A BOOSTER RESPONSE TO AN INVESTIGATIONAL MENINGOCOCCAL MENABCWY VACCINE IN ADOLESCENTS PREVIOUSLY VACCINATED WITH MENACWY, 4CMENB OR MENABCWY: A PHASE 2, OBSERVER-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY

Leszek Szenborn,[1] Stan L. Block,[2] Teresa Jackowska,[3] Wendy Daly,[4] Jo Anne Welsch,[5] Diego D'Agostino,[5] Linda Han,[6]* Igor Smolenov[7]**

1. Department of Pediatric Infectious Diseases, Wroclaw Medical University, Wroclaw, Poland; 2. Kentucky Pediatric and Adult Research Inc., Bardstown, KY, USA; 3. Department of Pediatrics, The Centre of Postgraduate Medical Education, Warsaw, Poland; 4. Bluegrass Clinical Research Inc. / Brownsboro Park Pediatrics, Louisville, KY, USA; 5. GSK, Amsterdam, the Netherlands; 6. Novartis Vaccines and Diagnostics Inc., Cambridge, MA, USA; 7. Novartis Vaccines, Amsterdam, the Netherlands
Current affiliations: *Vertex Pharmaceuticals Inc., Boston, MA, USA; **PATH, Seattle, WA, USA

Presenting author: Jo Anne Welsch
GSK, 81-87 Hullenbergweg,
1101 CL Amsterdam, the Netherlands
Email: jo.a.welsch@gsk.com
Tel: +1-510-990-5460

BACKGROUND

- Globally, most cases of invasive meningococcal disease are caused by infection with *Neisseria meningitidis* serogroups A, B, C, W and Y.[1]
- In a previous study, we evaluated the immunogenicity of 2 doses (0, 2 months schedule) of the investigational MenABCWY vaccine in adolescents and young adults compared to 2 doses of a licensed meningococcal serogroup B vaccine (4CMenB) and 1 dose of a licensed meningococcal serogroup ACWY vaccine (MenACWY) (NCT01272180).[2]
- This extension study evaluated antibody persistence up to 3 years after primary vaccination, and immune responses to a dose of MenABCWY 2 years after primary vaccination in the same participants (NCT01992536).

OBJECTIVES

- To assess the immune responses against serogroups A, B, C, W and Y after a booster dose of the investigational MenABCWY vaccine in healthy adolescents who previously received 2 primary doses of MenABCWY.
- To assess the immune responses against serogroups A, B, C, W and Y after a dose of the investigational MenABCWY vaccine in healthy adolescents who previously received 2 doses of 4CMenB or a single dose of MenACWY.
- To assess antibody persistence against serogroups A, B, C, W and Y at 24 and 36 months after the primary vaccination series.
- To evaluate the reactogenicity and safety of the study vaccines.

METHODS

Study design and participants

- Phase 2, multicenter, randomized, observer-blind extension study conducted in the USA and Poland between December 2013 and April 2015.
- Adolescents who had received all scheduled vaccinations and completed the study termination visit in the primary study were invited to participate in the extension study.

Vaccine composition

- The investigational **MenABCWY** vaccine consists of recombinant proteins (rMenB) and outer membrane vesicles (OMV), reconstituted with lyophilized MenACWY vaccine.
  - **rMenB+OMV (4CMenB)** is a liquid suspension for injection containing recombinant proteins of *Neisseria meningitidis* serogroup B (936-741, 287-953 and 961c: 50 µg of each protein) + OMV (full dose, 25 µg) adsorbed onto aluminum hydroxide.
  - **OMV**, outer member vesicles from serogroup B strain NZ98/254.
- The licensed **MenACWY** vaccine consists of meningococcal serogroups A, C, W, and Y oligosaccharides conjugated to diphtheria CRM_{197}.
- The investigational MenABCWY+1/4OMV vaccine formulation consists of rMenB and 1/4 dose of OMV (6.25 µg), reconstituted with lyophilized MenACWY vaccine. This formulation is shown in **Figure 1** but it has been discontinued, so the immunogenicity data is not presented in this poster.

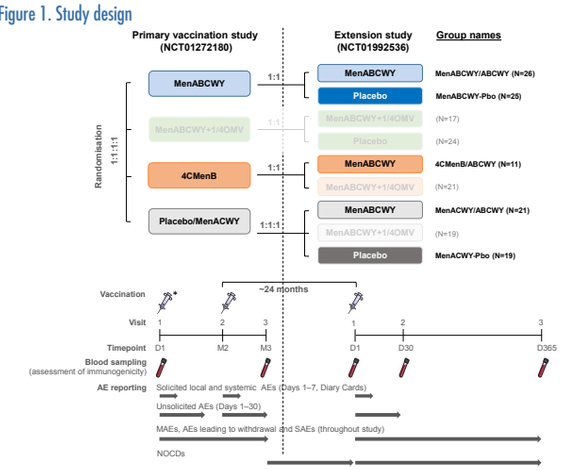
Immunogenicity

- Antibodies against serogroups A, C, W and Y were measured by high-throughput serum bactericidal assay with human complement (HT-hSBA) and reported as geometric mean titres (GMTs) and percentage of subjects with hSBA titres ≥ 1:8.
- Antibodies against serogroup B test strains were measured by HT-hSBA and reported as GMTs and percentage of subjects with hSBA titres ≥ 1:5.
- All analyses are descriptive in nature due to the low number of subjects in each group.

Reactogenicity and safety

- Adverse events (AEs) and new onset of chronic diseases (NOCDs) reporting periods are shown in **Figure 1**.

Figure 1. Study design



D, day; **M**, month; **N**, number of subjects enrolled in respective groups; **AEs**, adverse events; **SAEs**, serious adverse events; **MAEs**, medically-attended adverse events; **NOCDs**, new onset of chronic diseases
*The Placebo/MenACWY group of the primary vaccination study received placebo at D1 and a single dose of MenACWY at M2
Note: 7 subjects of the 194 enrolled received placebo because of misrandomization of the 4CMenB group and are not shown in any group, they were prematurely terminated from the study by the investigator at the request of the Sponsor; 4 subjects of the 194 enrolled were not assigned to any treatment and thus not shown in any group

RESULTS

Study participants and demographics

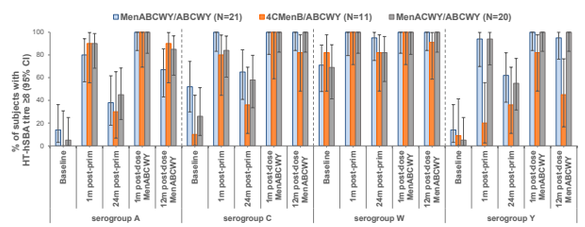
- From 416 subjects eligible from the primary vaccination study, 194 were enrolled in this extension study.
- The average age of the subjects was 18.4 ± 5.08 years. The majority of enrolled subjects were white, non-Hispanic or -Latino.
- Demographic and baseline characteristics were well balanced between vaccine groups.

Immune responses to meningococcal serogroups A, C, W and Y

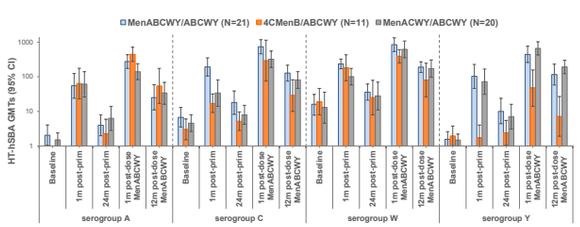
- Before MenABCWY vaccination, 38%, 30% and 45% of MenABCWY/ABCWY, 4CMenB/ABCWY and MenACWY/ABCWY vaccinees, respectively, had hSBA titres ≥8 against serogroup A; 65%, 36% and 58% against serogroup C; 95%, 82% and 82% against serogroup W and 62%, 36% and 55% against serogroup Y (**Figure 2A**).
- One month after MenABCWY vaccination, 96%, 100% and 84% of MenABCWY/ABCWY, 4CMenB/ABCWY and MenACWY/ABCWY vaccinees, respectively, had seroresponses against serogroup A; 85%, 100% and 95% against serogroup C; 85%, 82% and 83% against serogroup W and 96%, 73% and 95% against serogroup Y.
- MenACWY GMTs increased robustly at one month after the MenABCWY dose, and remained above baseline up to 12 months later across all vaccine groups (**Figure 2B**).

Figure 2. Kinetics of antibody titres against A, C, W and Y serogroups after primary vaccination with MenABCWY, 4CMenB or MenACWY and vaccination two years later with MenABCWY (Full analysis set, Day 365)

A. Percentage of subjects with HT-hSBA titres ≥8



B. GMTs



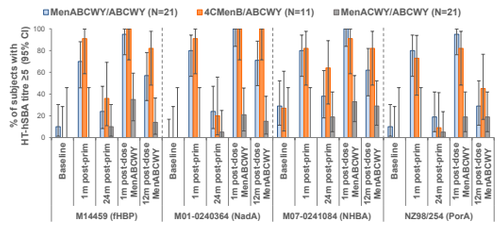
N, maximum number of subjects with available results; **m**, month; **post-prim**, post-primary vaccination; **CI**, confidence intervals; **GMT**, geometric mean titre

Immune responses to meningococcal serogroup B

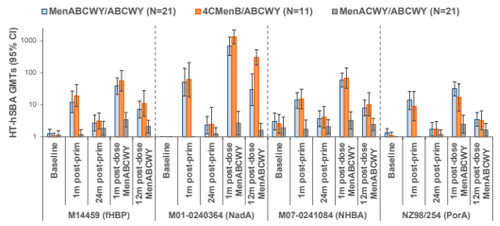
- Before vaccination with MenABCWY, percentages of subjects with hSBA titres ≥5 against the 4 serogroup B test strains were 20%–24% for NadA in the MenABCWY/ABCWY and 4CMenB/ABCWY groups vs 5% in the MenACWY/ABCWY group, 38%–64% vs 19% for NHBA, 24%–36% vs 10% for fHBP and 9%–19% vs 5% for PorA, respectively (**Figure 3A**).
- One month after the MenABCWY dose, percentages of subjects with hSBA titres ≥5 across strains increased to 82%–100% in the MenABCWY/ABCWY and 4CMenB/ABCWY groups, and to 19%–35% in the MenACWY/ABCWY group.
- MenB GMTs increased robustly at one month after the MenABCWY dose in the MenABCWY/ABCWY and 4CMenB/ABCWY groups, and remained well above baseline up to 12 months later (**Figure 3B**).

Figure 3. Kinetics of antibody titres against serogroup B test strains after primary vaccination with MenABCWY, 4CMenB or MenACWY and vaccination two years later with MenABCWY (Full analysis set, Day 365)

A. Percentage of subjects with HT-hSBA titres ≥5



B. GMTs



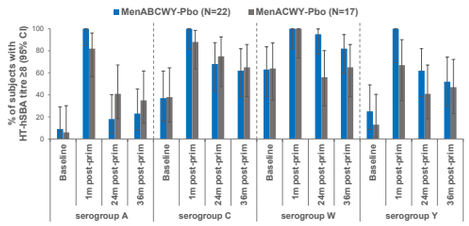
N, maximum number of subjects with available results; **m**, month; **post-prim**, post-primary vaccination; **GMT**, geometric mean titre

Antibody persistence at 36 months after primary vaccination

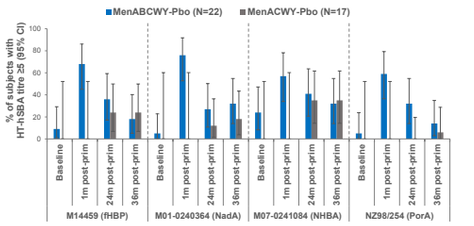
- The HT-hSBA responses against serogroups A, C, W and Y and serogroup B test strains at 36 months post-primary vaccination in subjects who received placebo at Month 24 (MenABCWY-Pbo and MenACWY-Pbo groups) are presented in **Figure 4**.

Figure 4. Persistence of bactericidal antibodies at 36 months after primary vaccination with MenABCWY or MenACWY (Full analysis set, Day 365)

A. Percentage of subjects with HT-hSBA titres ≥8 for A, C, W and Y serogroups



B. Percentage of subjects with HT-hSBA titres ≥5 for serogroup B test strains

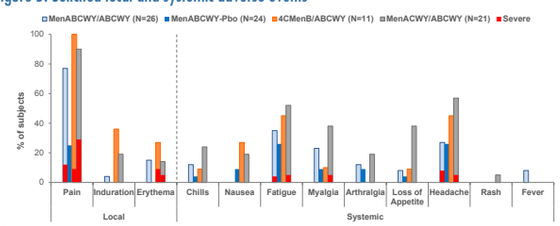


N, maximum number of subjects with available results; **m**, month; **post-prim**, post-primary vaccination; **CI**, confidence intervals

Reactogenicity and safety

- The most frequent solicited AEs after MenABCWY vaccination were injection site pain (77%–100%), fatigue (35%–52%), and headache (27%–57%) (**Figure 5**).
- Throughout this study, 5 SAEs were reported in 5 subjects. None were fatal and none were considered by the investigator as possibly related to study vaccination.
- Between the primary vaccination and the start of this extension study, 19 NOCDs were reported in subjects who previously received MenABCWY (19/92) and 21 in subjects who did not previously receive MenABCWY (21/102).
- Throughout this study, NOCDs were reported in 9 subjects. None of them were assessed by the investigator as possibly related to study vaccination.

Figure 5. Solicited local and systemic adverse events



N, maximum number of subjects with safety data reported

CONCLUSIONS

- Overall, the immune responses against all vaccine serogroups were good 1 month after MenABCWY booster vaccination in subjects who previously received the same vaccine formulation in the parent study.
- In adolescents previously vaccinated with 4CMenB or Placebo/MenACWY, a dose of MenABCWY two years later elicited robust immune responses to serogroups A, C, W and Y while response to serogroup B were lower in subjects in the Placebo/MenACWY group.
- The immune responses in adolescents who received either MenABCWY (two doses) or MenACWY (single) dose in the parent trial waned in the 24 months since primary vaccination, but the antibody levels were similar between 24 and 36 months post-primary vaccination.
- The booster dose of MenABCWY was well tolerated and raised no safety concerns.
- All analyses were descriptive in nature due to the low number of subjects in each group.

REFERENCES

1. World Health Organization. *Wkly Epidemiol Rec*. 2011;86:521–39
2. Block SL et al. *Vaccine*. 2015;33:2500–10

DISCLOSURES

Funding: The development of this study was funded by Novartis Vaccines and Diagnostics Inc., now part of the GSK group of companies. GlaxoSmithKline Biologicals SA funded the development of the abstract and poster presentation.

Potential conflicts of interest: **JA Welsch** and **D D'Agostino** are employees of the GSK group of companies. **JA Welsch, D D'Agostino, L Han** 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** also received shares as part of their employee remuneration. **SL Block** is a grant investigator and received a research grant from Novartis Vaccines (now part of the GSK group of companies). **L Szenborn, T Jackowska** and **W Daly** report no conflicts of interest.

Medical writing and editorial support for this poster were provided by Kristel Vercauteren (XPE Pharma & Science, Wavre, Belgium, c/o GSK).

The authors would like to thank the adolescents who participated in this trial and their parents, the investigators, study nurses, and other staff members for contributing to this study.