Rationale for a Pentavalent Meningococcal Serogroup ABCWY Vaccine: a Review of Epidemiologic and Clinical Data

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INTRODUCTION

- Serogroups A, B, C, W, Y cause vast majority of global invasive meningococcal disease (IMD)[1]
- IMD preventive strategies currently rely on 2 separate vaccines—one for meningococcal serogroups A, C, W, and Y (MenACWY) and one for meningococcal serogroup B (MenB)[2]—requiring up to 4 vaccinations to provide broad protection throughout adolescence and early adulthood[3]
- A pentavalent vaccine (MenABCWY) could simplify IMD immunization and ensure broad protection against these 5 prevalent IMD-causing serogroups with fewer vaccinations throughout adolescence and early adulthood[4]

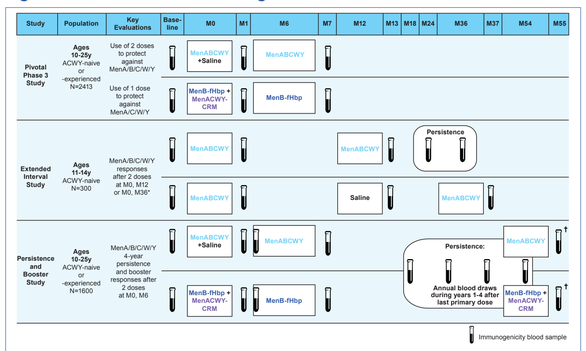
OBJECTIVE

- To assess potential utility of MenABCWY as a solution to challenges posed by evolving IMD epidemiology as well as different MenACWY and MenB vaccination schedules

METHODS

- To assess value of MenABCWY from population health and epidemiologic perspectives, global IMD burden was evaluated by reviewing surveillance reports and PubMed articles published between January 2010–June 2020 in 77 countries[1]
- To assess MenABCWY clinical value, data from 3 MenABCWY clinical development program studies (phases 2, 2b, and 3 in >4000 adolescents and young adults; **Figure 1**) were reviewed
  - MenABCWY, currently in clinical development, is composed of:
    - MenB-fHbp (Trumenba®, bivalent rLP2086; Pfizer Inc, Collegeville, PA, USA): licensed for preventing invasive MenB disease in individuals 10–25 years of age (US) or ≥10 years of age (outside of US)[5,6]
    - MenACWY-TT (Nimenrix®; Pfizer Europe MA EEIG, Brussels, Belgium): licensed for preventing invasive MenA/C/W/Y disease in individuals ≥6 weeks of age (outside of US)[7]
  - All study participants were MenB vaccine–naive before study entry
  - Immunogenicity evaluations were performed with serum bactericidal antibody using exogenous human complement (hSBA) assays against MenA/C/W/Y strains and 4 diverse, vaccine-heterologous MenB strains[8]
    - Immunogenicity endpoints included
      - Percentages of participants achieving
        - Seroresponses (≥4-fold rises in hSBA titers from baseline)
        - Seroprotective hSBA titers (≥1:8 or ≥1:16, depending on strain [ie, greater than the accepted correlate of protection of ≥1:4[9]])
        - Composite responses (seroprotective hSBA titers against all 4 MenB strains combined)
      - hSBA geometric mean titers (GMTs)
    - Noninferiority hypothesis testing was based on differences in seroresponse and composite response rates between MenABCWY and comparators, and used a −10% noninferiority margin (ie, lower limit of 2-sided 95% CI for differences >−10%)
  - Safety evaluations included percentages of participants reporting
    - Solicited local reactions and systemic events after each vaccination
    - Unsolicited non-serious adverse events (AEs), serious AEs, medically attended AEs, immediate AEs, and newly diagnosed chronic medical conditions

Figure 1. MenABCWY Clinical Program Overview



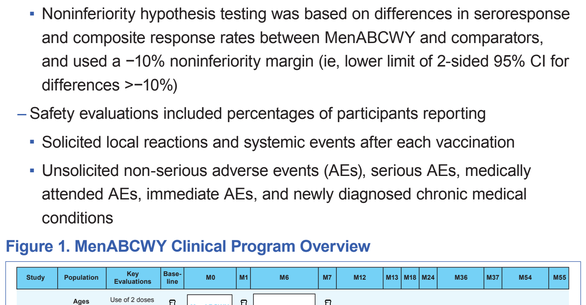
A/C/W/Y=meningococcal serogroups A/C/W/Y; M=month; MenA/B/C/W/Y=meningococcal serogroups A/B/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine.
*Study is ongoing; only findings from 2 doses at M0, M12 are presented.
†Safety follow-up continued through M60.

RESULTS

Review of Global IMD Epidemiology

- Overall IMD incidence during 2010–2018 was low and generally decreased over time, with pronounced occurrence of sporadic outbreaks **(Figure 2)**[1]

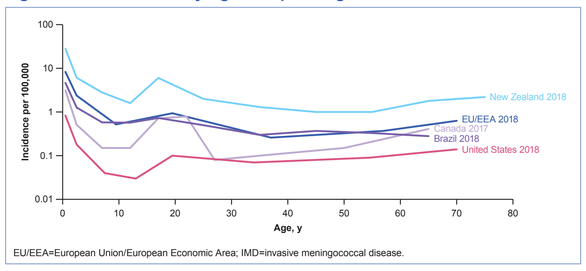
Figure 2. Overall IMD Incidence During 2010–2018[1]



IMD=invasive meningococcal disease; N/A=not available.

- IMD incidence highest in infants, followed by young children **(Figure 3)**[1]
  - Secondary peak in adolescents/young adults in many countries
  - Increased incidence among older adults in some countries

Figure 3. IMD Incidence by Age Group During 2017–2018[1,10]



EU/EEA=European Union/European Economic Area; IMD=invasive meningococcal disease.

- Serogroups A, B, C, W, Y caused vast majority of IMD[1]
  - Serogroup B dominated in many regions
  - Increases in serogroups W and Y in some regions
  - Defined serogroup peaks associated with outbreaks in some African countries
  - Serogroup X localized to African meningitis belt other than sporadic cases

RESULTS (continued)

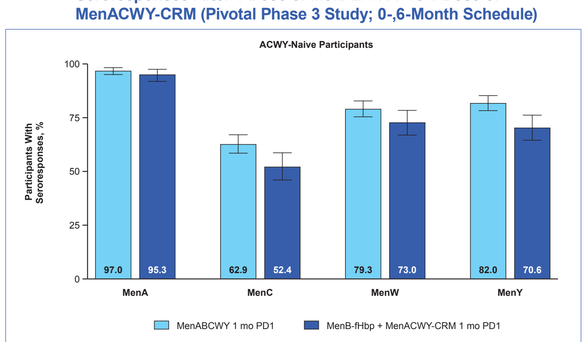
Review of MenABCWY Clinical Data

Immune responses for serogroups A/C/W/Y after a single MenABCWY dose (pivotal phase 3 study)

- MenA/C/W/Y seroresponse rates among ACWY-naive participants noninferior to those after 1 MenACWY-CRM dose **(Figure 4)**
  - Results similar for ACWY-experienced participants (93.4%–97.4% vs 93.7%–96.9%)
- MenA/C/W/Y seroresponse rates among ACWY-naive participants statistically greater (ie, lower limit of 95% CI for differences >0%) for MenC and MenY
- 82.4%–100% of ACWY-naive and -experienced MenABCWY recipients had seroprotective MenA/C/W/Y titers

A single MenABCWY dose induces robust immune response against MenA/C/W/Y that are comparable with those induced by a single dose of MenACWY-CRM

Figure 4. Percentages of Participants With MenA/C/W/Y hSBA Seroresponses After 1 Dose of MenABCWY vs 1 Dose of MenACWY-CRM (Pivotal Phase 3 Study; 0-,6-Month Schedule)



hSBA=serum bactericidal assay using human complement; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine; PD1=postdose 1.
Error bars represent 95% CIs.

Immune responses for all 5 serogroups after 2 MenABCWY doses administered at Months 0 and 6 (pivotal phase 3 study)

- MenA/C/W/Y
  - MenA/C/W/Y seroresponse rates among ACWY-naive participants noninferior to those receiving 1 MenACWY-CRM dose **(Figure 5A)**
    - Results similar for ACWY-experienced participants (93.0%–97.1% vs 93.7%–96.9%)
  - MenA/C/W/Y seroresponse rates among ACWY-naive participants statistically greater for MenC, MenW, and MenY
  - 99.0%–100% of ACWY-naive and -experienced MenABCWY recipients had seroprotective MenA/C/W/Y titers
  - MenA/C/W/Y GMTs higher in MenABCWY group than in MenB-fHbp + MenACWY-CRM group at same time point among both ACWY-experienced **(Figure 6)** and -naive (not shown) participants
- MenB
  - MenB seroresponse and composite response rates noninferior to those after 2 MenB-fHbp doses **(Figure 5B)**
  - Seroresponse rates for strains expressing factor H binding protein (fHbp) variants B24 and B44 and composite response rates statistically greater
  - 83.4%–98.7% of MenABCWY recipients had seroprotective MenB titers

A 2-dose MenABCWY primary series administered at Months 0 and 6 induces robust immune response against all 5 serogroups that are comparable with or statistically greater than those induced by separate administration of MenACWY-CRM and MenB-fHbp

Immune responses for all 5 serogroups after 2 MenABCWY doses administered at Months 0 and 12 (extended interval study)

- MenA/C/W/Y seroresponse rates after 2 MenABCWY doses following 0-,12-month schedule were consistent with those following 0-,6-month schedule in pivotal phase 3 study **(Figure 7A)**
- For MenB, seroresponse and composite response rates following 0-,12-month schedule trended higher than those following 0-,6-month schedule **(Figure 7B)**

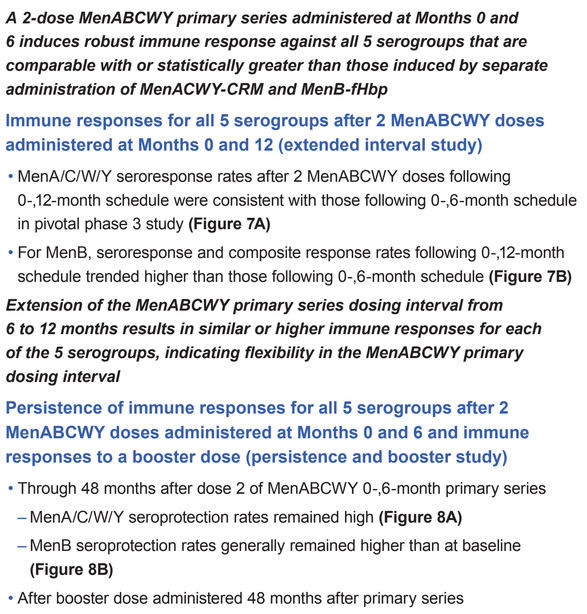
Extension of the MenABCWY primary series dosing interval from 6 to 12 months results in similar or higher immune responses for each of the 5 serogroups, indicating flexibility in the MenABCWY primary dosing interval

Persistence of immune responses for all 5 serogroups after 2 MenABCWY doses administered at Months 0 and 6 and immune responses to a booster dose (persistence and booster study)

- Through 48 months after dose 2 of MenABCWY 0-,6-month primary series
  - MenA/C/W/Y seroprotection rates remained high **(Figure 8A)**
  - MenB seroprotection rates generally remained higher than at baseline **(Figure 8B)**
- After booster dose administered 48 months after primary series
  - Seroprotection achieved by all participants for MenA/C/W/Y **(Figure 8A)**
  - Seroprotection rates for MenB higher than after primary series **(Figure 8B)**
  - For all 5 serogroups, GMTs after booster dose generally higher than those after primary series, indicating anamnestic responses **(Figure 9)**

Immune responses after 2 MenABCWY doses administered at 0 and 6 months may provide improved protection over 4 years compared with a single MenACWY-CRM dose and are boostable for all 5 serogroups

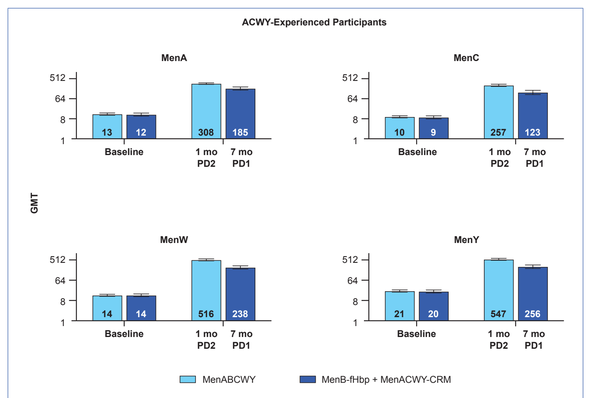
Figure 5. Percentages of Participants With (A) MenA/C/W/Y hSBA Seroresponses After 2 Doses of MenABCWY vs 1 Dose of MenACWY-CRM and (B) MenB* hSBA Seroresponses or Composite Responses After 2 Doses of MenABCWY vs 2 Doses of MenB-fHbp (Pivotal Phase 3 Study; 0-,6-Month Schedule)



fHbp=factor H binding protein; hSBA=serum bactericidal assay using human complement; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB=meningococcal serogroup B; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine; PD1=postdose 1; PD2=postdose 2.
Error bars represent 95% CIs.
*MenB strains indicated by vaccine-heterologous fHbp variants they express.

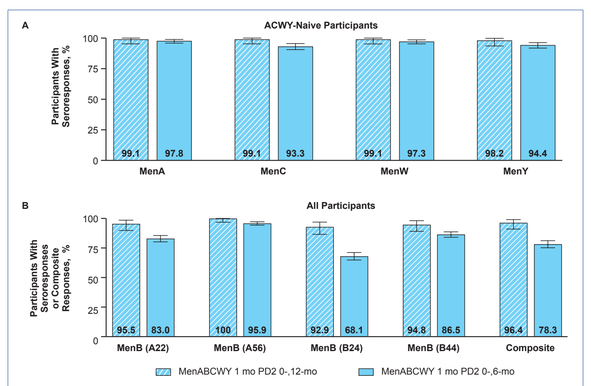
RESULTS (continued)

Figure 6. hSBA GMTs Against MenA/C/W/Y Strains at Baseline and After 2 Doses of MenABCWY vs 7 Months After 1 Dose of MenACWY-CRM (Pivotal Phase 3 Study; 0-,6-Month Schedule)



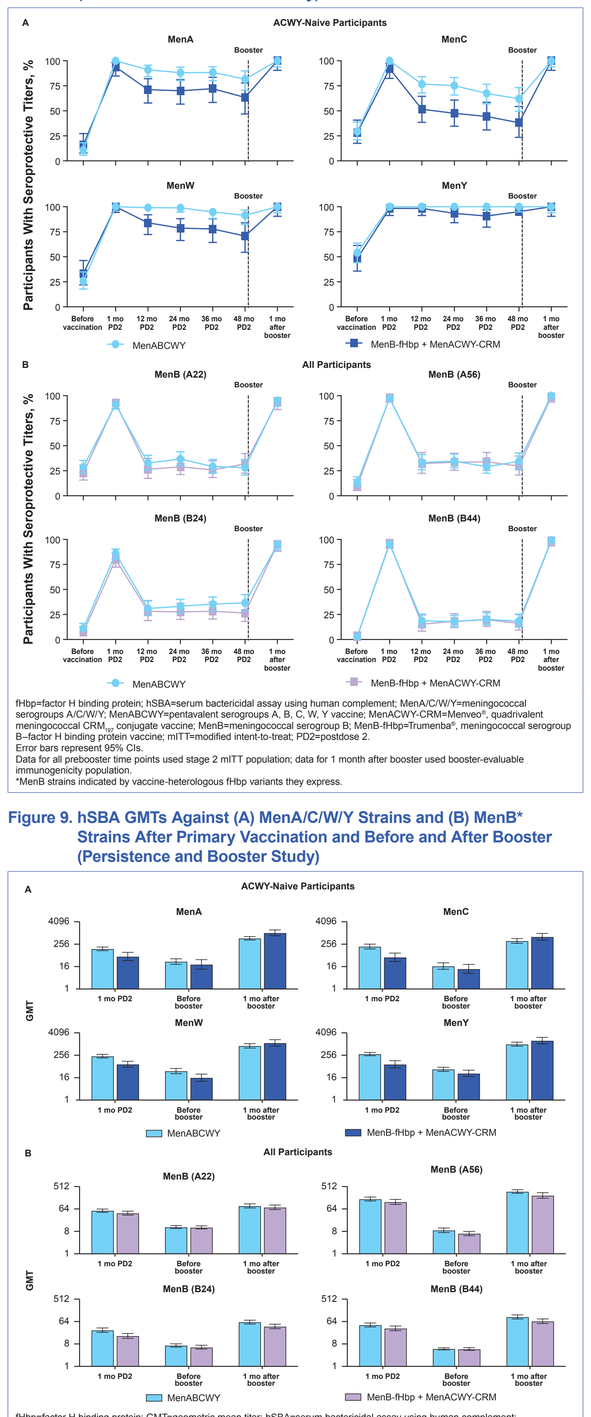
GMT=geometric mean titer; hSBA=serum bactericidal assay using human complement; mITT=modified intent-to-treat; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine; PD1=postdose 1; PD2=postdose 2.
Error bars represent 95% CIs.
Data shown for the mITT population.

Figure 7. Percentages of Participants With (A) MenA/C/W/Y hSBA Seroresponses and (B) MenB* hSBA Seroresponses or Composite Responses Following a 0-,12-Month or 0-,6-Month MenABCWY Schedule (Extended Interval and Pivotal Phase 3 Studies)



fHbp=factor H binding protein; hSBA=serum bactericidal assay using human complement; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenB=meningococcal serogroup B; PD2=postdose 2.
Data for 0-,6-month schedule are from pivotal phase 3 study, which included participants 10-25y of age; extended interval study participants were 11-14y of age.
Error bars represent 95% CIs.
*MenB strains indicated by vaccine-heterologous fHbp variants they express.

Figure 8. Percentages of Participants with Seroprotective hSBA Titers Against (A) MenA/C/W/Y Strains and (B) MenB* Strains Over Time (Persistence and Booster Study)



fHbp=factor H binding protein; hSBA=serum bactericidal assay using human complement; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB=meningococcal serogroup B; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine; mITT=modified intent-to-treat; PD2=postdose 2.
Error bars represent 95% CIs.
Data for all preboooster time points used stage 2 mITT population; data for 1 month after booster used booster-evaluable immunogenicity population.
*MenB strains indicated by vaccine-heterologous fHbp variants they express.

Figure 9. hSBA GMTs Against (A) MenA/C/W/Y Strains and (B) MenB* Strains After Primary Vaccination and Before and After Booster (Persistence and Booster Study)

fHbp=factor H binding protein; GMT=geometric mean titer; hSBA=serum bactericidal assay using human complement; MenA/C/W/Y=meningococcal serogroups A/C/W/Y; MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB=meningococcal serogroup B; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine; PD2=postdose 2.
Error bars represent 95% CIs.
*MenB strains indicated by vaccine-heterologous fHbp variants they express.

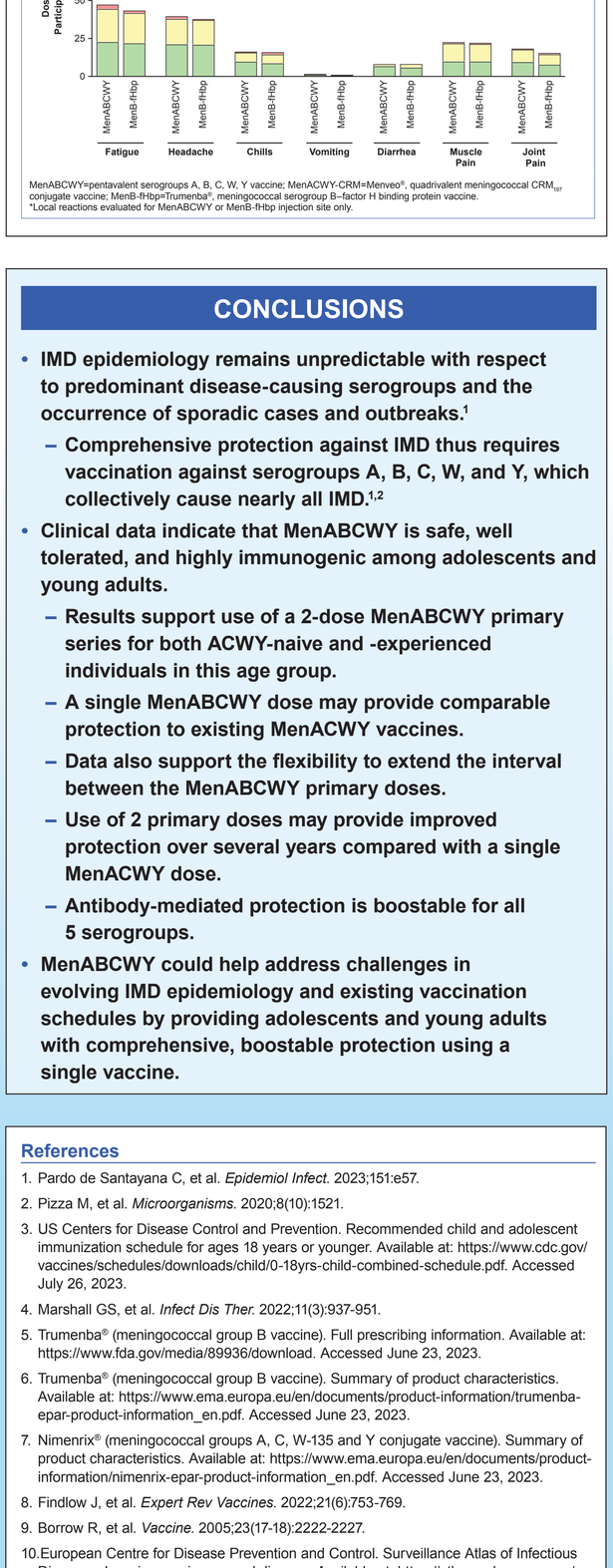
MenABCWY safety and tolerability

- MenABCWY reactogenicity profile consistent with that of MenB-fHbp, with trend toward increased rates of local reactions for MenABCWY that was not clinically meaningful **(Figure 10)**
  - Reactogenic events mostly mild or moderate in severity
  - No clinically meaningful differences between doses 1 and 2
  - No clinically meaningful differences between ACWY-naive and ACWY-experienced participants
  - Reactogenicity profile after booster dose generally consistent with that after primary series
- No MenABCWY recipients withdrew because of reactogenicity events or related AEs

MenABCWY was well tolerated and no safety concerns were identified

RESULTS (continued)

Figure 10. Percentages of All Participants Regardless of ACWY Experience Reporting (A) Local Reactions,* (B) Fever, and (C) Other Systemic Events Within 7 Days After Each Dose (Pivotal Phase 3 Study; 0-,6-Month Schedule)



MenABCWY=pentavalent serogroups A, B, C, W, Y vaccine; MenACWY-CRM=Menveo®, quadrivalent meningococcal CRM_{197} conjugate vaccine; MenB-fHbp=Trumenba®, meningococcal serogroup B–factor H binding protein vaccine.
*Local reactions evaluated for MenABCWY or MenB-fHbp injection site only.

CONCLUSIONS

- **IMD epidemiology remains unpredictable with respect to predominant disease-causing serogroups and the occurrence of sporadic cases and outbreaks.[1]**
  - **Comprehensive protection against IMD thus requires vaccination against serogroups A, B, C, W, and Y, which collectively cause nearly all IMD.[1,2]**
- **Clinical data indicate that MenABCWY is safe, well tolerated, and highly immunogenic among adolescents and young adults.**
  - **Results support use of a 2-dose MenABCWY primary series for both ACWY-naive and -experienced individuals in this age group.**
  - **A single MenABCWY dose may provide comparable protection to existing MenACWY vaccines.**
  - **Data also support the flexibility to extend the interval between the MenABCWY primary doses.**
  - **Use of 2 primary doses may provide improved protection over several years compared with a single MenACWY dose.**
  - **Antibody-mediated protection is boostable for all 5 serogroups.**
- **MenABCWY could help address challenges in evolving IMD epidemiology and existing vaccination schedules by providing adolescents and young adults with comprehensive, boostable protection using a single vaccine.**

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Disclosures

All authors are current employees of Pfizer and may hold stock or stock options.

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