup C ELISA antibody concentrations for pre-vaccination samples, but significant correlations were found in post-vaccination sera.

Further evidence of the specificity of the hSBA response to MenACWY-CRM vaccine is illustrated in the analysis of the W polysaccharide specific IgG GMCs. This data shows that pre-vaccination GMCs measured against serogroup W were low in both groups and GMCs increased between pre- and post-vaccination only in the MenACWY-CRM group, not in the placebo group. We used ≥2.0 μg/mL as the cut-off for analysis.[23,24] However, this cut-off was established in a Finnish efficacy study, which proposed this as a MenA correlate of protection. In that previous study, the concentration was measured in a majority of vaccinated individuals for whom the serogroup A polysaccharide vaccine was shown to be effective. No clear correlate of protection has been established for MenW.

In the present study, 94% of MenACWY-CRM recipients had putative protective levels of serogroup W IgG concentrations (≥2 μg/mL) at 1 month post-vaccination and similar percentages of subjects achieved this level regardless of whether they were baseline hSBA seronegative (90% ≥2 μg/mL) or seropositive (95% ≥2 μg/mL). In contrast, none of the placebo group subjects had serogroup W IgG concentrations ≥2.0 μg/mL at 1 month post-vaccination.

Taken together, the serogroup W hSBA and ELISA results imply that the bactericidal antibodies detected in pre-vaccination serum samples were, for the most part, not specific to serogroup W capsular polysaccharides. This highlights a limitation in the conditional definition of seroresponse. The definition assumes that pre-vaccination hSBA titers in subjects classified as baseline seropositive are largely specific to serogroup W capsular polysaccharides. As this appears not to be the case, the majority of subjects could more properly have been categorized as baseline seronegative for the relevant anti-capsular antibodies induced by the glycoconjugate vaccine. For seronegative subjects, seroresponse was defined as a post-vaccination hSBA titer ≥8, and 98% of MenACWY-CRM recipients had hSBA titers ≥8 against serogroup W.

The causes of the high naturally acquired (pre-vaccination) bactericidal antibodies in this population to serogroup W, as well as serogroups C and Y, cannot be attributed to antibodies specific for capsular polysaccharide antigens only. Antibody priming with cross-reactive antigens such as subcapsular protein antigens can occur during environmental exposure to *Neisseria spp*[28] or certain types of enteric bacteria.[29] Additional analysis with other serogroup W strains with different subcapsular antigens could have provided additional bactericidal data to clarify the high naturally acquired antibodies in this population, but was not possible in this case.

Table 2
Total IgG ELISA results against serogroup W, by pre-vaccination hSBA titer

	Baseline hSBA titer	Pre-vaccination ELISA GMC (μg/mL)	Post-vaccination ELISA GMC (μg/mL)	Post-vaccination % subjects with ≥2 μg/mL (95% CI)
MenACWY-CRM (N = 50)	hSBA<1:4 (N = 10)	0.28 (0.13–0.62)	17 (6.69–45)	90% (55–100%)
	hSBA ≥1:4 (N = 40)	0.39 (0.26–0.59)	21 (13–34)	95% (83–99%)
	Overall	0.37 (0.26–0.52)	20 (13–31)	94% (83–99%)
Placebo (N = 20)	hSBA<1:4 (N = 4)	0.14 (0.04–0.5)	0.14 (0.031–0.62)	0% (0–60%)
	hSBA ≥1:4 (N = 16)	0.14 (0.031–0.62)	0.26 (0.12–0.54)	0% (0–21%)
	Overall	0.14 (0.17–0.5)	0.23 (0.12–0.43)	0% (0–17%)

hSBA, serum bactericidal activity with human complement; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; CI, confidence interval.

The safety data demonstrate that MenACWY-CRM vaccination was generally well tolerated and had an acceptable safety profile. Only transient or mild to moderate solicited local and systemic reactions occurred. None of the subjects reported serious reactions. Previous MenACWY-CRM studies have also shown MenACWY-CRM to have an established safety profile in children,[15] adolescents,[16–18] and adults.[18–20]

In conclusion, this first study of a quadrivalent meningococcal polysaccharide conjugate vaccine in Korea demonstrates that a single dose of MenACWY-CRM was well tolerated and immunogenic in Korean adolescents and adults, as demonstrated by the percentages of subjects with hSBA titers ≥8 (79%, 99%, 98%, and 94% of subjects) and GMTs (48, 231, 147, and 107) against serogroups A, C, W, and Y, respectively, at 1 month post-vaccination.

Acknowledgements

The study was funded by Novartis Vaccines and Diagnostics. We acknowledge Drs Raju Gautam, PhD, Kathleen Jenks, PhD, Shanthi Voorn, PhD, Hari Sai Priya Baddela, PhD (Novartis Vaccines and Diagnostics), and Patricia de Groot, PhD (independent medical writer, CtrlP) for providing support in the manuscript preparation, revision, and editing.

Conflict of interest: Hoan Jong Lee has received honoraria for lectures and consultation from Novartis. Moon-Hyun Chung and Young Jin Hong have received honoraria from Novartis for lectures. Woo Joo Kim has received honoraria for lectures and consultation from Novartis Vaccines and GSK Biologicals. Jo Anne Welsch, Alemnew F. Dagnew, Hans Bock, Peter M. Dull, and Tatjana Odrljin are employees of Novartis Vaccines and Diagnostics. All other authors declare no further potential conflicts of interest.

References

1. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. *N Engl J Med* 2001;**344**:1378–88.
2. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in The Gambia, West Africa. *Trans R Soc Trop Med Hyg* 1987;**81**:536–8.
3. Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, et al. Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006;**367**:397–403.
4. Namani S, Koci R, Dedushi K. The outcome of bacterial meningitis in children is related to the initial antimicrobial therapy. *Turkish J Pediatr* 2010;**52**:354–9.
5. Agrawal S, Nadel S. Acute bacterial meningitis in infants and children. Epidemiology and management. *Pediatr Drugs* 2011;**13**:385–400.
6. American Academy of Pediatrics Committee on Infectious Diseases (AAP). Prevention and control of meningococcal disease: recommendations for use of meningococcal vaccines in pediatric patients. *Pediatrics* 2005;**116**:496–505.
7. Harrison LH, Pass MA, Mendelsohn AB, Egri M, Rosenstein NE, Bustamante A, et al. Invasive meningococcal disease in adolescents and young adults. *JAMA* 2001;**286**:694–9.
8. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcemia, and *Neisseria meningitidis*. *Lancet* 2007;**369**:2196–210.
9. Sabra A, Benger J. Meningococcal disease in children: a clinical review. *Turkish J Pediatr* 2011;**53**:477–88.
10. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine* 2009;**27S**:B51–63.
11. US Food and Drug Administration. Vaccines, Blood and Biologics. Menveo. FDA; 2013. Available at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm201342.htm (accessed February 7, 2014).
12. European Medicines Agency. EPAR summary. Menveo: meningococcal group A, C, W135, and Y conjugate vaccine. London, UK: EMA; 2012. Last updated 20/06/2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/001095/WC500090148.pdf (accessed February 7, 2014).
13. Klein NP, Reisinger KS, Johnston W, Odrljin T, Gill CJ, Bedell L, et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. *Pediatr Infect Dis J* 2012;**31**:64–71.
14. Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. *JAMA* 2008;**299**:173–84.
15. Black S, Klein NP, Shah J, Bedell L, Karsten A, Dull PM. Immunogenicity and tolerability of a quadrivalent meningococcal glycoconjugate vaccine in children 2–10 years of age. *Vaccine* 2010;**28**:657–63.
16. Arguedas A, Soley C, Loaiza C, Rincon G, Guevara S, Perez A, et al. Safety and immunogenicity of one dose of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, when administered to adolescents concomitantly or sequentially with Tdap and HPV vaccines. *Vaccine* 2010;**28**:3171–9.
17. Jackson LA, Baxter R, Reisinger K, Karsten A, Shah J, Bedell L, et al. Phase III comparison of an investigational quadrivalent meningococcal conjugate vaccine with the licensed meningococcal ACWY conjugate vaccine in adolescents. *Clin Infect Dis* 2009;**49**:e1–0.
18. Gasparini R, Conversano M, Bona G, Gabutti G, Anemona A, Dull P, et al. Randomized trial on the safety, tolerability, and immunogenicity of MenACWY-CRM, an investigational quadrivalent meningococcal glycoconjugate vaccine, administered concomitantly with a combined tetanus, reduced diphtheria, and acellular pertussis vaccine in adolescents and young adults. *Clin Vaccine Immunol* 2010;**17**:537–44.
19. Stamboulian D, Lopardo G, Lopez P, Cortez-Barbosa C, Valencia A, Bedell. et al. Safety and immunogenicity of an investigational quadrivalent meningococcal CRM (197) conjugate vaccine, MenACWY-CRM, compared with licensed vaccines in adults in Latin America. *Int J Infect Dis* 2010;**14**:e868–75.
20. Reisinger KS, Baxter R, Block SL, Shah J, Bedell L, Dull PM. Quadrivalent meningococcal vaccination of adults: phase III comparison of an investigational conjugate vaccine, MenACWY-CRM, with the licensed vaccine, Menactra. *Clin Vaccine Immunol* 2009;**16**:1810–5.
21. Cho HK, Lee H, Kang JH, Kim KN, Kim DS, Kim YK, et al. The causative organisms of bacterial meningitis in Korean children in 1996–2005. *J Korean Med Sci* 2010;**25**:895–9.
22. Gheesling LL, Carlone GM, Pais LB, Holder PF, Maslanka SE, Plikaytis BD, et al. Multicenter comparison of *Neisseria meningitidis* serogroup C anti-capsular polysaccharide antibody levels measured by a standardized enzyme-linked immunosorbent assay. *J Clin Microbiol* 1994;**32**:1475–82.
23. Peltola H, Mäkelä H, Käyhty H, Jousimies H, Herva E, Hällström K, et al. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children 3 months to 5 years of age. *N Engl J Med* 1977;**297**:686–91.
24. Mäkelä PH, Käyhty H, Weckström P, Sivonen A, Renkonen OV. Effect of group A meningococcal vaccine in army recruits in Finland. *Lancet* 1975;**2**:883–6.
25. Granoff DM, Maslanka SE, Carlone GM, Plikaytis BD, Santos GF, Mokatrin A, et al. A modified enzyme-linked immunosorbent assay for measurement of antibody responses to meningococcal C polysaccharide that correlate with bactericidal responses. *Clin Diagn Lab Immunol* 1998;**5**:479–85.
26. Mueller JE, Yaro S, Traore Y, Sangare L, Tarnagda Z, Njanpop-Lafourcade BM, et al. Neisseria meningitidis serogroups A and W-135: carriage and immunity in Burkina Faso, 2003. *J Infect Dis* 2006;**193**:812–20.
27. Sikkema DJ. Relationship between serum bactericidal activity and serogroup-specific immunoglobulin G concentration for adults, toddlers and infants immunized with *Neisseria meningitidis* serogroup C vaccines. *Clin Diagn Lab Immunol* 2000;**7**:764–8.
28. Sánchez S, Troncoso G, Criado MT, Ferreirós C. In vitro induction of memory-driven responses against *Neisseria meningitidis* by priming with *Neisseria lactamica*. *Vaccine* 2002;**26**:2957–63.
29. Robbins JB, Myerowitz RL, Whisnant JK, Argaman M, Schneerson R, Handzel ZT, et al. Enteric bacteria cross-reactive with *Neisseria meningitidis* groups A and C and *Diplococcus pneumoniae* types I and III. *Infect Immun* 1972;**6**:651–6.