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INVESTIGATIONAL MENINGOCOCCAL ABCWY VACCINE IS EFFECTIVE AGAINST A BROAD PANEL OF SEROGROUP B INVASIVE DISEASE STRAINS IN US ADOLESCENTS: A PHASE 2, CONTROLLED, RANDOMIZED STUDY

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BACKGROUND

- 5 meningococcal serogroups (A, B, C, W and Y) account for nearly all invasive meningococcal disease globally, although the distribution of serogroups varies geographically and over time.
- An investigational meningococcal vaccine was developed against these 5 serogroups (MenABCWY).
- In previous studies, MenABCWY induced a robust immune response against vaccine-specific antigens and had an acceptable safety profile, in adolescents and young adults.[1]
- The endogenous complement human serum bactericidal assay (enc-hSBA), which uses the intrinsic complement present in the vaccinees' sera,[2] has been developed as a method of analyzing responses across a broad panel of *Neisseria meningitidis* serogroup B (MenB) strains.

OBJECTIVES

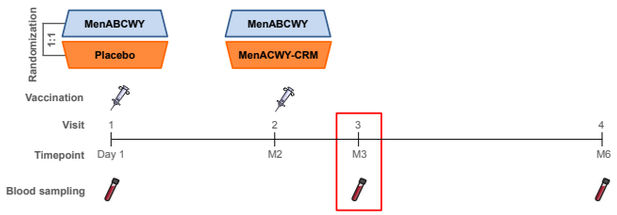
- To assess the effectiveness of the MenABCWY vaccine against a large epidemiologically representative, randomly selected panel of endemic US MenB invasive disease isolates, compared to the effectiveness of a single dose of MenACWY-CRM in healthy adolescents 10–18 years of age, based on:
  - ➤ the percentage (%) of subjects without bactericidal serum activity at 1:4 dilution, using enc-hSBA, at baseline (Day 1, prior to the study vaccination) and 1 month (M) post-dose 2 (at M3)
  - ➤ the distribution of subjects by % of MenB invasive disease isolates killed at 1:4 dilution, using enc-hSBA, at baseline and at M3.

METHODS

Study design and participants

- Phase 2b, observer-blind, multicenter study (NCT02140762) performed in 8 centers in the US between May 2014 and February 2015.
- Healthy adolescents were enrolled and randomized (1:1) to receive 2 doses of MenABCWY vaccine (at Day 1 and at M2) or 1 dose of placebo at Day 1 and 1 dose of licensed MenACWY-CRM vaccine[3] at M2 (**Figure 1**).

Figure 1. Study design



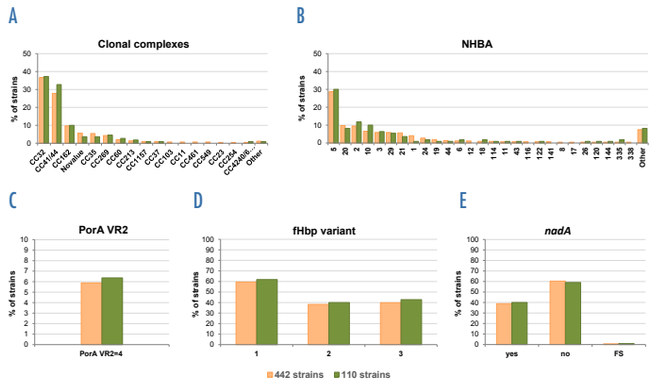
Vaccine	MenABCWY vaccine	MenACWY-CRM vaccine	Placebo
Composition	Lyophilized MenACWY reconstituted with 1 dose of rMenB+OMV	Meningococcal serogroups A, C, W, and Y oligosaccharide diphtheria CRM_{197} conjugate vaccine	Saline solution (NaCl, 0.9%)
Volume (per dose)	0.5 mL	0.5 mL	0.5 mL

M, month; **rMenB+OMV**, liquid suspension for injection containing recombinant proteins of *Neisseria meningitidis* serogroup B (936-741, 287-953 and 961c) + OMV adsorbed onto aluminum hydroxide; **OMV**, outer member vesicles from serogroup B strain NZ98/254; **CRM**, cross reactive material.

Effectiveness assessment

- MenB disease isolates were randomly selected from the Centers for Disease Control and Prevention (CDC) repository of 442 US endemic invasive meningococcal serogroup B disease isolates systematically collected between 2000 and 2008.
- 110 strains (25% of total CDC collection) were qualified by a predetermined protocol approved by health authorities and included in the study panel; the enc-hSBA assay was qualified for the 110 strains in the study panel.
- There were no differences between the 442 CDC strains and the panel of 110 strains in terms of distributions of multi locus sequence typing (MLST) clonal complex (cc), NHBA peptide, PorA VR2 identity, fHbp variant and the presence of the *nadA* gene (**Figure 2**).
- Each serum sample was tested against 20 to 50 strains, depending on serum volume available.
- Antibody levels against these strains were assessed using enc-hSBA, at baseline, M3 and M6 (**Figure 1**). Here, we present results up to M3.
- The serum was collected from each subject at each time point under carefully controlled conditions to preserve internal, endogenous complement activity.
- enc-hSBA testing was performed at 1:4 dilution, the read-outs for each strain were presented as "killed" or "non-killed".
- Vaccine effectiveness (VE) for individual strains was defined as 1- (% of subjects without enc-hSBA activity in MenABCWY group / % of subjects without enc-hSBA activity in MenACWY-CRM group) x 100. For the 110 strains combined, VE was calculated as the pooled VE for individual strains.

Figure 2. Comparison of meningococcal serogroup B strains, CDC panel versus study panel, by MLST clonal complex (A), NHBA peptide (B), PorA VR2 identity (C), fHbp variant (D), *nadA* gene presence (E)



MLST, multi locus sequence typing; **NHBA**, Neisserial Heparin Binding Antigen; **PorA VR2=4**, Porin A VR2 identity is P1.4; **fHbp**, factor H binding protein; ***nadA***, *Neisseria* adhesion A; **FS** refers to the presence of a frameshift mutation in the *nadA* gene.

Note: The 442 strains are from CDC panel and the 110 strains are from study panel.

RESULTS

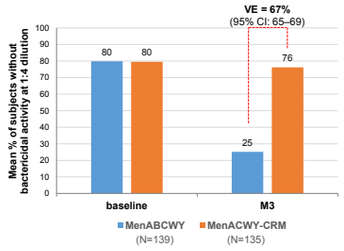
Study participants and their characteristics

- 305 adolescents were enrolled, 301 (99%) were vaccinated: 152 received MenABCWY and 149 received MenACWY-CRM; 276 (90%) completed the study.
- Demographic characteristics of study participants were similar between groups (mean age at first dose: 12 [± 2.3] years, 40%–44% females, 73%–75% White/Caucasian).

Effectiveness

- At baseline, the mean % (averaged across all 110 strains) of seronegative subjects (without bactericidal activity at 1:4 dilution) was 80% in both groups (**Figure 3**).
- At M3, the mean % of seronegative subjects declined to 25% in the MenABCWY group and remained similar (76%) in the MenACWY-CRM group (**Figure 3**).
- VE was assessed against 105 of 110 strains included in the panel. For 5 strains, all subjects had bactericidal activity at 1:4 dilution at baseline and at M3. Therefore, these 5 strains were excluded from analysis of the overall VE at 1:4 dilution.
- VE at M3 was 67% (95% confidence interval: 65–69) (**Figure 3**).

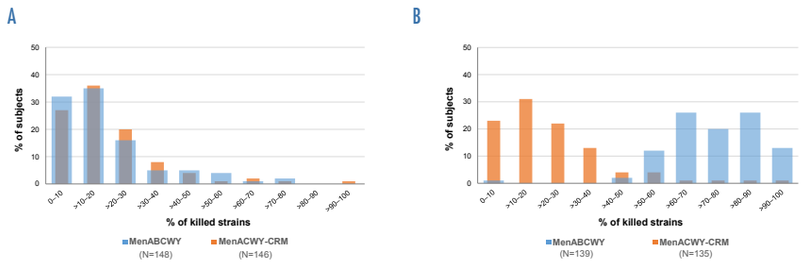
Figure 3. Effectiveness of MenABCWY vaccine against a random panel of meningococcal serogroup B strains compared to MenACWY-CRM vaccine measured by bactericidal activity at 1:4 dilution (full analysis effectiveness set for M3)



M, month; **VE**, vaccine effectiveness; **CI**, confidence interval; **N**, number of subjects included in full analysis effectiveness set for M3.

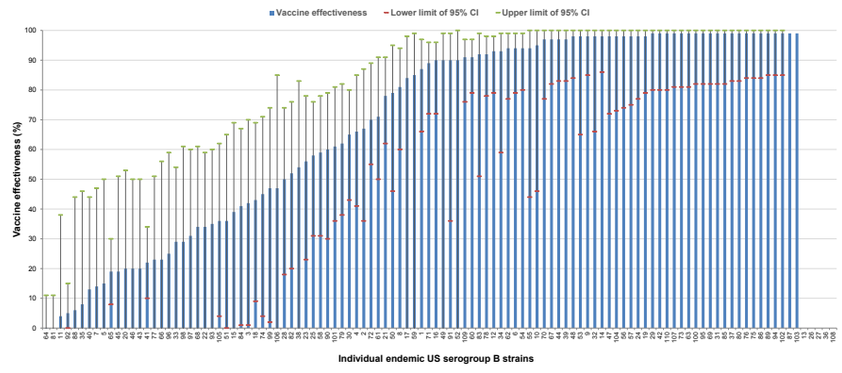
- At baseline, most subjects in both groups had bactericidal antibodies against <20% of tested strains, with 5%–7% of subjects having antibodies against >50% of strains (**Figure 4A**).
- At M3, 97% of subjects in the MenABCWY group were protected against >50% of tested strains and 59% were protected against >70% of strains; protection in the MenACWY-CRM group was unchanged from baseline (**Figure 4B**).
- Individual VE at M3 for each serogroup B invasive disease strain is presented in **Figure 5**.

Figure 4. Distribution of subjects by percentages of serogroup B strains killed at 1:4 dilution at baseline (A) and at M3 (B) (full analysis effectiveness set)



M, month; **N**, number of subjects included in full analysis effectiveness set for M3.

Figure 5. MenABCWY vaccine effectiveness against each of the randomly selected endemic US *Neisseria meningitidis* serogroup B invasive disease strains as measured by serum bactericidal activity at 1:4 dilution (full analysis effectiveness set)



CI, confidence interval. **Note:** CI lines below 0 were removed for ease of figure display.

CONCLUSIONS

- This is the first study showing VE of MenABCWY against a broad panel of endemic US serogroup B invasive disease strains in healthy adolescents using a direct serological assessment.
- Effectiveness of the MenABCWY vaccine administered as a 2-dose series to healthy US adolescents was 67%.
- After 2 doses of MenABCWY, almost all subjects in the MenABCWY group were protected against at least half of the tested strains and more than half of the subjects were protected against >70% of strains.
- The study results support previous estimates for breadth of coverage for endemic US serogroup B strains using Meningococcal Antigen Typing System.[4]
- MenABCWY vaccine was well tolerated with no safety concerns identified; similar safety data were reported for other MenABCWY studies.[1]

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DISCLOSURES

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Potential conflicts of interest: **JA Welsch** and **P Pedotti** are employees of the GSK group of companies. **JA Welsch**, **P Pedotti, L Han, P Dull** and **I Smolenov** were employees of Novartis Vaccines (now part of the GSK group of companies) at the time of the study. **L Han** and **I Smolenov** hold shares in the GSK group of companies as part of their previous employee remuneration. **S Senders** and **R Middleton** report no conflicts of interest.

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