IMMUNOGENICITY AND SAFETY OF INVESTIGATIONAL VACCINE FORMULATIONS AGAINST MENINGOCOCCAL SEROGROUPS A, B, C, W, AND Y IN ADOLESCENTS

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ABSTRACT

Background

We investigated novel formulations of meningococcal ABCWY vaccines in adolescents, using recombinant proteins (rMenB) and outer membrane vesicles (OMV) components of a European-approved serogroup B vaccine, with a licensed quadrivalent polysaccharide-protein conjugate ACWY vaccine (clinicaltrials.gov NCT01210885).

Methods

In this phase 2, multicenter, observer-blind, controlled study 495 (494 vaccinated) healthy 11–18 year-old adolescents were randomized to six study groups for two injections, two months apart, of the indicated vaccine formulations. Serum bactericidal activities with human complement (hSBA) were measured before and 1 month after each vaccination; adverse events were assessed throughout the study.

Results

Immunogenicity: After two vaccinations ACWY Groups I–IV seroresponse rates were: A (97–98%), C (95–97%), W (74–86%) and Y (92–96%), higher than in Group VI after one MenACWY vaccination, A (86%), C (68%), W (60%) and Y (78%). In Groups I–V, 94–100% elicited hSBA titers ≥ 5 to rMenB antigens after two doses, with only Groups III and IV having titers ≥ 5 to OMV (78% and 71%, respectively).

Safety: Solicited local reaction rates were higher in Groups I–IV (84–90%) than Groups V (80%) or VI (60%) after one dose, but similar across groups after the second dose (65–84%), consisting mainly of transient injection site pain. Solicited systemic reactions, mainly myalgia and headache, were reported by 62–76% and 46–59% after doses 1 and 2, respectively in Groups I–V, and 55% and 56% in Group VI. Fever (≥ 38.0°C) was rare ranging from 2–6% across groups. There was no vaccine-related SAE.

Conclusion

Various investigational ABCWY formulations elicited responses similar to those anticipated from the constituent ACWY and B vaccines, with generally acceptable tolerability.

BACKGROUND

- Meningococcal meningitis and sepsis are caused by *Neisseria meningitidis*, a gram-negative, encapsulated bacterium classified into 13 major serogroups on the basis of the chemical composition of distinctive capsular polysaccharides, of which five are responsible for the majority of disease (A, B, C, Y, and W-135). The epidemiology of meningococcal disease varies widely geographically (e.g. mainly B, C, and Y in North America, B and C in Europe, A in Africa, etc.), and peak incidence rates of meningococcal disease are generally found in infants and adolescents. High case fatality rates, with significant and substantial morbidity in survivors, make meningococcal disease a major public health concern. The rapidity of onset and frequent failure to respond to the most up-to-date medical interventions make prophylactic vaccination the only realistic means to control this disease.
- In the late 1960's vaccines were developed based on the immunologic response to the defining capsular polysaccharides. These vaccines were improved upon, to include herd protection and protection of infants, with the development of polysaccharide-protein conjugates in the 1990's, and improved breadth of protection with the licensure of quadrivalent conjugate ACWY vaccines from 2005.
- Inherent characteristics of the serogroup B polysaccharide meant this route was unsuitable and it has necessitated a novel approach to vaccine development which recently culminated in the licensure in Europe and Australia of 4CMenB, a serogroup B vaccine (Bexsero®, Novartis Vaccines) based on recombinant proteins with outer membrane vesicles (OMV) from the New Zealand outbreak strain.
- The control of meningococcal disease would be the most effective with all five vaccine-preventable serogroups in one vaccine. In this phase 2 study, novel formulations of components from licensed meningococcal ACWY and B vaccines (Novartis Vaccines) were investigated in adolescents aged 11-18 years.

Registered at clinicaltrials.gov **NCT01210885**.

METHODS

PARTICIPANTS

- This phase 2, multicenter, observer-blind, controlled study was performed with healthy 11–18 year-old adolescents in multiple centers in Chile (2), Colombia (3) and Panama (6) from December 2010 to July 2011.
- Ethical approval was obtained from all centers, with written informed consent from all participants and their parents/guardians, and the study was performed according to relevant ICH and GCP guidelines.
- Eligibility criteria were age of 11-18 years, good health based on medical examination at time of enrolment, provision of written informed consent, and availability for the entire period of the study. Main exclusion criteria included any history of meningococcal vaccination, or known or suspected exposure to meningococcal disease, any known medical condition that may compromise immune responses, history of allergic reactions to vaccines, or recent receipt of other vaccinations.

STUDY DESIGN AND PROCEDURES

- Subjects were randomly allocated (1:1:1:1:1:1) to six study groups (**Table 1**) before the first vaccination, the first injections of the respective vaccines were administered in the deltoid of the non-dominant arm; a second vaccination of the same respective vaccine (or placebo in Group VI) was administered at two months.
- Blood samples were drawn before the first vaccination, and 1 month after each vaccination.
- Reactogenicity was assessed as local and systemic solicited reactions within 7 days after each vaccination using diary cards, and adverse events were assessed throughout the study period.

VACCINES

Experimental formulations were manufactured using the components of the Novartis licensed vaccines:

- Menveo®, a quadrivalent ACWY vaccine in which the serogroup-specific oligosaccharides of *Neisseria meningitidis* serogroups A, C, W and Y are conjugated to CRM_{197} protein (a nontoxic mutant of *Corynebacterium diphtheriae* toxin).
- Bexsero®4CMenB, a serogroup B vaccine composed of a recombinant protein component (rMenB) with OMV from New Zealand strain. The three principal antigens in rMenB are factor binding protein (fHbp), Neisseria adhesin A (NadA), and Neisserial heparin binding antigen (NHBA).

All formulations (**Table 1**) were prepared in a final volume of 0.5 mL, except for the Group II vaccine with a double dose of rMenB which was presented in 1.0 mL.

Table 1. Vaccine Treatment Groups – subjects, formulations, and schedules

Group	N	Age (years)	Males (%)	Vaccine formulation Name	Components[a]	Schedule
I	81	13.7 +/- 2.0	41	MenABCWY	MenACWY + rMenB	Two doses - 0, 2 months
II	81	13.9+/- 2.1	46	MenABx2CWY	MenACWY + 2x rMenB	Two doses - 0, 2 months
III	83	13.8 ± 2.3	47	MenABCWY+OMV	MenACWY + rMenB + OMV	Two doses - 0, 2 months
IV	82	13.9 ± 1.9	54	MenABCWY+½OMV	MenACWY + rMenB + ½ OMV	Two doses - 0, 2 months
V	85	14.4 ± 2.2	48	rMenB	rMenB	Two doses - 0, 2 months
VI	82	14.2 +/- 2.2	46	MenACWY	MenACWY	MenACWY at 0 month; Placebo at 2 months

[a] rMenB and OMV at equivalent doses to 4CMenB, unless noted

SEROLOGY

Sera were assayed at the Novartis Clinical Laboratory Sciences (Marburg, Germany) for serogroup-specific bactericidal activity with human complement (hSBA) at pre- and post-vaccination time points.

- Responses to the rMenB and OMV components were assessed using serogroup B strains selected for specificity for vaccine components factor binding protein (fHbp, strain 44/76-SL), Neisseria adhesin A (NadA, strain 5/99), and NZ98/254 (OMV). Responses to the ACWY components were assessed using strains F8238 (MenA), C11 (MenC), M01-240070 (MenW) and 860800 (MenY).
- For serogroups A, C, W and Y, responses were reported as geometric mean titers (GMTs) and as proportions achieving a seroresponse. In subjects with a pre-vaccination hSBA < 4 a seroresponse was defined as a post-vaccination hSBA ≥ 8. For subjects with a pre-vaccination hSBA ≥ 4, a seroresponse was defined as an increase in hSBA titer of at least four times the pre-vaccination titer.
- For serogroup B, responses were reported as geometric mean titers (GMTs) and as proportions with titers hSBA ≥ 5 (equivalent to the protective titer with 95% confidence).

As this was an exploratory trial there was no formal statistical hypothesis, and immunogenicity and safety assessments were descriptive only.

RESULTS

PARTICIPANTS

- A total of 495 subjects were enrolled, and 494 received study vaccines, of whom 478 (97%) were included in the "per protocol" analysis of immunogenicity. Exclusions were principally due to missing blood samples, unavailability of serological results or deviations from vaccination schedule.

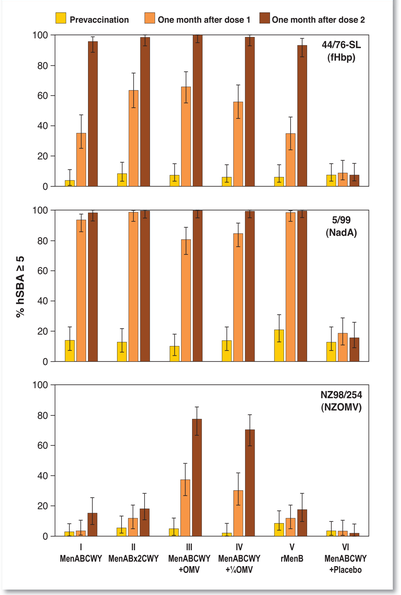
IMMUNOGENICITY – SEROGROUP B (FIGURE 1, TABLE 2)

- Bactericidal antibodies against two recombinant serogroup B antigen components (fHbp, NadA) in Groups I-V were increased after one dose of rMenB.
- Almost 100% of subjects achieved an hSBA titer ≥ 5 after the second dose, with further increases in GMTs than after the first dose .
- As expected, only Groups III & IV displayed significant responses to OMV (78% & 71%, respectively).

IMMUNOGENICITY – SEROGROUPS ACWY (FIGURE 2, TABLE 3)

- Bactericidal antibodies against serogroups ACWY were increased in Groups I–IV after a single dose and were similar to those in the ACWY group, A (86%), C (68%), W (60%) and Y (78%).
- A second dose in Groups I–IV elicited higher seroresponse rates for A (97–98%), C (95–97%), W (74–86%) and Y (92–96%).
- Two doses of rMenB alone (Group V) elicited bactericidal responses against non-B serogroups (i.e., reference strains for serogroups A (87%), C (29%), and W (47%)).

Figure 1. Proportions of each study group with hSBA titers ≥ 5 against serogroup B antigens before and one month after each vaccination



REACTOGENICITY AND SAFETY (TABLE 4)

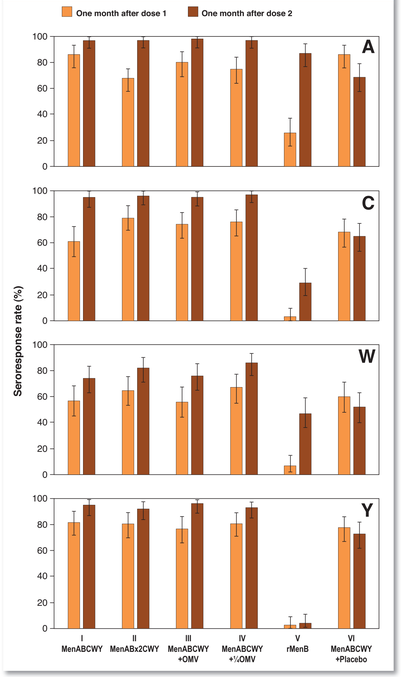
Local reactions

- Local solicited reaction rates after one dose were higher (84–90%) in the groups given vaccines containing both rMenB and ACWY components (Groups I–IV) than either rMenB (Group V) or ACWY (Group VI) alone.
  - Local reaction rates were lower after the second vaccination across all groups.
  - Most common local reaction was mild to moderate, transient pain at the injection site.

Systemic reactions

- After the first vaccination systemic solicited reactions were reported by 62–76% of the MenABCWY groups (I-IV), 62% of the rMenB group (group V), and 55% of the ACWY (group VI).
  - Reporting rates were lower (46–56%) across all groups after the second vaccination.
  - The most frequent solicited systemic reactions were myalgia and headache.

Figure 2. Seroresponse rates (95% CI) in each study group to serogroup A, C, W and Y after first and second vaccinations



- Fever (≥ 38.0°C) was rare, ranging from 2 to 6% across groups after the first vaccination, 3 to 7% after the second, with only one report of temperature ≥ 40°C, which occurred after a placebo injection in Group VI.

Other adverse events

- There were no vaccine-related SAEs
- Adverse events (AE) were experienced by 32 to 37% of subjects, with similar proportions in each group, but only 7 to 17% were considered as possibly related to vaccination.
  - The highest rate of possibly related (17%) was in the MenABCWY+OMV group.
  - The most common AEs by System Order Class were "infections and infestations" (12 to 20%), the majority of which were considered unrelated to vaccination.

Table 2. Geometric mean titers (GMTs) of serogroup B strains before, and one month after each after vaccination

Group	I	II	III	IV	V	VI
Strain 44/76-SL (fHbp)						
Pre-vaccination	1.17 (0.96-1.42) N = 80	1.33 (1.09-1.61) N = 79	1.34 (1.11-1.62) N = 81	1.24 (1.03-1.51) N = 81	1.31 (1.08-1.59) N = 82	1.34 (1.1-1.62) N = 82
1 month post 1st vaccination	4.22 (3.01-5.92) N = 79	9.98 (7.1-14) N = 78	13 (9.06-18) N = 80	9.03 (6.45-13) N = 80	3.74 (2.67-5.25) N = 78	1.65 (1.18-2.31) N = 81
1 month post 2nd vaccination	61 (49-77) N = 77	97 (78-123) N = 79	107 (85-135) N = 78	111 (88-139) N = 80	50 (40-63) N = 78	1.35 (1.08-1.7) N = 81
Strain 5/99 (NadA)						
Pre-vaccination	2.38 (1.9-2.99) N = 80	2.09 (1.67-2.62) N = 80	1.83 (1.46-2.29) N = 82	2.01 (1.6-2.52) N = 81	2.59 (2.07-3.24) N = 82	2.26 (1.8-2.82) N = 82
1 month post 1st vaccination	44 (33-59) N = 79	94 (71-124) N = 78	24 (18-32) N = 79	35 (26-46) N = 81	72 (54-95) N = 78	2.26 (1.71-2.99) N = 80
1 month post 2nd vaccination	262 (217-317)	368 (306-442)	323 (269-389)	340 (282-410)	347 (288-419)	2.15 (1.78-2.58)
Strain NZ98/254 (OMV)						
Pre-vaccination	1.66 (1.4-1.96) N = 80	1.52 (1.29-1.79) N = 80	1.7 (1.44-2) N = 82	1.66 (1.4-1.96) N = 81	1.94 (1.65-2.29) N = 82	1.49 (1.27-1.76) N = 82
1 month post 1st vaccination	1.98 (1.59-2.46) N = 79	2.15 (1.73-2.68) N = 78	4.9 (3.94-6.08) N = 80	3.47 (2.8-4.31) N = 81	1.77 (1.42-2.2) N = 78	1.71 (1.38-2.13) N = 80
1 month post 2nd vaccination	2.5 (1.99-3.14) N = 77	2.99 (2.39-3.74) N = 79	12 (9.98-16) N = 80	8.87 (7.08-11) N = 79	2.32 (1.84-2.91) N = 77	1.7 (1.36-2.13) N = 81

Table 3. Geometric mean titers (GMTs) of serogroups A, C, W and Y before, and one month after each after vaccination

Group	I	II	III	IV	V	VI
Serogroup A						
Pre-vaccination	1.45 (1.21-1.72) N = 80	1.34 (1.13-1.6) N = 80	1.28 (1.08-1.52) N = 82	1.22 (1.02-1.45) N = 81	1.2 (1.01-1.43) N = 82	1.4 (1.18-1.67) N = 82
1 month post 1st vaccination	56 (36-85) N = 78	73 (48-112) N = 78	49 (32-74) N = 79	41 (27-62) N = 81	3.36 (2.2-5.14) N = 78	105 (68-160) N = 78
1 month post 2nd vaccination	146 (105-203) N = 77	205 (148-283) N = 79	172 (125-238) N = 80	157 (114-218) N = 80	60 (43-84) N = 77	33 (24-46) N = 81
Serogroup C						
Pre-vaccination	4.6 (3.47-6.11) N = 80	3.8 (2.87-5.03) N = 80	4.57 (3.46-6.04) N = 82	4.56 (3.44-6.05) N = 80	4.59 (3.47-6.06) N = 82	4.04 (3.05-5.35) N = 81
1 month post 1st vaccination	54 (39-76) N = 79	78 (56-110) N = 78	76 (54-107) N = 80	82 (58-115) N = 80	5.83 (4.14-8.2) N = 78	59 (42-84) N = 79
1 month post 2nd vaccination	317 (250-401) N = 77	380 (301-481) N = 78	286 (226-361) N = 79	340 (268-431) N = 79	15 (12-19) N = 77	39 (31-49) N = 80
Serogroup W						
Pre-vaccination	19 (13-29) N = 80	17 (11-26) N = 79	20 (13-30) N = 82	18 (12-28) N = 80	22 (14-33) N = 81	19 (13-29) N = 82
1 month post 1st vaccination	143 (108-189) N = 79	204 (154-270) N = 78	183 (138-241) N = 79	199 (151-264) N = 80	24 (18-32) N = 77	188 (142-248) N = 80
1 month post 2nd vaccination	344 (285-414) N = 77	440 (365-531) N = 77	356 (296-427) N = 80	385 (320-464) N = 79	131 (108-158) N = 77	146 (122-176) N = 81
SerogroupY						
Pre-vaccination	4.3 (3.38-5.47) N = 80	4.11 (3.23-5.23) N = 79	4.35 (3.43-5.52) N = 82	4.24 (3.35-5.39) N = 82	4.45 (3.51-5.65) N = 82	5.76 (4.54-7.31) N = 82
1 month post 1st vaccination	76 (56-103) N = 79	77 (57-104) N = 78	67 (50-91) N = 79	75 (56-101) N = 81	4.56 (3.38-6.16) N = 78	77 (57-104) N = 81
1 month post 2nd vaccination	196 (159-243) N = 77	219 (178-271) N = 79	187 (152-231) N = 80	180 (147-221) N = 81	4.26 (3.45-5.25) N = 78	62 (51-77) N = 82

Table 4. Percentages of subjects reporting solicited local and systemic reactions within 7 days of vaccination

Group	I	II	III	IV	V	VI
Formulation	MenABCWY	MenABx2CWY	MenABCWY +OMV	MenABCWY +½ OMV	rMenB	MenACWY, then placebo
Injection: 1	N = 81	N = 81	N = 83	N = 82	N = 85	N = 82
Any	86%	90%	95%	91%	82%	68%
Local	84%	89%	93%	90%	80%	60%
Systemic	64%	67%	76%	76%	62%	55%
Injection: 2	N = 80	N = 80	N = 81	N = 81	N = 81	N = 82
Any	74%	70%	86%	78%	79%	80%
Local	68%	65%	84%	77%	74%	72%
Systemic	48%	46%	59%	48%	54%	56%

CONCLUSIONS

- **Various investigational ABCWY formulations using components of licensed ACWY and serogroup B vaccines elicited responses similar to those anticipated from the constituent vaccines.**
- **Only formulations that included OMV resulted in a robust immune response against the outer membrane protein PorA (NZ98/254 reference strain).**
- **There was generally acceptable tolerability with all investigational vaccine formulations.**

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