BLA Clinical Review Memorandum

Application Type	BLA
STN	125770.0
CBER Received Date	October 21, 2022
PDUFA Goal Date	October 20, 2023
Division / Office	DBPAP/DVRPA; OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Margaret Bash, M.D. Medical Officer – Principal Investigator LBP/DBPAP/OVRR/CBER Lucia Lee, M.D. Medical Officer- Team Leader CRB1/DVRPA/OVRR/CBER
Review Completion Date / Stamped Date	October 20, 2023
Supervisory Concurrence	Maria Allende, M.D. Chief, Clinical Review Branch 1 R. Douglas Pratt, M.D., MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Pfizer Ireland Pharmaceuticals
Established Name	Meningococcal Groups A, B, C, W, and Y Vaccine
Trade Name	Penbraya
Pharmacologic Class	Vaccine
Formulation	After reconstitution, a single dose (approximately 0.5 mL) contains • 5 µg each of meningococcal serogroup A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid [TT] (total 44 µg TT) • 60 µg meningococcal B fHbp subfamily A • 60 µg meningococcal B fHbp subfamily B • 0.25 mg aluminum as $AlPO_4$
Dosage Form and Route of Administration	Suspension, intramuscular
Dosing Regimen	2 doses administered at 0 and 6 months
Indication and Intended Population	Active immunization to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y Population: 10 through 25 years of age
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

ACWY	meningococcal groups A, C, W, and Y
AE	adverse event
$AlPO_4$	aluminum phosphate
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CRM	cross-reactive material
e-diary	electronic diary
ER	emergency room
FDA	Food and Drug Administration
fHbp	factor H binding protein
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
IND	Investigational New Drug application
IR	Information Request
LL	lower limit
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MenA	*Neisseria meningitidis* serogroup A
MenABCWY	*Neisseria meningitidis* serogroups A, B, C, W, and Y vaccine
MenACWY-CRM	meningococcal serogroups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine (Menveo [GSK Vaccines])
MenACWY-TT	meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix [Pfizer Europe MA EEIG])
MenB vaccine	meningococcal serogroup B vaccine (Trumenba [Wyeth Pharmaceuticals LLC])
MenB	*Neisseria meningitidis* serogroup B
MenC	*Neisseria meningitidis* serogroup C
MenW	*Neisseria meningitidis* serogroup W
MenY	*Neisseria meningitidis* serogroup Y
mITT	modified intent-to-treat
N. meningitidis	*Neisseria meningitidis*
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
OMV	outer membrane vesicle
PREA	Pediatric Research Equity Act
RCDC	Reverse Cumulative Distribution Curve
SAE	serious adverse event
sBLA	supplemental Biologics License Application
SOC	System Organ Class
TT	tetanus toxoid
UC	ulcerative colitis
U.S.	United States

1. EXECUTIVE SUMMARY

On October 21, 2022, Pfizer Ireland Pharmaceuticals submitted a Biologics License Application (BLA) for a pentavalent meningococcal vaccine [PENBRAYA; MenABCWY], comprised of *Neisseria meningitidis* serogroups A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid (TT) carrier protein, and 2 recombinant lipidated factor H binding proteins (fHbp) [1 subfamily A, 1 subfamily B variant] of *N. meningitidis* serogroup B. MenABCWY is for use in individuals 10 through 25 years of age (hereafter abbreviated 10-25 years of age), and administered as a 2-dose series at 0 and 6 months. The Applicant provided safety and immunogenicity data from three studies (C3511001, B1971057, and C3511004) to support an indication for prevention of invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y.

Immunogenicity (Effectiveness)

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp present in the outer membrane of *N. meningitidis* group B. Effectiveness was evaluated by measuring antibodies with assays that uses human complement to assess serum bactericidal activity (hSBA). MenABCWY effectiveness was demonstrated by showing that hSBA responses to serogroups A, B, C, W and Y following the combination vaccine were non-inferior to hSBA responses one month following the last vaccination with U.S.-licensed MenB and MenACWY vaccines. The susceptibility of group B meningococci to bactericidal antibody is dependent upon both the antigenic similarity of the fHbp subfamily A or subfamily B vaccine antigen to the fHbp protein expressed by the bacterial strain and the amount of fHbp expressed at the bacterial surface. The four primary MenB strains each expressed a variant from subfamily A or B (i.e., A22, A56, B24, B44), including test strains expressing prevalent fHBP variants in the U.S. (B24 and A22). The primary strains expressing low or medium quantities of fHBP were chosen to ensure a stringent measure of anti-fHBP-mediated bactericidal killing.

Study C3511001 was designed as a randomized, active-controlled, observer-blinded study conducted in individuals 10-25 years of age in the United States (U.S.) and Europe. MenABCWY (N=1763) or meningococcal group B vaccine (Trumenba; MenB) (N=650) was administered at 0 and 6 months. Meningococcal groups A, C, Y, and W oligosaccharide diphtheria CRM_{197} conjugate vaccine (MenACWY-CRM, GSK Vaccines, SRL) was concomitantly administered with Trumenba at Month 0. All participants were MenB vaccine naïve. MenACWY conjugate vaccine-naïve and MenACWY conjugate vaccine-experienced participants were enrolled in the study. The primary endpoints for seroreponses to Men A, C, W, Y components (ACWY vaccine-naïve and ACWY vaccine-experienced participants) and the B components (seroresponse using 4 MenB primary strains, composite response) were met. Seroresponse was defined as a ≥4-fold increase in hSBA post-vaccination titer compared to pre-vaccination titer. Composite response was defined as the percentage of participants with post-vaccination hSBA titer greater than the lower limit of quantitation (LLOQ) for all 4 primary MenB strains.

- For MenACWY seroresponse, the noninferiority (NI) criteria following MenABCWY Dose 2 compared to a single dose of MenACWY-CRM were met: the lower limit (LL) of the 95% confidence interval (CI) for the percentage difference in participants with a seroresponse to each serogroup was >-10% (ACWY vaccine-naïve participants: LL was -0.2, 34.4, 18.8, and 18.0, respectively, for MenA, C, W, and Y; ACWY vaccine-

experienced participants: in the same order, the LL was -6.5, -4.6, -2.2, and -4,6, respectively).

- For MenB responses, the NI criteria following MenABCWY Dose 2 compared to MenB Dose 2 were met for the 5 endpoints (4 MenB primary strains, composite endpoint); the LL of the 2-sided 95% CI for the percentage difference of participants with seroresponse using each primary MenB test strain and for the percentage difference of participants with a composite response was >-10%; for the primary MenB test strain expressing A22, A56, B24, or B44 variant, the LL was -0.7, -1.0, 5.2, and 2.9, respectively, and 4.2 for the composite response.

Since noninferiority was demonstrated for MenABCWY primary MenB responses compared with Trumenba for the primary endpoints and MenB responses were comparable for secondary outcomes (GMT, percentage of participants with hSBA titer greater than the assay lower limit of quantitation [LLOQ], reverse cumulative distribution curves [RCDCs]), as observed in Study B1971057, MenABCWY secondary Men B strain evaluation was not performed.

Among ACWY vaccine-experienced participants, the MenA and Men C hSBA GMT after 2 doses of MenABCWY was lower than GMTs to both serogroups after 1 dose of MenACWY-CRM. However, the differences in hSBA GMTs were not reflected in lower seroresponse rates. In the limited antibody persistence data from Study B1971057 Stage 2, similar proportions of participants who received two doses of MenABCWY maintained hSBA titers ≥LLOQ for all four serogroups compared with those who received MenACWY-CRM + MenB. Therefore, in the population studied, the observed hSBA GMT differences between groups are unlikely to result in lower rates of protection over time.

Overall, review of the clinical trial design, the pre-specified endpoints and statistical success criteria, and immunogenicity results support the effectiveness of MenABCWY administered at 0 and 6 months to individuals 10-25 years of age.

Safety

The safety of MenABCWY in individuals 10-25 years of age was evaluated in 3 studies (2744 MenABCWY, 1802 comparator). In the two active controlled studies (C3511001, B1971057 Stage 1), 2306 participants received at least 1 dose of MenABCWY and 1706 received a comparator vaccine(s) [vaccination Visit 1: MenB+MenACWY-CRM; vaccination Visit 2: MenB]. A total of 1792 participants (vaccine and comparator groups combined) had a history of prior meningococcal conjugate vaccination. Study B1971057 Stage 2 included 144 MenABCWY and 96 comparator participants. In Study C3511004, a total of 294 participants received MenABCWY.

The safety monitoring for Study C3511001 and B1971057 Stage 1 were the same; solicited local and systemic adverse reactions were monitored for 7 days after study vaccination using an electronic diary (e-diary). Spontaneous reports of adverse events (AEs) were collected through 1 month after the last vaccination, and through 6 months after the last vaccination for serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs). In Study C3511001, the most commonly reported (≥15%) solicited adverse reactions after Dose 1 and Dose 2, respectively, were pain at the injection site (89% and 84%), fatigue (52% and 48%), headache (47% and 40%), muscle pain (26% and 23%), injection site redness (26% and 23%), injection site swelling (25% and 24%), joint pain (20.2% and 18.3%), and chills (20.1% and 16.4%).

In the 2 controlled studies (C3611001, B1971057 Stage 1), the most common non-serious unsolicited AEs reported within 30 days after any vaccination were events in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of *Infections and Infestations* and *Injury, Poisoning and Procedural Complications*; the events were anticipated for a study population of adolescents and young adults. During the time period from the first study visit through 6 months after the last vaccination, SAEs were reported by 0.9% of participants in the MenABCWY group and 1.1 % of participants in the comparator group, and most commonly reported in the SOCs of *Injury, Poisoning and Procedural Complications* and *Psychiatric Disorders*. Upon review of the case narratives, none of the SAEs were assessed by FDA/CBER clinical review team to be related to MenABCWY.

Overall (3 studies), an autoimmune condition with confirmed diagnosis was reported for 0 MenABCWY and 7 (0.4%) MenB+MenACWY-CRM participants, a neuroinflammatory condition with confirmed diagnosis was reported for 2 (0.07%) MenABCWY participants and 1 (0.06%) MenB+MenACWY-CRM participant. Upon review of the case narratives, none of the autoimmune or neuroinflammatory conditions were assessed by FDA/CBER clinical review team to be related to MenABCWY.

Overall Conclusions
The totality of scientific evidence supports approval of a 2-dose MenABCWY regimen for prevention of invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10-25 years of age.

Postmarketing Studies
In accordance with Pediatric Research Equity Act (PREA) requirements, submission of clinical study reports for MenABCWY safety and immunogenicity studies (B1971067 and C3511005) in children 1 to <10 years were deferred for this BLA because MenABCWY is ready for approval for use in individuals 10-25 years of age before pediatric studies are completed. Also, the Applicant committed to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Overall, for serogroups A,C,W,Y and MenB expressing the A22 variant, the seroresponse rates (defined as the percentage of participants with ≥4-fold increase in one month post-vaccination hSBA titer compared with pre-Vaccination 1) in participants 18 through 25 years of age (hereafter abbreviated 18-25 years of age) was lower than seroresponse rates in participants 10 through <18 years of age (hereafter abbreviated 10-<18 years of age), due to higher baseline titers prior to Vaccination 1. hSBA responses among females and males were similar.

In Study C3511001, the percentage of MenABCWY participants reporting any solicited systemic reaction after any vaccination was notably higher in females (F) (87.2%) compared to males (M) (75.6%), mainly due to differences in headache (F 65.6%, M 49.2%) and fatigue (F 69.8%, M 57.5%). There were no clinically important differences in the percentage of MenABCWY participants who reported any solicited local reactions after any vaccination in subgroup analyses by sex or solicited reactions (local or systemic) by age (10 to <18 years of age, 18 to <26 years of age).

No definitive conclusions could be made about differences in hSBA responses or frequencies of solicited reactions by race, ethnicity, or geographic region, since >74% of participants of the overall study population were White or non-Hispanic/non-Latino.

1.2 Patient Experience Data

Patient experience data were not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 General Product Information

MenABCWY (PENBRAYA) vaccine is comprised of *N. meningitidis* serogroups A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid carrier protein, and 2 recombinant lipidated factor H binding protein (fHbp) [1 subfamily A, 1 subfamily B variant] of *N. meningitidis* serogroup B. The meningococcal B components in PENBRAYA are the same as in Trumenba (Wyeth Pharmaceuticals, Inc). Trumenba is licensed in the U.S. for use in individuals 10-25 years of age and can be administered as a 2-dose schedule at 0 and 6 months. The serogroup A, C, W, and Y conjugates are the same components contained in Nimenrix (Pfizer Europe MA EEIG), which is not licensed in the U.S., but is approved in Europe as a single dose (primary vaccination).

2.2 Disease or Health-Related Conditions Studied

Invasive Meningococcal Disease

N. meningitidis is a significant cause of endemic and epidemic invasive meningococcal disease worldwide. Six serogroups (A, B, C, W, X and Y) are responsible for the majority of clinical disease, which is commonly meningitis and septicemia. A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, and seizure disorder) and approximately 10% of cases are fatal.

In 2021, based on Active Bacterial Core (ABC) surveillance data, the Centers for Disease Control and Prevention (CDC) estimated that the overall rate of invasive meningococcal disease was 0.06/100,000 population in the U.S. Rates were 0.02 cases per 100,000 population for adolescents 11 through 17 years of age, and 0.03 cases per 100,000 population for individuals 18 through 22 years of age. Meningococcal disease in the U.S. is often sporadic, but outbreaks of meningococcal disease also occur.

2.3 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication

Antibiotic chemoprophylaxis is available; however, disease manifestations (e.g., bacteremia, sepsis) are prevented only if individuals at risk are identified in a timely manner.

2.4 Safety and Efficacy of Pharmacologically Related Products

Meningococcal A, C, W, Y (MenACWY) Vaccines

Three meningococcal conjugate vaccines (Menactra [Sanofi Pasteur Inc.], Menveo [GSK Vaccines], and MenQuadfi [Sanofi Pasteur Inc.]) are currently licensed and available in the U.S. to protect children and adults against meningococcal disease caused by serogroups A, C, Y and W. The safety and effectiveness of each of these three vaccines are described in the full prescribing information for each of the corresponding vaccines (i.e., Menactra, Menveo, MenQuadfi).

Meningococcal B (MenB) Vaccines

Two MenB vaccines (Trumenba [Wyeth Pharmaceuticals LLC], Bexsero [GSK Vaccines]) are currently licensed and available in the U.S. to protect individuals 10 to 25 years of age against meningococcal disease caused by serogroup B *N. meningitidis*. The safety and effectiveness of each of these vaccines are described in the full prescribing information for the corresponding vaccine (i.e., Trumenba, Bexsero).

Meningococcal B vaccines using the outer membrane vesicle (OMV) from an outbreak or epidemic disease strain have been studied and used as a public health measure in Chile, Cuba, Brazil, Norway and New Zealand.[4]

2.5 Previous Human Experience with the Product

The postmarketing safety experience with Trumenba and a non-U.S. licensed meningococcal serogroups A, C, W, and Y polysaccharide tetanus toxoid (TT) conjugate vaccine (MenACWY-TT vaccine; Pfizer Inc.) is relevant to MenABCWY since MenABCWY includes the same serogroup A, C, W, and Y TT-conjugated polysaccharide components and MenB recombinant protein components. Please see Section 6.2 of the Trumenba full prescribing information.

2.6 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

2019

- End of Phase 2: written responses only (WRO) and clarifications
  CBER recommendations for Study C3511001 design include ACWY vaccine-naïve and vaccine-experienced participants since the intended population for use is 10-25 years of age; revise serogroup A,C,W, and Y response definition, MenB endpoints, and statistical success criteria for all serogroups; include as a secondary endpoint an assessment of A,C,W, and Y seroresponses 1 month after the first dose in the MenABCWY serogroup vs. the first dose of MenACWY-CRM in the control group to enable characterization of hSBA responses after each MenABCWY dose.

- iPSP: plans for a single MenABCWY study (C3511001) in children 1 to <10 years of age. The comparative safety database is expected to include 2000 MenABCWY vaccine recipients.

2020-2021

- Manufacturing comparability assessments, clinical batch data, and written responses to CBER information requests satisfactorily supported the Applicant's proposal not to conduct a MenABCWY clinical lot consistency study.

- Study B1971057: summary tables indicated lower GMTs to MenA (ACWY vaccine-naïve and vaccine-experienced participants) and to MenC, W and Y (ACWY vaccine-experienced participants) following successive MenABCWY vaccinations, compared to corresponding hSBA responses following concomitant administration of Trumenba and Menveo. The Applicant was asked to provide clinical or pre-clinical data that may address concerns that the polysaccharide conjugate components may be adversely affected by combination with the MenB components and to address the relevance of reduced responses to priming and immune memory. The Applicant was also asked to provide a status update for Study B1971057 Stage 2 and Study C3511004, and a timeframe when immunogenicity data from both studies could be submitted to CBER to address concern about reduced responses MenA, C, W, and Y following successive MenABCWY vaccinations.

- Study C351001: a separate evaluation of MenABCWY responses using MenB secondary strains to demonstrate breadth of coverage of MenABCWY in individuals 10-26 years of age might not be needed if: a) the clinical benefit of Trumenba 2-dose schedule (0, 6 months) in the same age group is confirmed (Study B1971057 Stage 1); and, b) MenB primary strain hSBA data from Study C3511001 show that hSBA responses to MenABCWY are non-inferior for primary endpoints and comparable for all secondary outcomes (e.g., GMT, proportion ≥LLOQ, RCDC), as was observed in Study B1971057 Stage 1. If clinical benefit (including breadth of coverage) of the Trumenba 2-dose schedule is not verified upon FDA's review of data in an sBLA, or MenABCWY outcomes from Study C3511001 and Study B1971057 are inconsistent, a MenABCWY secondary strain evaluation would be needed to support licensure of MenABCWY in adolescents and young adults.

2022

- Amended agreed iPSP: agreement for revised final report submission date.
- Pre-BLA CMC: written responses only. Agreements for setting specifications for drug substance and intermediates, drug product, and combined vaccine drug product; data to support proposed shelf life; content and format of BLA module 3.
- Pre-BLA Clinical: written responses only. Agreement that planned clinical data package (Studies C3511001 and B1971057 Stage 1) would support FDA review for the proposed indication and dosing schedule (i.e., for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y, when administered as a 2-dose series [0- and 6-month schedule]). Descriptive data from Phase 2 Study B1971057 Stage 2 alone would not be adequate to support approval of MenABCWY for use as a booster dose. An extended dosing interval for the 2-dose series based on data from Study C3511004 would be taken into consideration, but detailed discussions would be deferred to the appropriate time during the BLA review period.

2.7 Other Relevant Background Information

In MenABCWY studies C3511001 and B1971057 Stage 1, hSBA responses following MenABCWY were compared to participants who received US-licensed MenACWY-CRM (Menveo) and MenB (Trumenba). For primary immunization, Menveo is approved as a single dose for individuals 2-55 years of age and Trumenba is approved as a 2-dose (0 and 6 months) or 3-dose series in individuals 10-25 years of age.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission of this BLA was adequately organized and integrated to accommodate the conduct of a complete review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Safety and immunogenicity data from 1 main study (C3511001) and 2 supportive studies (B1971057, C3511004) were provided in this application to support licensure of MenABCWY and were conducted in accordance with Good Clinical Practice and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR 50.25. In accordance with 21 CFR 312.120, the Applicant provided the required elements to ensure that each study conformed with Good Clinical Practice.

Bioresearch monitoring (BIMO) inspections were issued for four clinical study sites that enrolled participants in Study C3511001. The four completed inspections did not reveal substantive issues that impact the data submitted in this BLA.

3.3 Financial Disclosures

Covered clinical study (name and/or number): C3511001, B1971057, C3511004
Was a list of clinical investigators provided? X Yes ☐ No
Total number of investigators identified: 1,181
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5 (total of 4 investigators; 1 investigator participated in 2 studies). The 5 study investigators comprised 0.4% study investigators who participated in the 3 studies.
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 4 (total of 3 investigators; 1 investigator participated in 2 studies) Is an attachment provided with details of the disclosable financial interests/arrangements? x Yes ☐ No Is a description of the steps taken to minimize potential bias provided? x Yes ☐ No
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 12 Is an attachment provided with the reason? x Yes ☐ No

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Release tests and in-process tests were developed and validated as appropriate for all intermediates, drug substances, and drug product. The proposed shelf lives for the MenACWY-TT component and the MenB component when stored at 2–8°C is supported by the information submitted to the BLA. Please refer to the CBER CMC review memo for additional details.

4.2 Assay Validation

The Applicant demonstrated that the anti-MenB and anti-MenACWY hSBAs are adequately validated for use in their intended purpose of evaluating the primary endpoints in clinical Studies

C3511001, C3511004, and B1971057. Testing of control sera indicated that assays have remained stable from the time of assay validation through the clinical sample testing period. Specificity studies confirmed that bactericidal activity measured in the MenA, MenC, MenW or MenY hSBA assays was not notably increased by anti-fHbp antibody-mediated killing. Therefore, additional testing of study participant sera for serogroup-specific IgG antibody concentration was not needed to ensure that activity measured in these hSBA assays was specifically mediated by antibodies to the capsular polysaccharides.

MenB strain selection

The four primary MenB strains each expressed a variant from the 2 subfamilies, A or B (i.e., A22, A56, B24, B44), including test strains expressing the most prevalent subfamily A and subfamily B fHBP variants in the U.S. (B24 and A22). Susceptibility of the isolates to bactericidal killing was hierarchical (i.e., serum of vaccinated individuals that contained fHBP antibodies which were bactericidal against less susceptible strains was predictive of serum bactericidal killing of more susceptible strains). The primary strains expressed low or medium quantities of fHBP (depending on the strain).

Ten secondary strains were used to evaluate the breadth of coverage following Trumenba vaccination. The 10 secondary strains, each expressing fHBP variant A29, A06 A07, A12, A15 A19, B03, B09, B15 or B16 were selected to further characterize the ability of the vaccine to protect against invasive disease caused by prevalent strains in the U.S. and representative of diverse circulating *N. meningitidis* causing endemic disease in the U.S. Candidate strains expressing the targeted fHbp variants were then tested in the hSBA assay to verify (b) (4) (b) (4) and bactericidal killing by known positive samples.

4.3 Nonclinical Pharmacology/Toxicology

Preclinical studies demonstrated immunogenicity of MenACWY-TT and MenB (Trumenba) components of MenABCWY, with generation of functional antibody responses. Trumenba elicited antibodies that were bactericidal against meningococcal serogroup B strains in human complement serum bactericidal assays (hSBAs) that expressed antigens heterologous to those present in the vaccine.

4.4 Mechanism of Action

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody dependent killing of *N. meningitidis* (Goldschneider, 1969). Vaccination with MenABCWY induces the production of bactericidal antibodies specific to the capsular polysaccharides of N*. meningitidis s*erogroups A, C, W, and Y and to fHbp subfamily A and B variants of N*. meningitidis s*erogroup B. The susceptibility of serogroup B meningococci to bactericidal antibody is dependent upon both the antigenic similarity of the fHbp subfamily A or subfamily B vaccine antigen to the fHbp protein expressed by the bacterial strain and the amount of fHbp expressed at the bacterial surface (Wang et al., 2011).

4.5 Statistical

Primary immunogenicity and safety results were confirmed by the FDA/CBER statistician's independent analyses. There were no statistical issues that would affect the clinical interpretation of the safety and immunogenicity data contained in the study reports. Please refer to review memo by Dr. Xinyu Tang for more information.

4.6 Pharmacovigilance

The pharmacovigilance reviewer concluded that the proposed pharmacovigilance plan, which includes routine postmarketing safety surveillance consisting of monitoring for any unanticipated risks in surveillance systems and postmarketing adverse reaction reports as well as a commitment to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy, is adequate to monitor postmarketing safety. Please refer to the detailed review by Dr. Sarada Panchanathan.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Study C3511001 was the main study to demonstrate the effectiveness of MenABCWY when administered at 0 and 6 months. The safety of MenABCWY was evaluated in 3 studies (C3511001, B1971057, and B1971004).

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following STN# 125770/0 Amendments (Am) were reviewed (listed by module):

- Am 0: 1.1, 1.2, 1.3, 1.4, 1.6, 1.9, 1.12; 2.2, 2.5, 2.7; 5.2, 5.3, 5.4
- Am 2: 1.11 Response to information request (IR) re: datasets
- Am 5: 1.11 Response to IR re: postmarketing experience
- Am 8: Response to IR re: datasets (1.11) and corresponding tables (5.3)
- Am 9: 1.14 Updated Labeling
- Am 27: 5.3.5.1 Pregnancy registry study protocol synopsis: updated milestone dates for postmarketing study
- Am 30: 1.11 Response to information request (IR) re: datasets
- Am 32: 1.9.2 Revised milestone dates in Request for Deferral of Pediatric Research Equity Act (PREA) studies
- Am 35: Response to PI comments (1.11), draft labeling (1.14)
- Am 36: 1.11 Response to IR re: updated Study C3511005 milestones dates
- Am 38: 1.14 Draft labeling
- Am 40: 1.14 Draft labeling
- Am 41: 1.14 Draft labeling
- Am 42: 1.9.2 Revised milestone dates for PREA studies
- Am 43: 1.14 Final labeling
- Am 45: 1.14 Minor revision to final labeling

5.3 Table of Clinical Studies

Table 1. Clinical Studies

Study Number / Location / Participant Age	Description	Vaccination Schedule	Safety Population MenABCWY	Safety Population MenB + MenACWY-CRM
Vaccination (0- and 6-Month Schedule)	--	--	--	--
C3511001 USA, Europe 10-25 years of age	Phase 3, randomized, active-controlled, observer-blind, safety and immunogenicity	MenABCWY Month 0: MenABCWY + saline Month 6: MenABCWY Comparator Month 0: MenB + MenACWY-CRM Month 6: MenB	1763	649
B1971057 Stage 1 USA, Europe 10-25 years of age	(First-in-human study for MenABCWY) randomized, active-controlled, observer-blind, safety and immunogenicity	MenABCWY Month 0: MenABCWY + saline Month 6: MenABCWY Comparator Month 0: MenB + MenACWY-CRM Month 6: MenB	543	1057
Extended Interval (0- and 12-Month Schedule)	--	--	--	--
C3511004 USA 11-14 years of age	Phase 2, randomized, observer-blind [only safety and immunogenicity data through Month 13 were included in the BLA][a]	Group 1: MenABCWY 0- and 12-month schedule Month 0: MenABCWY Month 12: MenABCWY Group 2: MenABCWY 0- and 36-month schedule Month 0: MenABCWY Month 12: Saline Month 36: MenABCWY	Group 1 N=146 Group 2 N=148	0
Booster Vaccination	--	--	--	--

Study Number / Location / Participant Age	Description	Vaccination Schedule	Safety Population MenABCWY	Safety Population MenB + MenACWY-CRM
B1971057 Stage 2 USA, Europe 14-30 years of age	Phase 2, randomized, active-controlled, open-label Booster Vaccination 4 years after Vaccination 2	MenABCWY Booster Vaccination 4 years after MenABCWY Vaccination 2 MenB + MenACWY-CRM Booster Vaccination 4 years after Trumenba Vaccination 2	144	96
Total	**--**	**--**	**2744**	**1802**

Source: Adapted from clinical-overview.pdf, Table 1.
Abbreviations: BLA=Biologics License Application; MenABCWY=*Neisseria meningitidis* serogroups A, B, C, W, and Y vaccine; MenB=meningococcal serogroup B factor H binding protein (Trumenba); MenACWY-CRM=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo)

5.4 Consultations

5.4.1 Advisory Committee Meeting

Not applicable.

5.5 Literature Reviewed

Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med. (1969);129:1307-1326.

Wang X, et al. Prevalence and genetic diversity of candidate vaccine antigens among invasive Neisseria meningitidis isolates in the U.S. Vaccine 2011; 29:4739-4744.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study C3511001

NCT# 04440163
Title: "A Phase 3, Randomized, Active-Controlled, Observer-Blinded Trial to Assess the Safety, Tolerability, and Immunogenicity of MenABCWY in Healthy Participants ≥10 to <26 Years of Age"

6.1.1 Objectives. Endpoints, Statistical Criteria

Primary Objectives

1. To demonstrate that the MenA, MenC, MenW, and MenY hSBA responses after 2 doses of MenABCWY are noninferior to the hSBA responses induced by 1 dose of MenACWY-CRM in ACWY-naïve and in ACWY-experienced participants.

   Endpoint: Percentage of participants with a seroresponse* to A, C, W, and Y
   Timepoints:
   - ACWY-naïve participants: 1 month after 2 doses of MenABCWY (Group 1) vs. 1 month after 1 dose of MenACWY-CRM (Group 2)
   - ACWY-experienced participants: 1 month after 2 doses of MenABCWY (Group 3) vs. 1 month after 1 dose of MenACWY-CRM (Group 4)

   Non-inferiority criteria:
   - ACWY-naïve participants: for each serogroup, LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse (seroresponse $_{Group\ 1}$ minus seroresponse $_{Group\ 2}$) for Men A, C, W, and Y is >-10% at 1 month post-Vaccination 2 for Group 1 compared with 1 month post-Vaccination 1 for Group 2.
   - ACWY-experienced participants: NI criteria were the same as for ACWY-naïve participants.

2. To demonstrate that the hSBA responses to MenB (primary strains) after 2 doses of MenABCWY are noninferior to the hSBA responses after 2 doses of MenB vaccine.
   5 endpoints:
   #1-4: percentage of participants with a seroresponse* to each of the primary MenB variants (A22, A56, B24, and B44)

Non-inferiority criteria: LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse* to each of the four primary strains is >-10% at 1 month post-Vaccination 2 (seroresponse $_{\text{Groups 1+3}}$ versus seroresponse $_{\text{Groups 2+4}}$).

#5: Composite response: defined as the percentage of participants with post-vaccination hSBA titer ≥LLOQ to all 4 primary MenB strains

Non-inferiority criterion: LL of the 2-sided 95% CI for the percentage difference in participants with a composite response is >-10% at 1 month post-Vaccination 2 (Groups 1+3 versus Groups 2+4).

Reviewer Comment: *Please see Section 4.2 for rationale for selection of MenB primary strains.*

*Seroresponse: a 4-fold response, was defined as:

- For participants with a pre-Vaccination 1 (baseline) hSBA titer <LOD, a 4-fold response was defined as an hSBA titer of ≥4 times the LOD
- For participants with a pre-Vaccination 1 hSBA titer ≥LOD and <LLOQ, a 4-fold response was defined as an hSBA titer ≥4 times the LLOQ
- For participants with a pre-Vaccination 1 hSBA titer ≥LLOQ, a 4-fold response was defined as an hSBA titer ≥4 times the baseline titer.

For each of the Men A, C, Y and W strains, the LOD was 1:4 and the LLOQ was 1:8. For the 4 MenB primary strains (expressing variant A22, B56, B24, and B44, respectively), the LOD for each strain was 1:4; the LLOQs were 1:16 for A22, and 1:8 for B56, B24 and B44.

Safety Objective

To describe the safety profile of MenABCWY (Groups 1,3,5,7 combined) vs. Trumenba (Groups 2,4,6,8 combined).

Endpoints: Immediate AEs; solicited local and systemic adverse reactions; non-serious, unsolicited AEs; SAEs; medically attended adverse events (MAE: defined as non-serious AE that results in an evaluation at a medical facility); NDCMCs (defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects).

Secondary Objective

To demonstrate that the MenA, MenC, MenW, and MenY hSBA responses after 1 dose of MenABCWY are noninferior to the hSBA response induced by 1 dose of MenACWY-CRM in ACWY-naïve and in ACWY-experienced participants. Timepoint: 1 month post-Vaccination 1.

Endpoints: same as primary objective #1
NI criteria: Except for the timepoint (1 month post-Vaccination 1 in both study groups), the NI criteria are the same as primary objective #1

Tertiary/Exploratory Objectives

1. To describe the percentage of participants with hSBA responses to meningococcal serogroups A, C, W, and Y after 2 doses of MenABCWY, compared with corresponding responses after 1 dose of MenACWY-CRM (in ACWY-naïve and ACWY-experienced participants, separately).

Endpoints for serogroups A,C,W and Y: percentage of participants with hSBA titer ≥1:8, GMT

2. To describe hSBA responses (secondary MenB strains) after 2 doses of MenABCWY.
   Timepoint: 1 month post-Vaccination 2
   Endpoints for each MenB secondary strain:
   - Percentage of participants with hSBA titer ≥LLOQ at baseline and 1 month after Vaccination 2 (Groups 1+3).
   - Percentage of participants with hSBA titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at baseline and 1 month after Vaccination 2 (Groups 1+3).
   - hSBA GMTs: at baseline (pre-Vaccination 1), 1 month after Vaccination 2 (Groups 1+3).

Reviewer Comment: *Further immunogenicity assessments using MenB secondary strains was not performed, since noninferiority was demonstrated for MenABCWY primary endpoints and responses were comparable to Trumenba for secondary outcomes (GMTs, percentages of participants with hSBA titer ≥LLOQ, reverse cumulative distribution curves), as observed in Study B1971057.*

6.1.2 Design Overview

Study C3511001 was designed as a randomized, controlled, observer-blind study. A total of 2431 participants were randomized in a 2:1 (vaccine: comparator) ratio to receive MenABCWY + saline at Month 0 then MenABCWY at Month 6, or MenB (Trumenba) + MenACWY-CRM (Menveo) at Month 0 and MenB (Trumenba) at Month 6.

Enrollment was stratified by age (10-17 years, 18-25 years), ACWY vaccination history (i.e., ACWY-naïve and ACWY-experienced), and geographic region (80% U.S. sites, 20% non-U.S.). All participants were naïve to any meningococcal serogroup B vaccine prior to enrollment. ACWY-experienced was defined as receiving not more than 1 prior dose of a U.S.-licensed MenACWY vaccine no sooner than 4 years prior to the date of study randomization.

Blinding: The study personnel preparing and administering the vaccines were unblinded to the vaccine assignment. The study investigator, participants, participants' parent(s)/legal guardian(s), and study personnel who evaluated participant safety were blinded to the vaccine assignment.

Table 2. Design, Study C3511001

ACWY Vaccine History	Study Group	N	Vaccination 1 Month 0	Vaccination 2 Month 6
ACWY-naïve	I	450	MenABCWY+saline	MenABCWY
ACWY-naïve	2	225	MenB+MenACWY-CRM	MenB
ACWY-experienced	3	675	MenABCWY+saline	MenABCWY
ACWY-experienced	4	338	MenB+MenACWY-CRM	MenB
Groups 1-4 only, blood draw	--	--	25 mL	--
ACWY-naïve [safety only][a]	5	500	MenABCWY+saline	MenABCWY
ACWY-naïve [safety only][a]	6	50	MenB+MenACWY-CRM	MenB
ACWY-experienced [safety only][a]	7	125	MenABCWY+saline	MenABCWY
ACWY-experienced	8	50	MenB+MenACWY-CRM	MenB

ACWY Vaccine History	Study Group	N	Vaccination 1 Month 0	Vaccination 2 Month 6
[safety only][a]				

Source: Adapted from c3511001-protocol.pdf, Table 1.
a. Blood samples were collected only for Study Groups 1-4. Safety evaluations at 1 month after each vaccination was conducted by at the study site (Study Groups 1-4) or by telephone (Study Groups 5-8).

Duration of Participation: 12 months

6.1.3 Population

Summarized Inclusion Criteria

- Male or female, 10-25 years of age at the time of randomization
- ACWY-naïve participants: Participants who have never received a prior dose of a meningococcal vaccine containing ACWY serogroups
- ACWY-experienced participants: Participants who have received not more than 1 prior dose, no sooner than 4 years prior to the date of randomization of Menactra or Menveo

Summarized Exclusion Criteria

- Previous anaphylactic reaction to any vaccine or vaccine-related component.
- A known or suspected defect of the immune system that would prevent an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy.
- History of microbiologically proven disease caused by *N. meningitidis* or *N. gonorrhea*
- Significant neurological disorder or history of seizure (excluding simple febrile seizure).
- Any neuroinflammatory or autoimmune condition, including, but not limited to transverse myelitis, uveitis, optic neuritis, and multiple sclerosis.
- Previous vaccination with any meningococcal serogroup B vaccine, any purely polysaccharide (nonconjugate) meningococcal vaccine, or monovalent/bivalent meningococcal vaccine.
- Current use of systemic antibiotics with no foreseeable date of discontinuation prior to anticipated date of enrollment (first vaccination).
- Pregnant female participants, breastfeeding female participants, fertile male participants, and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception.

Temporary Exclusion Criteria

Can be vaccinated when the following conditions have resolved, and the individual is eligible for vaccination:

- Febrile illness (temperature ≥38.0°C) or other acute illness within 48 hours before investigational product administration
- Received a non-live vaccine within 14 days, or any live vaccine within 28 days, before investigational product administration
- Less than 5 days into a course of systemic antibiotic therapy
- Received systemic (oral, intravenous, or intramuscular) corticosteroid therapy in the prior 28 days

6.1.4 Study Treatments or Agents Mandated by the Protocol

- MenABCWY (PENBRAYA; 0.5 mL dose): contains 60 µg each of 2 recombinant lipidated fHbp variants from Men B (1 fHbp subfamily A [A05], 1 subfamily B [B01]), 5 µg each of *N. meningitidis* serogroup A, C, Y, and W-135 polysaccharides conjugated individually to tetanus toxoid (TT), and aluminum as $AlPO_4$. Lot #19-005010 (MenB), lot #20-000490 (MenACWY-TT).
- Meningococcal B Vaccine (Trumenba; 0.5 mL dose): same composition as MenB component described above. Lot #20-000165.
- MenACWY-CRM (Menveo; 0.5 mL dose): contains 10 µg *N. meningitidis* serogroup A oligosaccharide and 5 µg of each of serogroup C, Y, and W oligosaccharides, conjugated individually to CRM_{197} protein (total 25.4 to 65.5 µg CRM_{197}). Lot #20-001102, 20-002626, 20-005540, and 20-001544.

6.1.5 Directions for Use

MenABCWY: a vial of lyophilized MenACWY-TT is reconstituted with MenB ((b) (4) in a pre-filled syringe) using a vial adaptor. The entire contents of the syringe containing the MenB Component is injected into the vial. After reconstitution, the entire contents of the vial is drawn into the syringe. Each dose (approximately 0.5 mL) is administered intramuscularly.

Meningococcal B Vaccine (Trumenba; Wyeth Pharmaceuticals, Inc): supplied as suspension in a pre-filled syringe (0.5mL). Administered intramuscularly.

MenACWY-CRM (Menveo; GlaxoSmithKline Biologicals SA): supplied as solution in a single dose vial (0.5mL). Administered intramuscularly.

6.1.6 Sites and Centers

75 sites in the following 5 countries: U.S. (n=63), Czech Republic (n=7), Denmark (n=1), Hungary (n=5), Poland (n=6).

6.1.7 Surveillance/Monitoring

- Immediate AEs: assessed during the 30 minutes after each vaccination. Defined as an AE occurring during the 30-minute post-vaccination observation period. Recorded by study personnel in case report form (CRF).

- Solicited local and systemic adverse reactions: assessed during the 7 days after each study vaccination
  - Local: pain, redness, and swelling. Recorded at the MenABCWY and MenB injection sites only.
  - Systemic: fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain.

  Recorded daily by participants using an e-diary. If the reaction exceeded the maximum size the caliper is able to measure (>21 caliper units), the parent(s)/legal guardian(s) or the participants also used a measuring tape/ruler to measure the maximum diameter of redness and/or swelling at the injection site and reported this measurement to the study investigator. Please see the solicited local and systemic reaction tables in Section 6.1.12.3 for severity scales.

- AEs
  - All AEs, SAEs, MAEs, NDCMCs.

  - Timepoints: 30 days after each vaccination; during the vaccination phase (from Vaccination 1 through 1 month after Vaccination 2); during the follow-up phase (defined as 1 month after Vaccination 2 through 6 months after Vaccination 2); from Vaccination 1 through 6 months after Vaccination 2.

  Any AEs, SAEs, MAEs and NDCMCs were assessed at the study visit (Study Groups 1-4) or by telephone (Study Groups 5-8) at 1 month after each vaccination and recorded on the CRF. Study staff contacted all participants by telephone to collect information about SAEs and NDCMCs that occurred through 6 months after the last vaccination.

6.1.8 Endpoints and Criteria for Study Success

See Section 6.1.1.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see Section 6.1.1 for objectives, endpoints, and non-inferiority criteria.

Sample Size

Planned enrollment of 2413 participants (1750 MenABCWY, 663 MenB + MenACWY-CRM), 1688 MenABCWY participants would result 1350 MenABCWY evaluable participants, and assuming 20% non-evaluable participants. With 360, 180, 540, and 270 evaluable participants in Groups 1, 2, 3, and 4, respectively, the study power would be:

- >99.9% to demonstrate noninferiority for the first primary objective relating to the ACWY response in ACWY-naïve participants
- >99.4% to demonstrate noninferiority for the first primary objective relating to the ACWY response in ACWY-experienced participants
- >91.6% for the second primary objective relating to the MenB response
- The combined power, across both primary objectives, is 91.0%

Analysis Populations

- Evaluable Immunogenicity (defined for each vaccination): received the investigational products at Month 0 as randomized, blood draws for assay testing within the required time frames (Month 0, 1 month after the first vaccination, window: 28-49 days), had at least 1 valid and determinate MenACWY assay result at the specified timepoint (i.e. post-Vaccination 1, post-Vaccination 2), did not receive prohibited vaccines or treatment through the specified timepoint, no important protocol deviations through the specified timepoint.

- Modified intent to treat (mITT): participants who received at least 1 study vaccination and had at least 1 valid and determinate MenB or MenACWY assay result available at any time point from Month 0 to 1 month post-Vaccination 2.

- Safety
  - Defined for each vaccination: randomized participants who receive at least 1 dose of the investigational product and have safety data reported after vaccination (post-Vaccination 1, post-Vaccination 2), Participants were analyzed according to the vaccine received.

- Follow-up safety population: received 1 dose of investigational product and for whom safety information is available from 1 month post-Vaccination 2 through 6 months post-Vaccination 2.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In this subsection, the number of MenABCWY participants represents participants in Study Groups 1,3,5, and 7 combined, and the number of MenB + MenACWY-CRM participants represents participants in Study Groups 2,4,6, and 8 combined.

A total of 2431 individuals were randomized (1778 MenABCWY, 653 comparator), and 2413 (99.3%) were vaccinated (1763 MenABCWY, 650 comparator). The safety population included a total of 2412 participants (1763 MenABCWY, 649 comparator).

Of the 1617 participants randomized to the immunogenicity subsets, the post-Vaccination 1 evaluable population included a total of 1446 (89.4%) participants (961 MenABCWY, 485 MenACWY-CRM). The post-Vaccination 2 evaluable population included a total of 1274 (78.8%) participants (851 MenABCWY, 423 MenB).

6.1.10.1.1 Demographics

Table 3. Demographic Characteristics, Safety Population, Vaccine Group as Administered (Actual ACWY History and Subset[a]), Study C3511001

Demographic Characteristics	Groups 1/3/5/7 Combined MenABCWY+Saline (N[b]=1763) n[c] (%)	Groups 2/4/6/8 Combined MenB+MenACWY-CRM (N[b]=649) n[c] (%)
Sex	--	--
Male	846 (48.0)	330 (50.8)
Female	917 (52.0)	319 (49.2)
Race	--	--
White	1359 (77.1)	522 (80.4)
Black or African American	184 (10.4)	61 (9.4)
Asian	45 (2.6)	12 (1.8)
American Indian or Alaska Native	10 (0.6)	6 (0.9)
Native Hawaiian or other Pacific Islander	4 (0.2)	0
Multiracial	30 (1.7)	8 (1.2)
Not reported	131 (7.4)	40 (6.2)
Ethnicity	--	--
Hispanic/Latino	438 (24.8)	183 (28.2)
Non-Hispanic/non-Latino	1314 (74.5)	461 (71.0)
Not reported	11 (0.6)	5 (0.8)
Age group	--	--
10 to <18 years	1188 (67.4)	409 (63.0)
18 to <26 years	575 (32.6)	240 (37.0)
Age at first vaccination (years)	--	--
Mean (SD)	15.9 (4.57)	16.6 (4.48)
Median	16.0	16.0
Min, max	(10.0, 25.0)	(10.0, 25.0)

Demographic Characteristics	Groups 1/3/5/7 Combined MenABCWY+Saline (N[b]=1763) n[c] (%)	Groups 2/4/6/8 Combined MenB+MenACWY-CRM (N[b]=649) n[c] (%)
Sex	--	--
Geographic location	--	--
U.S.	1261 (71.5)	487 (75.0)
Ex-U.S.	502 (28.5)	162 (25.0)

Source: Pfizer CSR, Study C3511001; _c3511001-report-body.pdf, Table 10, pgs. 51-54
Abbreviations: Ex-.U.S=global not including the United States; SD=standard deviation
Notes: Groups 1, 3, 5, and 7 received MenABCWY+saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2, 4, 6, and 8 received MenB+MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination. One participant who received MenB+saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables. One participant who received MenABCWY+MenACWY-CRM at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.
a. "Actual ACWY history" is based on prior receipt of a meningococcal serogroup A, C, W, and Y vaccine. "Actual subset" refers to either immunogenicity or safety subset.
b. N=number of participants in the specified group, or the total sample. This value is used as the denominator for the percentage calculations.
c. n=Number of participants with the specified characteristic.

6.1.10.1.2 Participant Disposition

Table 4. Participant Disposition, Study C3511001

Population	MenABCWY[a] N n (%)	MenB + MenACWY-CRM[b] (Visit 1) MenB[b] (Visit 2) N n (%)
Randomized[c] (all participants)	1778	653
Safety	1763 (99.2)	650 (99.5)
Randomized (immunogenicity subset)[d]	1080	537
Evaluable immunogenicity	--	--
Post-vaccination visit 1	1072	535
Post-vaccination visit 2	851	423

Source: Adapted from c3511001-report-body.pdf, Table 9.
a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months.
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months.
c. Individuals were initially randomized, based on ACWY history (prior receipt of a meningococcal serogroup A, C, W, and Y vaccine), to an immunogenicity subset.
d. The values in this row are used as the denominators for percentage calculations for the evaluable populations.

The most common reasons for exclusion from the post-Vaccination 1 evaluable immunogenicity population were that the participant did not receive the study intervention as randomized, the participant was non-compliant with the blood draw visit, the blood sample was collected outside the protocol-defined vaccination window, or the participant did not have valid and determinate MenACWY assay result at the specified visit.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Men A,C,W, and Y Components (MenABCWY Dose 2 vs. MenACWY-CRM Dose 1)

For serogroups A, C, W and Y, seroresponse rates after MenABCWY Dose 2 were noninferior to corresponding seroresponse rates after MenACWY-CRM Dose 1 in ACWY vaccine-naïve and ACWY vaccine-experienced participants 10-25 years of age (Table 5). The LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse for Men A, C, W, and Y was >-10%.

Table 5. Seroresponse Rates (A,C,W,Y) at 1 Month After MenABCWY Dose 2 Versus 1 Month After MenACWY CRM Dose 1, Evaluable Immunogenicity Population, Study C3511001

Serogroup ACWY Vaccination History	MenABCWY Dose 2[a] Seroresponse Rate %[c] N=439-451 (Naïve) N=376-387 (Experienced)	MenACWY-CRM Dose 1[b] Seroresponse Rate %[c] N=244-254 (Naïve) N=222-227 (Experienced)	Difference in Seroresponse Rate (MenABCWY – MenACWY-CRM) % (95%CI)[d]
A	--	--	--
ACWY-naïve	97.8	95.3	2.5 (-0.2, 6.0)
ACWY-experienced	93.8	96.9	-3.2 (-6.5, 0.5)
C	--	--	--
ACWY-naïve	93.3	52.4	41.0 (34.4, 47.5)
ACWY-experienced	93.8	94.7	-0.9 (-4.6, 3.3)
W	--	--	--
ACWY-naïve	97.3	73.0	24.3 (18.8, 30.4)
ACWY-experienced	97.1	96.4	0.7 (-2.2, 4.3)
Y	--	--	--
ACWY-naïve	94.4	70.6	23.8 (18.0, 30.1)
ACWY-experienced	93.0	93.7	-0.7 (-4.6, 3.8)

Source: Adapted from c3511001-report-body.pdf, Table 13.
Abbreviations: CI=confidence interval; hSBA=serum bactericidal assay using human complement; LL=lower limit; LLOQ=lower limit of quantitation; LOD=limit of detection; MenACWY-CRM=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo); MenB=meningococcal serogroup B factor H binding protein (Trumenba).
a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months.
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months.
c. %=n/N. n=number of participants with hSBA titer fold rise ≥4 from baseline (pre-Dose 1) for the given strain.
N=number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. Seroresponse was defined as ≥4-fold increase, as follows: (1) For participants with a baseline hSBA titer <1:4 (LOD), a ≥4-fold response was defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥LOD and <LLOQ, a ≥4-fold response was defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥LLOQ, a ≥4-fold response was defined as an hSBA titer ≥4 times the baseline titer. The LLOQ=1:8 for serogroups A, C, W, and Y.
d. Noninferiority was demonstrated if LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse for Men A,C,W, and Y was >-10%.

MenB Component (MenABCWY Dose 2 vs. MenB Dose 2)

Seroresponses were assessed using 4 MenB primary strains expressing variants A22, A56, B24, and B44, respectively.

For ACWY vaccine-naïve and for ACWY vaccine-experienced participants 10-25 years of age, the NI criteria following MenABCWY Dose 2 compared to Trumenba (MenB) Dose 2 were met for 5 endpoints (4 MenB primary strains, composite endpoint); the LL of the 2-sided 95% CI for the percentage difference of participants with seroresponse with each primary MenB test strain and for the percentage difference of participants with a composite response was greater than -10% (Table 6).

Table 6. Serogroup B Seroresponse Rates and Composite Response at 1 Month After MenABCWY Dose 2 Versus MenB Dose 2, Evaluable Immunogenicity Population, Study C3511001

Serogroup B Variant	MenABCWY Dose 2[a] Seroresponse Rate %[c] N=755-845	MenB Dose 2[b] Seroresponse Rate %[c] N=383-419	Difference in Seroresponse Rate (MenABCWY – MenACWY-CRM) % (95%CI)[d]
Seroresponse[e]	--	--	--
A22	83.0	79.0	4.0 (-0.7, 8.9)
A56	95.9	94.5	1.4 (-1.0, 4.3)
B24	68.1	57.2	10.9 (5.2, 16.6)
B44	86.5	79.2	7.3 (2.9, 11.9)
Composite[e]	--	--	--
Pre-Dose 1	1.2	2.0	
Post-Dose 2	78.3	68.7	9.6 (4.2, 15.2)

Source: Adapted from c3511001-report-body.pdf, Table 14.
hSBA assay using primary MenB strains PMB80 (variant A22), PMB2001 (variant A56), PMB2948 (B24), PMB2707 (B44).
a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months.
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months.
c. %=n/N. n=number of participants with hSBA titer fold rise ≥4 from baseline (pre-Dose 1) for the given strain. N = number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. Seroresponse was defined as ≥4-fold increase, as follows: (1) For participants with a baseline hSBA titer <1:4 (LOD), a ≥4-fold response was defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥LOD and <LLOQ, a ≥4-fold response was defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥LLOQ, a ≥4-fold response was defined as an hSBA titer ≥4 times the baseline titer. The LLOQ=1:16 for A22; 1:8 for A56, B24, and B44.
d. Noninferiority was demonstrated if LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse for serogroup B (4 primary strains, composite response) was >-10%.
e. Composite response was defined as an hSBA titer ≥LLOQ for all 4 primary MenB strains.

6.1.11.2 Analyses of Secondary Endpoint

Men A,C,W, and Y Components (MenABCWY Dose 1 vs. MenACWY-CRM Dose 1)

Among ACWY vaccine-naïve participants 10-25 years of age, seroresponse rates for serogroups A, C, W and Y after MenABCWY Dose 1 were 97.0%, 62.9%, 79.3%, and 82.0%, respectively. Among ACWY vaccine-experienced participants, seroresponse rates for serogroups A, C, W and Y after MenABCWY Dose 1 were 94.8%, 93.4%, 97.4%, and 94.3%, respectively. The seroresponse rates following MenACWY-CRM Dose 1 are presented in Table 5.

Seroresponse rates after MenABCWY Dose 1 were noninferior to corresponding rates after MenACWY-CRM Dose 1 in ACWY vaccine-naïve and ACWY vaccine-experienced participants 18 through 25 years of age (hereafter abbreviated 18-25 years of age). The LL of the 2-sided 95% CI for the percentage difference in participants with a seroresponse for Men A, C, W, and Y was >-10%; for ACWY vaccine-naïve participants, the LL was -1.0% (A), 3.0% (C), -0.1% (W), and 5.0% (Y), and for ACWY vaccine-experienced participants, the LL was -5.2% (A), -4.9% (C), -1.6% (W), and -3.0% (Y).

6.1.11.3 Subpopulation Analyses

For serogroups A,C,W,Y and MenB expressing the A22 variant, the seroresponse rates (defined as the percentage of participants with ≥4-fold increase in post-vaccination hSBA titer compared to pre-Vaccination 1) in participants 18-25 years of age was lower than seroresponse rates in participants 10 to <18 years of age (hereafter abbreviated 10-<18 years of age), due to higher baseline titers prior to Vaccination 1. hSBA responses among females and males were similar. No definitive conclusions could be made about differences in hSBA responses by race, ethnicity or geographic region, since >70% of participants were White, non-Hispanic/non-Latino, or enrolled from U.S. sites.

6.1.11.4 Exploratory Analyses

Men A,C,W, and Y Components (MenABCWY Dose 2 vs. MenACWY-CRM Dose 1)

- hSBA GMTs by ACWY Vaccination History

  One month after MenABCWY Dose 2, the serogroup A GMT was 306.7 among ACWY vaccine-experienced participants and 171.0 among ACWY vaccine-naïve participants, which was approximately 1.8-fold increase in GMT when comparing GMTs by ACWY vaccination history. Similar to serogroup A, the increases in GMT to serogroups C, W and Y were approximately 2 times higher among ACWY vaccine-experienced participants than ACWY vaccine-naïve participants.

  One month after MenACWY-CRM Dose 1, the serogroup A GMT was 611.2 among ACWY vaccine-experienced participants and 148.8 among ACWY vaccine-naïve participants (approximately 4.0-fold increase in GMT). The increases in GMT to serogroups C, W and Y ranged from 8 to 14 times higher among ACWY vaccine-experienced participants than ACWY vaccine-naïve participants.

  Reviewer Comment: *Among ACWY vaccine-experienced participants, the Men A seroresponse (defined as ≥4-fold increase post-vaccination compared to pre-vaccination) was similar after MenABCWY Dose 2 and MenACWY-CRM Dose 1 (93.8% vs. 96.9%, respectively) and the primary endpoint was met (LL of 95% CI for the percent difference in seroresponse rate was greater than -10%).The MenA hSBA GMT after 2 doses of MenABCWY was lower than the MenA GMT after 1 dose of MenACWY-CRM (306.7 vs. 611.2, respectively). However, the differences in hSBA GMTs were not reflected in lower seroresponse rates. In the limited persistence data from Study B1971057 Stage 2 (see Section 6.2.11.2), similar proportions of participants who received two doses of MenABCWY maintained hSBA titers ≥LLOQ for all four serogroups compared with those who received MenACWY-CRM + MenB. Therefore, in the population studied, the observed hSBA GMT differences between groups are unlikely to result in lower rates of protection over time.*

- Percentage of Participants with hSBA Titer ≥1:8

  At 1 month after MenABCWY Dose 2, the percentage of participants 10-25 years of age with hSBA titers ≥1:8 for the 4 serogroups (A,C,W,Y) ranged from 99.1% to 99.8% (ACWY vaccine-naïve) and 99.0% to 100.0% (ACWY vaccine-experienced). At 1 month after MenACWY-CRM Dose 1, the percentage of participants with hSBA titers ≥1:8 for the 4 serogroups (A,C,W,Y) ranged from 74.4% to 99.2% (ACWY vaccine-naïve) and 97.4% to 100% (ACWY vaccine-experienced).

MenB Component (MenABCWY Dose 2 vs. MenB Dose 2)

- hSBA GMTs

  At 1 month after MenABCWY Dose 2, GMTs ranged from 17.8 (B24) to 182.0 (A56), which were numerically higher for all primary strains than corresponding GMTs after MenB Dose 2.

- Percentage of Participants with MenB hSBA Titer ≥LLOQ

  At 1 month after MenABCWY Dose 2, the percentages of participants with hSBA titer ≥LLOQ were similar to MenB post-Dose 2 for A22 and A56 (92.2% and 88.1%, respectively, for A22; 98.7% and 98.0%, respectively, for A56) and higher than MenB post-Dose 2 for B24 and B44 (83.4% and 74.0%, respectively, for B24; 94.3% and 87.4%, respectively, for B44).

6.1.12 Safety Analyses

6.1.12.1 Methods

Please see Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Table 7 presents an overview of AEs among MenABCWY recipients (Study Groups 1,3,5,7 combined) and MenB+MenABCWY-CRM recipients (Study Groups 2,4,6,8 combined).

Table 7. Overview of Adverse Events, Safety Population, Study C3511001

Event	MenABCWY[a] n/N (%)	MenB + MenACWY-CRM[b] n/N (%)
Immediate unsolicited AE within 30 minutes after any vaccination	0/1763 (0)	0/649 (0)
Solicited injection site reaction within 7 days after any vaccination	1634/1728 (94.6)	581/635 (91.5)
Solicited systemic adverse reaction within 7 days after any vaccination	1427/1748 (81.6)	527/646 (81.6)
AEs within 30 days after any vaccination	170/1763 (9.6)	57/649 (8.8)
SAEs	--	--
Within 30 days after any vaccination	3/1763 (0.2)	0/649 (0)
Up to 6 months after last vaccination	11/1763 (0.6)	4/649 (0.6)
NDCMCs up to 6 months after last vaccination	25/1763 (1.4)	2/649 (0.3)

Source: Adapted from c3511001-cber-req-ae-tables-31jan2023.pdf, Table 4-5a and Table 4-5b; c3511001-cber-req-reacto-tables-16feb2023.pdf, Table 3-1b and Table 3-5b.
a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months (Study Groups 1,3,5,7 combined).
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months (Study Groups 2,4,6,8 combined).
c. AEs %=n/N. n=Number of participants reporting at least 1 occurrence of the specified adverse event. N= number of participants in the specified study group.
d. Solicited adverse reactions: n=number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales; N=number of participants reporting at least 1 yes or no response for the specified reaction.
e. Withdrawn=number of participants who did not complete the last study visit/contact
MenACWY-CRM vaccine=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo; GlaxoSmithKline Biologicals SA); MenB=meningococcal serogroup B factor H binding protein (Trumenba; Wyeth Pharmaceuticals, Inc).

There were no immediate AEs (AEs occurring within 30 minutes after vaccination) reported during the study.

6.1.12.3 Solicited Adverse Reactions

Table 8 presents the solicited local adverse reactions and Table 9 presents the solicited systemic adverse reactions reported within 7 days following each vaccination(s). For both MenABCWY and comparator groups, the most frequently reported solicited local reaction was injection site pain.

Table 8. Percentage of Participants 10-25 Years of Age Reporting Solicited Local Adverse Reactions Within 7 Days After MenABCWY or MenB Vaccination, Safety Population, Study C3511001

Local Reactions	MenABCWY + Saline[a] Dose 1 N=1724-1725 %	MenABCWY[a] Dose 2 N=1456 %	MenB + MenACWY-CRM[b] Dose 1 N=630-631 %	MenB + MenACWY-CRM[b] Dose 2 N=529 %
Pain[c]	--	--	--	--
Mild	32.3	29.1	31.1	33.1
Moderate	49.4	48.8	47.7	40.3
Severe	7.5	6.5	6.3	5.3
Redness[d]	--	--	--	--
Mild	8.9	7.7	7.3	6.6
Moderate	14.4	12.6	10.0	7.2
Severe	2.6	3.0	2.2	0.9
Swelling[d]	--	--	--	--
Mild	10.6	10.4	8.3	6.4
Moderate	13.3	12.8	12.4	8.1
Severe	1.2	1.0	0.8	0.2

Source: Adapted from c3511001-cber-req-reacto-tables-16feb2023.pdf, pages 2-8, Table 3-1b.
Local reactions are summarized for the MenABCWY or Trumenba injection site only.
%=n/N. n=number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales. N=number of participants reporting at least 1 yes or no response for the specified reaction.
a MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months (Study Groups 1,3,5,7 combined).
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months (Study Groups 2,4,6,8 combined).
c. Mild (does not interfere with activity); Moderate (interferes with activity); Severe (prevents daily activity).
d. Mild (2.0 to 5 cm); Moderate (>5 to 10 cm); Severe (>10 cm).
MenACWY-CRM vaccine=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo; GlaxoSmithKline Biologicals SA); MenB=meningococcal serogroup B factor H binding protein (Trumenba; Wyeth Pharmaceuticals, Inc).

After vaccination Visit 1, the median onset of solicited local reactions in both study groups was 1-2 days (both groups: range 1-6) and lasted a median of 2-3 days (MenABCWY: range 1-156, MenB+MenACWY-CRM: range 1-23). After vaccination Visit 2, the median onset of solicited local reactions in both study groups was 1-2 days (both groups: range 1-7) and lasted a median of 2 days (MenABCWY: range 1-10, MenB: range 1-41).

Table 9. Percentage of Participants 10-25 Years of Age Reporting Solicited Systemic Adverse Reactions Within 7 Days After Each Vaccination, Safety Population, Study C3511001

Systemic Reactions	MenABCWY + Saline[a] Dose 1 N=1739-1740 %	MenABCWY[a] Dose 2 N=1459 %	MenB + MenACWY-CRM[b] Dose 1 N=638 %	MenB + MenACWY-CRM[b] Dose 2 N=532 %
Fever (≥38°C)	--	--	--	--
≥38.0°C	5.9	2.4	5.8	1.5
38.0° to 38.4°C	3.7	1.9	2.0	0.4
>38.4° to 38.9°C	1.6	0.3	2.8	0.9
>38.9° to 40.0°C	0.6	0.2	0.9	0.2
>40.0°C	0.0	0.0	0.0	0.0
Vomiting[c]	--	--	--	--
Mild	2.5	1.4	2.0	0.8
Moderate	0.6	0.1	0.9	0.2
Severe	0.0	0.0	0.0	0.0

Systemic Reactions	MenABCWY + Saline[a] Dose 1 N=1739-1740 %	MenABCWY[a] Dose 2 N=1459 %	MenB + MenACWY-CRM[b] Dose 1 N=638 %	MenB + MenACWY-CRM[b] Dose 2 N=532 %
Diarrhea[d]	--	--	--	--
Mild	8.7	6.9	11.9	6.0
Moderate	2.0	1.4	1.6	2.4
Severe	0.3	0.0	0.0	0.0
Headache[e]	--	--	--	--
Mild	25.7	21.3	24.5	21.1
Moderate	19.2	16.8	20.4	16.2
Severe	1.9	1.7	2.0	0.6
Fatigue[e]	--	--	--	--
Mild	23.5	22.8	25.7	22.0
Moderate	25.5	21.8	25.7	19.9
Severe	3.2	2.9	3.3	1.7
Chills[e]	--	--	--	--
Mild	12.6	9.9	10.2	8.8
Moderate	6.7	6.0	7.8	5.8
Severe	0.8	0.4	1.6	1.5
Muscle pain (other than muscle pain at the injection site)[e]	--	--	--	--
Mild	13.6	10.0	13.5	10.0
Moderate	10.5	11.9	11.9	11.5
Severe	1.6	0.8	2.0	0.8
Joint pain[e]	--	--	--	--
Mild	10.7	9.6	12.9	7.9
Moderate	8.6	8.3	8.6	6.8
Severe	1.0	0.4	1.1	0.9

Source: Adapted from c3511001-cber-req-reacto-tables-16feb2023.pdf, pages 15-29, Table 3-5b.
Abbreviations: %=n/N. n=number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales. N=number of participants reporting at least 1 yes or no response for the specified reaction.
a. MenABCWY + saline administered at 0 month followed by MenABCWY at 6 months (Study Groups 1,3,5,7 combined).
b. MenB and MenACWY-CRM administered at 0 month followed by MenB at 6 months (Study Groups 2,4,6,8 combined).
c. Mild (1 to 2 times in 24 hours); Moderate (>2 times in 24 hours); Severe (requires intravenous hydration).
d. Mild (2 to 3 loose stools in 24 hours); Moderate (4 to 5 loose stools in 24 hours); Severe (6 or more loose stools in 24 hours).
e. Mild (does not interfere with activity); Moderate (interferes with activity); Severe (prevents daily activity).

Antipyretic use was similar among MenABCWY and MenB+MenACWY-CRM recipients during the 7 days after vaccination Visit 1 (29.5% vs. 28.1%), and higher among MenABCWY than MenB recipients during the 7 days after vaccination Visit 2 (25.1% vs. 20.5%).

After vaccination Visit 1, the median onset of solicited systemic reactions in both study groups was 2-3 days (both groups: range 1-7) and lasted a median of 2 days (MenABCWY: range 1-177, MenB+MenACWY-CRM: range 1-54). After vaccination Visit 2, the median onset of solicited systemic reactions in both study groups was 1-3 days (both groups: range 1-7) and lasted a median of 1-2 days (MenABCWY: range 1-47, MenB: range 1-33).

Subgroup Analyses MenABCWY

The percentage of MenABCWY participants reporting any solicited systemic reaction after any vaccination was notably higher in females (87.2%) compared to males (75.6%), mainly due to differences in headache (F 65.6%, M 49.2%) and fatigue (F 69.8%, M 57.5%). There were no

clinically important differences in the percentage of MenABCWY participants who reported any solicited local reaction after any vaccination in subgroup analyses by sex or solicited reactions (local or systemic) by age (10 to <18 years of age, 18 to <26 years of age). No definitive conclusions could be made about differences in frequencies of solicited reactions by race or ethnicity, since most participants were White (79.0%) and non-Hispanic/non-Latino (73.5%), respectively.

6.1.12.4 Adverse Events

AEs Within 30 Days After Vaccination

Overall, 9.6% and 8.8% of MenABCWY and MenB+MenACWY-CRM recipients, respectively, reported at least 1 AE (non-serious AE, SAE, MAE, NDCMC) within 30 days after any vaccination.

Non-serious, Unsolicited AEs Within 30 Days After Vaccination

Within 30 days after vaccination, the most common non-serious unsolicited AEs, categorized by MedDRA SOC, were:

- *Infections and Infestations*: Vaccination Visit 1: 2.3% MenABCWY, 3.4% MenB+MenACWY-CRM; Vaccination Visit 2: 2.5% MenABCWY, 1.4% MenB. COVID-19 was the most frequently reported preferred term for both MenABCWY and comparator groups, and for both visits.
- *Injury, Poisoning and Procedural Complications*: Vaccination Visit 1; 0.6% MenABCWY, 0.8% MenB+MenACWY-CRM; Vaccination Visit 2; 0.6% MenABCWY, 0.3% MenB. Fall was the most frequently reported preferred term for both MenABCWY and comparator groups, and for both visits.

For both study groups, events assessed as related to study intervention by the study investigator and FDA/CBER clinical review team were generally events that were consistent with solicited reactions assessed during the 7-day post-vaccination surveillance period.

MAEs Within 30 Days After Vaccination

An MAE was defined as a non-serious AE that resulted in an evaluation at a medical facility.

The most frequently reported SOC was *Infections and infestations*. Vaccination Visit 1: 3.6% MenABCWY, 4.2% MenB+MenACWY-CRM; Vaccination Visit 2: 3.6% MenABCWY, 2.8% MenB. COVID-19 was the most frequently reported preferred term for both MenABCWY and comparator groups, and for both visits.

A total of 3 MAEs (0.1%) were assessed as related to study intervention by the study investigator and by FDA/CBER clinical review team: 2 MenABCWY (swollen tongue on Day 1 after Dose 2; hematoma at the injection site on Day after Dose 1), 1 MenB+MenACWY-CRM (headache on Day 1 after vaccination Visit 1).

NDCMCs

An NDCMC was defined as a disease or medical condition, not previously identified, that is expected to be persistent or is otherwise long-lasting in its effects. There were no autoimmune or neuroinflammatory conditions reported in the MenABCWY group. In the comparator group, there were 2 autoimmune conditions (alopecia areata, Hashimoto thyroiditis), and 1 neuroinflammatory condition (restless leg syndrome) reported. Please see Section 8.

6.1.12.5 Serious Adverse Events

SAEs Within 30 Days After Any Vaccination

A total of 3 (0.2%) MenABCWY participants reported 5 SAEs: 1 recipient reported 3 SAEs after vaccination Visit 1, 1 participant reported 2 SAEs after vaccination Visit 2; no (0%) MenB+MenACWY-CRM recipients reported an SAE after any vaccination. None of the SAEs reported by MenABCWY recipients were assessed as related to vaccination by the study investigator or FDA/CBER clinical review team. One MenABCWY participant reported spinal injury due to a motor vehicle accident. Narratives for the other 2 MenABCWY recipients are as follows:

- MenABCWY (Study Group 1; suicide attempt, anxiety, depression): female with history of ongoing friendship stressors, auditory hallucinations, and family history of bipolar disorder was hospitalized for suicide attempt 6 days after MenABCWY Dose 1. She was diagnosed with severe depression and anxiety. Her condition stabilized with medical treatment for psychosis and depression after an 8-day hospital stay, and continued outpatient treatment for anxiety and depression. The participant's symptoms were resolving at the time she withdrew from the study.
- MenABCWY (Study Group 1; disruptive mood dysregulation): male with medical history of psychiatric illnesses (disruptive mood dysregulation disorder, oppositional defiant disorder, attention deficit hyperactivity disorder [ADHD], depression, anxiety) was hospitalized for worsening disruptive mood dysregulation disorder symptoms 14 days after MenABCWY Dose 2. His condition stabilized with intensive individual and family therapy during a 4-day hospital stay and continued to receive outpatient mental health services. Symptoms of disruptive mood dysregulation disorder were ongoing at the time the participant withdrew from study.

SAEs During the Follow-up Phase

Recipients reported at least 1 SAE during the time period from 1 month after Vaccination 2 through the 6-month follow-up visit: 4 (0.3%) of MenABCWY (depression (n=2), post-tonsillectomy bleed, tibial fracture) and 4 (0.8%) MenB (appendicitis, *E coli* UTI, migraine, drug overdose). None of the SAEs were assessed as related to study intervention by the study investigator or FDA/CBER clinical review team.

There were no deaths reported during the study for any study group.

6.1.12.6 Dropouts and/or Discontinuations

During the vaccination phase (i.e., from vaccination Visit 1 through 1 month after vaccination Visit 2), 3 (0.2%) MenABCWY recipients (suicide attempt, disruptive mood dysregulation; motor vehicle accident) and in 2 (0.3%) MenB + MenACWY-CRM recipients (depression with suicidal ideation; maculopapular rash) withdrew from the study due to an AE. No withdrawals due to AEs were reported during the follow-up phase (i.e., 1 month after vaccination Visit 2 through the 6-month follow-up visit).

6.1.13 Study Summary and Conclusions

Study C3511001 was the main study to support immunogenicity (effectiveness) of MenABCWY, administered as a 2-dose series (0 and 6 months), for individuals 10-25 years of age. Noninferiority of hSBA responses to 5 serogroups was demonstrated following MenABCWY Dose 2 compared to responses following 2 doses of MenB (Trumenba) and 1 dose of ACWY-CRM (Menveo), for ACWY vaccine-naïve and for ACWY vaccine-experienced participants. Trumenba and Menveo are both licensed and available in the U.S., and administered according

to the schedule approved for use (2-dose Trumenba, 1-dose Menveo). Further immunogenicity assessments using MenB secondary strains was not performed. Characterization of the MenB responses to primary strains, including nearly identical RCDCs, provided substantial evidence that the MenB component of MenABCWY is immunologically similar to Trumenba for which breadth of coverage has been confirmed by secondary strain evaluation. In addition, noninferiority was demonstrated for MenABCWY primary endpoints and responses were comparable to Trumenba for secondary outcomes (GMTs, percentages of participants with hSBA titer ≥LLOQ, RCDCs), as observed in Study B1971057.

Among ACWY vaccine-experienced participants, the Men A seroresponse (defined as ≥4-fold increase post-vaccination compared to pre-vaccination) was similar after MenABCWY Dose 2 and MenACWY-CRM Dose 1 (93.8% vs. 96.9%, respectively) and the primary endpoint was met (LL of 95% CI for the percent difference in seroresponse rate was greater than -10%).

Of note, in an exploratory analysis, the MenA hSBA GMT after 2 doses of MenABCWY was lower than the MenA GMT after 1 dose of MenACWY-CRM (306.7 vs. 611.2, respectively). However, the differences in hSBA GMTs were not reflected in lower seroresponse rates. In the limited observational persistence data from Study B1971057 Stage 2 (see Section 6.2.11.2), similar proportions of participants who received two doses of MenABCWY maintained hSBA titers ≥LLOQ for all four serogroups compared with those who received MenACWY-CRM + MenB. Therefore, in the population studied, the observed hSBA GMT differences between groups are unlikely to result in lower rates of protection over time.

The reactogenicity following 2 doses of MenABCWY at 0 and 6 months was similar to reactogenicity following MenB+MenACWY-CRM (Month 0) and Men B (Month 6), respectively. In MenABCWY and the comparator groups, reactogenicity was primarily due to the MenB component. No new safety signals were identified that have not already been described for Trumenba or Menveo vaccinations.

6.2 Study B1971057

NCT# 03135834
Title: “A Phase 3, Randomized, Active-Controlled, Observer-Blinded Study to Assess the Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 When Administered as a 2-Dose Regimen and a First-In-Human Study to Describe the Immunogenicity, Safety, and Tolerability of a Bivalent rLP2086-Containing Pentavalent Vaccine (MenABCWY) in Healthy Subjects ≥10 to <26 Years of Age”

In the context of evaluation of MenABCWY, Study B1971057 was a first-in-human study to describe the safety and immunogenicity of MenABCWY administered according to a 0- and 6-month schedule. The primary objective of Study B1971057 was to confirm the effectiveness of Trumenba administered on a 2-dose schedule; the design and results are not intended to be the primary safety and effectiveness data supporting licensure of MenABCWY.

An unblinded pilot cohort consisting of 10 participants 18 to <26 years of age were enrolled and assigned to receive MenABCWY; safety data from Day 0 through Day 7 were reviewed by an independent review committee prior to randomized enrollment of participants 10 to <26 years of age.

Stage 2 was conducted as an open-label sampling of participants from each Stage 1 study group to examine immunopersistence and the safety and immunogenicity of a dose of

MenABCWY administered approximately 4 years after completing a 2-dose series of MenABCWY in Stage 1. Participants enrolled from each of the four study groups had blood drawn at 12, 24, 36 and 48 months following Dose 2 in Stage 1, and at 48 months received the same vaccine(s) they had received in Stage 1 (MenABCWY or MenB + MenACWY-CRM). Study objectives and endpoints were descriptive.

6.2.1 Objectives

Stage 1

The primary study objectives and endpoints of Study B1971057 were to assess the safety and immunogenicity of a 2-dose regimen of Trumenba and are not included here. The secondary and exploratory MenABCWY immunogenicity and safety objectives and endpoints are listed.

Secondary Immunogenicity Objectives (MenABCWY Stage 1)

1. To describe the immune response induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced participants.
2. To describe the immune response induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of meningococcal serogroup A, C, W, and Y conjugate vaccine (MenACWY-CRM), as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced participants.
3. To describe the immune response induced by MenABCWY compared to the immune response induced by Trumenba as measured by hSBA performed with 4 primary MenB test strains, 2 expressing an LP2086 subfamily A protein and 2 expressing an LP2086 subfamily B protein, measured 1 month after the second vaccination in the ACWY-naïve and ACWY-experienced participants combined.

Secondary Safety Objectives (MenABCWY Stage 1)

To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after Vaccinations 1 and 2 in the ACWY-naïve and ACWY-experienced participants separately.

Stage 2

Secondary Immunogenicity Objectives (MenABCWY Stage 2)

1. To describe the immune response induced by MenABCWY compared to the immune response induced by MenACWY-CRM and Trumenba as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, at blood sampling time points prior to the additional vaccination at Study Month 54.
2. To describe the immune response induced by MenABCWY as measured by hSBA performed with ACWY and 4 primary MenB test strains, 1 month after an additional vaccination at Study Month 54.

Secondary Safety Objectives (MenABCWY Stage 2)

To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after the vaccination at Study Month 54.

6.2.2 Design Overview

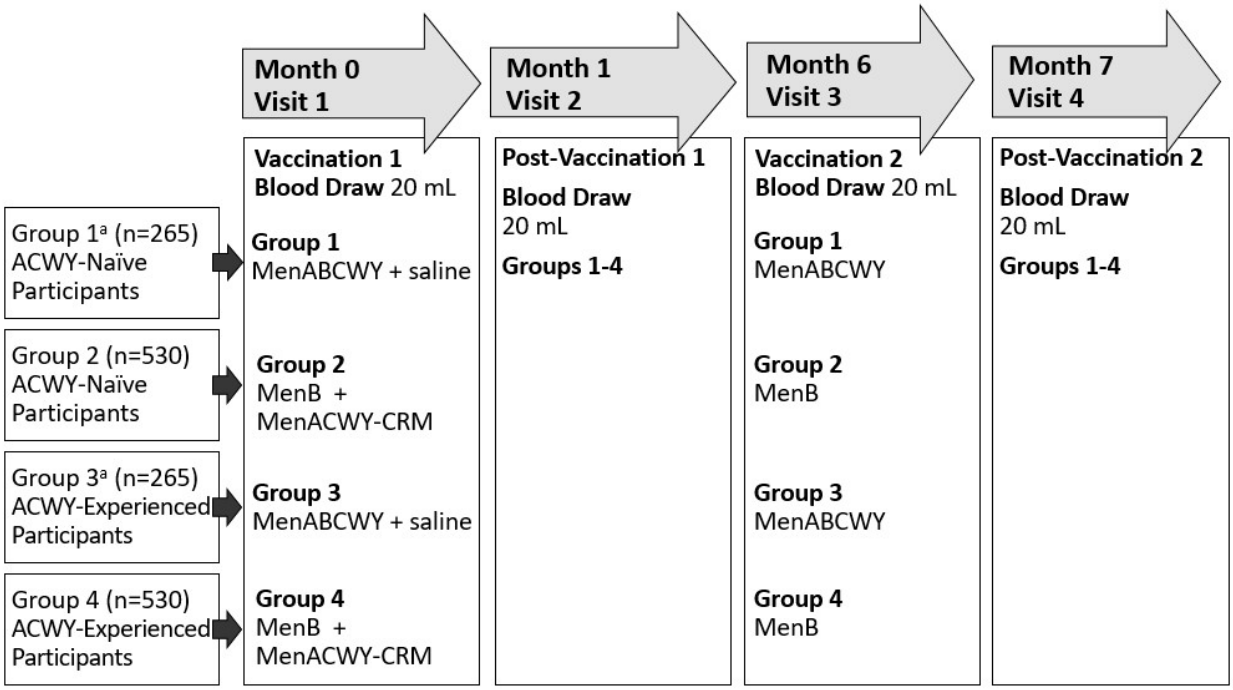
Stage 1

Study B1971057 was a randomized, active-controlled, observer-blinded multicenter trial in which participants were randomly assigned in a 2:1 ratio to receive MenB (Trumenba) + MenACWY-CRM (Menveo) at Month 0 and MenB (Trumenba) at Month 6, or MenABCWY + saline at Month 0, then MenABCWY at Month 6.

Randomization was stratified by prior vaccination history; ACWY-naïve participants and ACWY-experienced participants (having received 1 prior dose of a vaccine containing 1 or more ACWY groups ≥4 years prior to the date of randomization). Randomization was also stratified by geographic region.

Enrollment targets were adjusted to achieve appropriate representation by age (participants 10 to <18 years of age and participants 18 to <26 years of age), age within ACWY strata, and ACWY strata within a geographic region.

Figure 1. Study Design, Study B1971057 Stage 1



Source: FDA-generated figure.
a. Pilot cohort participants were assigned to either Group 1 or 3, but they received only MenABCWY at Vaccination 1. Pilot cohort participants did not receive saline at Vaccination 1.
MenACWY-CRM vaccine=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo; GlaxoSmithKline Biologicals SA); MenB=meningococcal serogroup B factor H binding protein (Trumenba; Wyeth Pharmaceuticals, Inc).

Duration: For participants who were not enrolled in Stage 2, participation was for 12 months ending with a safety phone call at Visit 5 (Study Month 12).

Blinding: The study personnel dispensing, preparing, and administering the vaccine were unblinded. The investigator, investigator staff, participants, and participants' parent(s)/legal guardian(s) were blinded to vaccine assignments during Stage 1. An unblinded clinician

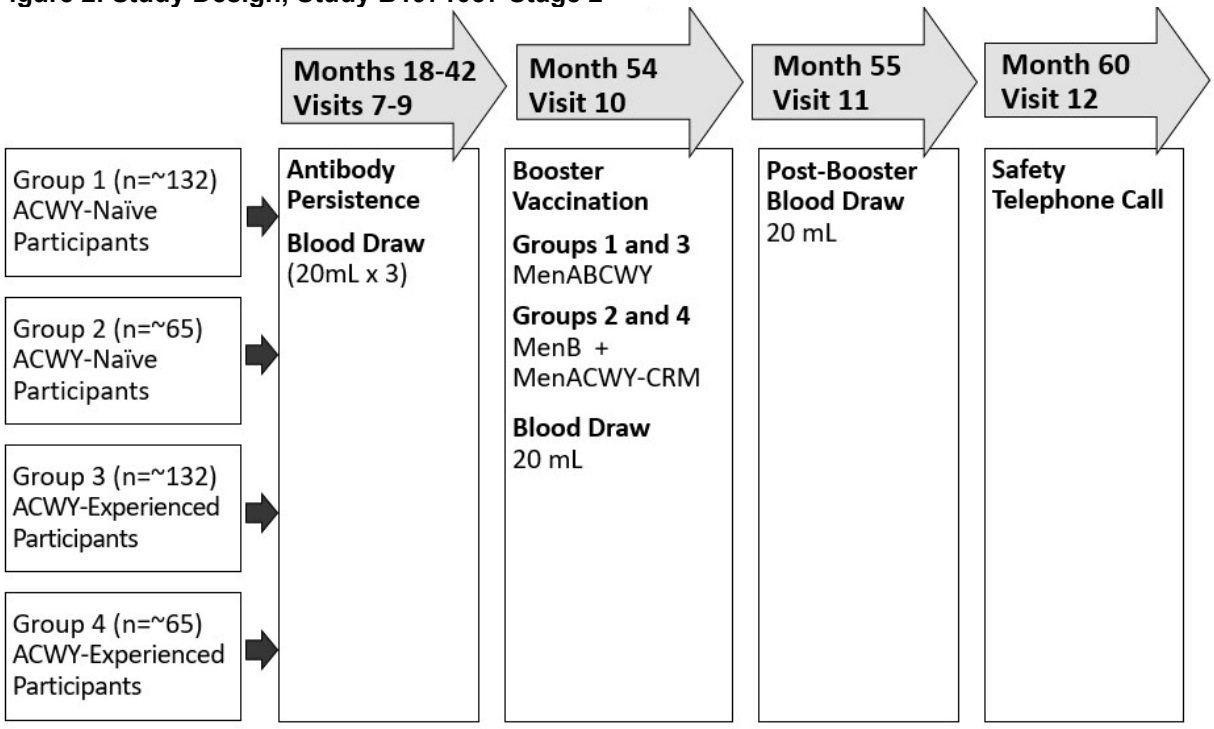
reviewed unblinded protocol deviations. All other study team members and laboratory personnel performing serology assays were blinded to vaccine assignment throughout Stage 1.

Stage 2

Stage 2 was an open-label extension of Study B1971057 to assess immunopersistence following vaccination in Stage 1, and to examine the immunogenicity and safety of a dose of MenABCWY or MenB+MenACWY-CRM administered approximately 4 years following completion of the two-dose regimen. Subsets of participants from each study group were recruited for Stage 2. Serology assessments occurred every 12 months for 4 years following the 2-dose series. A dose of the same vaccinations received in Stage 1 were administered at approximately Study Month 54. Immune responses to the additional dose were determined at 1 month and safety was monitored for 6 months following the Month 54 dose.

> ***Reviewer Comment:*** *Study B1971057 Stage 2 is presented in this application to support use of MenABCWY as a booster dose. As communicated in FDA/CBER's written responses to the pre-BLA meeting package, the descriptive data from this study are not adequate to support the use of MenABCWY as a booster dose. The open-label enrollment shows differential recruitment from each study group and differential proportions of participants who completed the study in each group. Due to the inclusion of participants from European sites in the ACWY-experienced group whose prior exposure was to a monovalent MenC vaccine, the sample sizes for Groups 3 and 4 are small for serogroups A, W, and Y.*
>
> *The immunogenicity data from Stage 2 were also reviewed to examine the potential impact of the observed lower of GMT's following Dose 2 compared to those following Dose 1 for serogroups A and C (see Section 6.2.11.1).*

Figure 2. Study Design, Study B1971057 Stage 2



Source: FDA-generated figure.
Notes: MenACWY-CRM vaccine=meningococcal (serogroups A, C, W and Y) oligosaccharide diphtheria CRM_{197} conjugate vaccine (Menveo; GlaxoSmithKline Biologicals SA); MenB=meningococcal serogroup B factor H binding protein (Trumenba; Wyeth Pharmaceuticals, Inc).

Blinding: Stage 2 of Study B1971057 was an open-label study.
Duration of Stage 2 was approximately 5 years.

6.2.3 Population

Participants were healthy individuals 11-25 years of age enrolled in the U.S. and Europe who were either MenACWY-naïve or MenACWY-experienced. MenACWY-experienced had received no more than 1 prior dose of a meningococcal vaccine containing 1 or more ACWY serogroups, at least 4 years prior to randomization.

In both Stage 1 and Stage 2, participants who had never received a vaccine containing any component of an A, C, W, Y vaccine were considered ACWY-naïve. Participants who received either an ACWY conjugate vaccine or a monovalent serogroup C conjugate vaccine were randomized as ACWY-experienced but, for the purposes of A, C, W, and Y immunogenicity analyses, were considered ACWY-naïve or ACWY-experienced based on the serogroup(s) present in the prior ACWY-containing vaccine.

Participants with any of the following were not included in the study:

- Previous vaccination with any meningococcal serogroup B vaccine or any purely polysaccharide (nonconjugate) meningococcal vaccine.
- Previous anaphylactic reaction to any vaccine or vaccine-related component.
- Receipt of any non-licensed allergen immunotherapy, or receipt of any licensed allergen immunotherapy if not on a stable maintenance dose.
- A known or suspected defect of the immune system that would have prevented an immune response to the vaccine, such as participants with congenital or acquired defects in B-cell function, those receiving chronic systemic (oral, intravenous, or intramuscular) corticosteroid therapy, or those receiving immunosuppressive therapy.
- Terminal complement deficiency.
- History of microbiologically proven disease caused by *N. meningitidis* or *Neisseria gonorrhea.*
- Significant neurological disorder or history of seizure (excluding simple febrile seizure).
- Receipt of any blood products, including immunoglobulin, within 6 months before the first study vaccination.
- Current chronic use of systemic antibiotics.
- Pregnant participants; breastfeeding participants; male and female participants of childbearing potential who were unwilling or unable to use a highly effective method of contraception.

Participants with the following could be vaccinated when the conditions were resolved:

- Febrile illness (T ≥38.0°C) or other acute illness within 48 hours before investigational product administration.
- Received a non-live vaccine within 14 days, or any live vaccine within 28 days, before investigational product administration.
- Less than 5 days into a course of systemic antibiotic therapy.
- Received systemic (oral, intravenous, or intramuscular) corticosteroid therapy in the prior 28 days.

Blood collection was delayed for participants who received systemic antibiotic therapy within 5 days prior to a scheduled blood draw.

Stage 1

Planned enrollment for Stage 1 was for approximately 1320 participants from U.S. and 270 participants from ex-U.S. sites.

Stage 2

Amendment 2 to the study protocol opened admission in Stage 2 to ACWY-experienced participants, moved the Stage 2 safety endpoints from secondary to primary, and designated some immunogenicity endpoints as exploratory.

Investigators were informed if a subject could be screened for Stage 2 based on a randomly generated list of eligible subjects and a randomly generated backup list to allow for replacement of subjects who decline participation in Stage 2 or who were deemed ineligible after screening at Visit 7.

Approximately 132 participants from each MenABCWY group (Groups 1 and 3) and approximately 65 from each MenB + MenACWY-CRM group (Groups 2 and 4) were planned for Stage 2. For MenB immunogenicity, the planned number of participants for Groups 1 and 3 combined was approximately 264 and the planned number of participants for Groups 2 and 4 combined was approximately 130.

> ***Reviewer Comment:*** *Recruitment and retention in Stage 2 was lower than planned. Of 942 participants contacted at the end of Stage 1, 353 proceeded to Stage 2. Of these, 68.6% completed the 48-month persistence blood draw and received an additional dose at ~ Month 54. A total of 239 participants completed the Stage 2 immunization phase. Some participants from European sites had received a MenC conjugate vaccine prior to study enrollment (MenACWY-experienced) and these participants were randomized to Groups 3 and 4. However, they were analyzed in Groups 3 and 4 only for serogroup C, and in Groups 1 and 2 for serogroups A, W, and Y. In the Stage 2 immune response analyses, the available immunogenicity data for Group 4 were from <20 participants for serogroups A, W, and Y hSBA.*

6.2.4 Study Treatments or Agents Mandated by the Protocol

Vaccines Administered

The following study products were administered to participants: Trumenba, MenABCWY (consisting of MenACWY-TT and MenB), MenACWY-CRM, and placebo.

Table 10. Investigational Product Lot Numbers, Study B1971057 Stage 1

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number (Pfizer)[a]
MenB (Trumenba)[b]	Wyeth Pharmaceuticals, Inc	M97261	16-004784
MenACWY-TT (Nimenrix)[b,c]	GlaxoSmithKline	R98867	16-005696
MenACWY-CRM (Menveo)	GlaxoSmithKline	M16102 M16099	17-000891 17-001434
Placebo (0.85% sodium chloride)	Pfizer	L07386	15-000990

Source: Protocol B1971057 Investigational Product Lot Numbers Table – Stage 1
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
b. Trumenba (MenB) solution was used to reconstitute Nimenrix lyophilized powder in order to formulate MenABCWY.
c. Nimenrix is not a US-licensed product.

Table 11. Investigational Product Lot Numbers, Study B1971057 Stage 2

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number (Pfizer)[a]
MenB (Trumenba)[b]	Wyeth Pharmaceuticals, Inc	CL3237 DA4348	20-000165 20-003058
MenACWY-TT (Nimenrix)[b,c]	Pfizer	20-005461	21-DP-00559
MenACWY-CRM (Menveo)	GlaxoSmithKline	AMVA513A AMVA550A AMVA636A	21-AE-00118 21-AE-00176 21-AE-00300

Source: Protocol B1971057 Investigational Product Lot Numbers Table – Stage 2, Final, Version 1.0, 17May2022.
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
b. Trumenba (MenB) solution was used to reconstitute Nimenrix lyophilized powder in order to formulate MenABCWY.
c. Nimenrix is not a US-licensed product.

6.2.5 Directions for Use

Please see Section 6.1.5.

6.2.6 Sites and Centers

Stage 1

A total of 68 sites screened 1676 participants and randomized 1610 participants. Participants were enrolled (#sites/#participants screened/# randomized) in Czech Republic (4/137/132), Finland (10/142/128), Poland (3/30/30), and U.S. (51/1367/1320).

Stage 2

Participants who participated in Stage 2 were enrolled at a total of 39 sites (3 sites in Czech Republic, 7 sites in Finland, 2 sites in Poland, and 27 sites in the U.S.).

6.2.7 Surveillance/Monitoring

Stage 1

In Stage 1, safety monitoring was as described for Study C3511001 (see Section 6.1.7).

Stage 2

During the persistence period, AEs or research related injuries within 48 hours after the blood draw of the previous visit were collected.

Solicited reactogenicity, immediate AEs, AEs, SAEs, MAEs, NDCMCs and days of work or school missed because of an AE were collected for 30 days following the vaccine dose administered at Study Month 54.

6.2.8 Endpoints and Criteria for Study Success

The MenABCWY endpoints of Study B1971057 Stage 1 and Stage 2 were descriptive.

Stage 1

To describe the immune response induced by 1 dose of MenABCWY compared to the immune response induced by 1 dose of MenACWY-CRM, as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced participants.

Endpoints:

- Proportions of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 2 (1 month following the first vaccination).
- Proportions of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 2 (1 month following the first vaccination).
- GMTs for each of the ACWY test strains at Visit 2 (1 month following the first vaccination).

To describe the immune response induced by 2 doses of MenABCWY compared to the immune response induced by 1 dose of meningococcal serogroup A, C, W, and Y conjugate vaccine (MenACWY-CRM), as measured by hSBA performed with ACWY test strains, in ACWY-naïve and ACWY-experienced participants.

Endpoints:

- Proportions of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 4 (1 month following the second vaccination) in Groups 1 and 3 (MenABCWY [ACWY-naïve and ACWY-experienced, respectively]) and at Visit 2 (1 month following the first vaccination) in Groups 2 and 4 (Trumenba + MenACWY [ACWY-naïve and ACWY-experienced, respectively]).
- Proportions of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 4 in Groups 1 and 3, and Visit 2 in Groups 2 and 4.
- hSBA GMTs for each of the ACWY test strains at Visit 4 in Groups 1 and 3, and Visit 2 in Groups 2 and 4.

To describe the immune response induced by MenABCWY compared to the immune response induced by Trumenba as measured by hSBA performed with 4 primary MenB test strains, measured 1 month after the second vaccination in the ACWY-naïve and ACWY-experienced participants combined.

Endpoints:

- Percentages of participants who achieve the 5 MenB endpoints 1 month after the second vaccination, which are defined for hSBA performed with each of the 4 primary test strains: PMB80 (A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44):
    - Composite endpoint defined as the proportion of participants achieving an hSBA titer ≥LLOQ (1:16 for A22 and 1:8 for A56, B24, and B44) for all 4 primary test strains combined, 1 month after the second vaccination.

  - Percentage of participants achieving at least a 4-fold increase in hSBA titer from baseline to 1 month after the second vaccination for each of the 4 primary test strains (4 endpoints).
    - For participants with a baseline hSBA titer below the LOD (i.e., an hSBA titer of <1:4), a 4-fold response is defined as an hSBA titer of ≥1:16 or the LLOQ (whichever titer is higher).
    - For participants with a baseline hSBA titer of ≥LOD (i.e., hSBA titer of ≥1:4) and <LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the LLOQ.
    - For participants with a baseline hSBA titer of ≥LLOQ, a 4-fold response is defined as an hSBA titer of ≥4 times the baseline titer.
- Percentages of participants with hSBA titers ≥LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Month 7.
- hSBA GMTs for each of the 4 primary MenB test strains at Month 7.

Stage 2

To describe the immune response induced by MenABCWY compared to the immune response induced by MenB + MenACWY-CRM as measured by hSBA performed with ACWY test strains and 4 primary MenB test strains, at blood sampling time points prior to the vaccination.

Endpoints:

- Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visits 1, 3, 7, 8, 9, and 10 (1 month, 6 months, 18 months, 30 months, and 42 months following MenACWY vaccination, in the ACWY-naïve and ACWY-experienced participants separately.
- Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visits 1, 3, 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced participants separately.
- hSBA GMTs for each of the ACWY test strains at Visits 1, 3, 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced participants separately.
- Percentage of participants with hSBA titers ≥LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visits 1, 3, 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced participants combined.
- hSBA GMTs for each of the 4 primary MenB test strains at Visits 1, 3, 7, 8, 9, and 10, in the ACWY-naïve and ACWY-experienced participants combined.

To describe the immune response induced by MenABCWY as measured by hSBA performed with ACWY and 4 primary MenB test strains 1 month after a vaccination administered 4 years after 2 doses administered 6 months apart.

Endpoints:

- Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:8 (or LLOQ, whichever is higher) at Visit 11.
- Percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 at Visit 11.
- hSBA GMTs for each of the ACWY test strains at Visit 11.
- Percentage of participants who achieve the 5 MenB endpoints at Visit 11.
- Percentage of participants with hSBA titers ≥LLOQ, ≥1:4, ≥1:8, ≥1:16, ≥1:32, ≥1:64, and ≥1:128 for each of the 4 primary MenB test strains at Visit 11.

- hSBA GMTs for each of the 4 primary MenB test strains at Visit 11.

Safety Endpoints, Stage 1 and Stage 2

To describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs, after each vaccination in Groups 1 and 3.

- Percentage of participants reporting local reactions (pain, redness, and swelling) and by severity within 7 days after each vaccination visit.
- Percentage of participants reporting systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain [other than muscle pain at any injection site], and joint pain) and by severity within 7 days after each vaccination visit.
- Percentage of participants reporting the use of antipyretic medication within 7 days after each vaccination visit.
- Percentage of participants with a) at least 1 SAE, b) at least 1 MAE, and c) at least 1 NDCMC during the following time periods:
  - 30 days after each vaccination.
  - 30 days after any vaccination.
  - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
  - During the Stage 1 follow-up phase (from 1 month after the second study vaccination [Visit 4] through 6 months after the second study vaccination [Visit 5]).
  - Throughout Stage 1 (from the first study vaccination [Visit 1] through 6 months after the second study vaccination [Visit 5]).
  - During the vaccination phase (from the vaccination at Visit 10 through 1 month after the vaccination [Visit 11]).
  - During the follow-up phase (from 1 month after the vaccination [Visit 11] through 6 months after the vaccination [Visit 12]).
  - From the vaccination (Visit 10) through 6 months after the vaccination (Visit 12).
- Percentage of participants with at least 1 AE occurring during the following time periods:
  - 30 days after each vaccination.
  - 30 days after any vaccination.
  - During the Stage 1 vaccination phase (from the first study vaccination [Visit 1] through 1 month after the second study vaccination [Visit 4]).
  - During the Stage 2 vaccination phase (from the vaccination [Visit 10] through 1 month after the vaccination [Visit 11]).
- Percentage of participants reporting at least 1 immediate AE after each vaccination.
- Participants missing school or work days because of AEs.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Stage 1

The study design, sample size, and statistical analysis plan addressed the hypothesis testing component of this study to verify the clinical benefit of a 2-dose schedule of Trumenba. An additional 530 participants were planned for enrollment in the MenABCWY arms based on the Applicant's stated rationale to allow a probability of 93.0% to observe at least 1 AE with a true incidence of 0.5%.

Stage 2

Open-label enrollment for descriptive analysis of antibody persistence and safety and immunogenicity of a dose administered approximately 48 months after the 2-dose series.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Stage 1

Overall, a total of 1610 participants were randomized to Study Groups 1 through 4; 1432 (88.8%) received Vaccination 2, 1390 (86.3%) completed the vaccination phase, and 936 (58.1%) completed all Stage 1 study visits. Ten participants withdrew before Vaccination 1, 168 (11%) did not receive Vaccination 2, and 496 of those who were vaccinated did not complete all Stage 1 study visits (41.9%).

The number of participants within the post-Vaccination 1 evaluable population was 1600 and within the post-Vaccination 2 evaluable population was 1432. Of those, the number who received MenABCWY was 543 and 486, ACWY-naïve and -experienced, respectively. The number of MenABCWY participants in the follow-up safety population was 463. The Stage 1 MenABCWY evaluable immunogenicity population was 438. The study was unblinded once all participants had completed Visit 5 at 6 months following Dose 2.

Stage 2

Enrollment and disposition of participants in Stage 2 is shown in Table 12.

Table 12. Population Disposition, Study B1971057 Stage 2

Population	Total	Group 1 ACWY-naïve[a] MenABCWY	Group 2 ACWY-naïve[a] MenB + MenACWY-CRM	Group 3 ACWY-experienced[a] MenABCWY	Group 4 ACWY-experienced[a] MenB + MenACWY-CRM
Randomized in Stage 1[a,b]	1610	272	537	272	529
Received Dose 2 (Stage 1)	1432 (88.9%)	242 (89.0%)	469 (87.3%)	244 (89.7%)	477 (90.2%)
Eligible for Stage 2[c]	1379 (85.7%)	232 (85.3%)	458 (85.3%)	231 (84.9%)	458 (86.6%)
Unblinded for Stage 2 enrollment	--	--	--	--	--
Contacted	942 (58.5%)	199 (73.2%)	405 (75.4%)	178 (65.4%)	160 (30.2%)
Agreed / entered Stage 2[d]	353 (21.9%)	114 (41.9%)	65 (12.1%)	101 (37.1%)	73 (13.8%)
Antibody persistence	--	--	--	--	--
12 mo	252 (71.7%)	114 (100%)	63 (96.9%	53 (52.5%)	23 (31.5%)
24 mo	332 (94.1%)	104 (91.2%)	61 (93.8)	96 (95%)	71 (97.3%)
36 mo	317 (89.9%)	97 (85 .1%)	55 (84.6%)	97 (96.0%)	68 (93.2%)
48 mo + Stage 2 dose	242 (68.6%)	67 (58.7%)	40 (61.5%)	77 (67.2%)	58 (79.5%)
Withdrawn prior to Stage 2 vaccination	109 (30.9%)	46 (40.4%)	24 (36.9%)	24 (23.8%)	15 (20.5%)
Received Stage 2 vaccination[e]	242	67	40	77	58
Completed Stage 2 vaccination phase	239 (98.8%)	67 (100%)	38 (95%)	77 (100%)	57 (98.3%)

Source: Adapted from Table 7 in Study B1 971057 interim Stage 2 study report pg. 41-43
Note: The vaccine group (as randomized), uses the actual ACWY history, which is based on prior receipt of a meningococcal serogroup A, C, W, and Y conjugate vaccine, or a monovalent meningococcal C conjugate vaccine.
Two participants were missing disposition records and did not receive the booster vaccination in Stage 2.
a. "Actual ACWY history" is based on prior receipt of a meningococcal serogroup A, C, W, and Y vaccine.
b. N=number of participants in the specified group, or the total sample. This value is the denominator for the percentage calculations.
c. Participants that completed the safety follow-up evaluation 12-18 months after Stage 1 vaccination visit 2 were selected to participate in Stage 2. A back-up list was generated to replace any primary participants that declined Stage 2 participation or could not be contacted.
d. Entered Stage 2 values are based on participant completion of Stage 2 informed consent. The values were used as the denominator for the percentage calculations for the Stage 2 section.
e. Includes all participants who received the Stage 2 vaccination(s) (MenABCWY or MenB+MenACWY-CRM) at Month 54. The values were used as the denominator for the percentage calculations for Stage 2. The vaccination phase was the time period from the time of Stage 2 vaccination through the 1 month post-vaccination follow-up visit.

Of those enrolled in Stage 2, 242 (68.6%) completed the persistence blood draw and received the Stage 2 vaccination(s), with 239 (98.8%) completing the immunization phase. The percentage of Stage 2 participants who withdrew prior to the additional dose also differed by group, with 40.4%, 36.9%, 23.8% and 20.5% withdrawing prior to 48 months for Groups 1-4, respectively.

Reviewer Comment:
The proportion of participants contacted to participate in Stage 2 was similar for Group 1 and Group 2 (73.2% and 75.4%, respectively) and differed for Group 3 (65.4%) and Group 4 (30.2%). The proportion who agreed to proceed to Stage 2 varied by group as determined by target enrollment numbers. Randomization between Groups 1 and 2, and Groups 3 and 4 was ~1:2 for Stage 1 while the target recruitment for Stage 2 was reversed at ~2:1 for MenABCWY: Trumenba + MenACWY. The design of Stage 2 as an open-label unblinded recruitment for target sample sizes that were disproportional to the original randomization and curtailment of enrollment to match the enrollment plan results in different recruitment and enrollment proportions by vaccination group. Stage 2 may not provide a representative subset of the study.

6.2.10.1.1 Demographics

Stage 1

Demographic characteristics were generally similar across groups. Overall, 85.6% of participants were White, 10.3% Black or African American, 1.0% Asian, and 3% other racial groups; 42.6% of participants were male and 57.4% were female. Most participants were from the U.S. (81.9%).

Stage 2

Demographic characteristics were similar across groups. Overall, 92.1% of participants were White, 5.8% Black or African American, 0.4% Asian and <2% other racial groups. There were 5.4% Hispanic/Latino participants. The median age at the time of the Stage 2 vaccination was 20 years, and 45.8% of participants were male.

6.2.10.1.2 Participant Disposition

Stage 1

The most common reasons for exclusion from the evaluable immunogenicity population were that the participant had received prior vaccines that met exclusion criteria, diagnoses of autoimmune conditions of received corticosteroid therapy within 28 days of immunization, or the blood sample was collected outside the protocol-defined vaccination window.

Stage 2

The most common reasons for withdrawal prior to the Stage 2 dose was lost to follow-up and no longer meeting eligibility criteria.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Secondary Endpoints

Stage 1

MenACWY Component

One month after Vaccination 1, the percent of ACWY-naïve participants achieving titers ≥1:8 for the serogroups A, C, W and Y ranged from 92.4% to 99.6% for MenABCWY + saline recipients. Among ACWY-experienced participants, proportions achieving titers ≥1:8 at 1 month after Vaccination 1 were 99.5% to 100%.

One month after Vaccination 2, 100% of ACWY-naïve MenABCWY recipients achieved titers ≥1:8 for serogroups A, C, W, and Y. Among ACWY-experienced participants, 99.5% to 99.6% for all 4 serogroups had titers ≥1:8 following the second dose of MenABCWY.

Among ACWY-naïve participants, hSBA GMTs at 1 month after Vaccination 1 were similar or trended higher for MenABCWY + saline recipients compared to MenB + MenACWY-CRM recipients (215.8 and 203.2, respectively, for MenA; 111.5 and 81.4, respectively, for MenC; 98.4 and 71.2, respectively, for MenW; and 141.9 and 96.6, respectively, for MenY). Among ACWY-experienced participants, GMTs at 1 month after Vaccination 1 were similar or lower for MenABCWY + saline compared to MenB + MenACWY-CRM recipients (568.6 and 916.1, respectively, for MenA; 814.9 and 827.0, respectively, for MenC; 1214.9 and 1176.7, respectively, for MenW; and 1174.0 and 1000.2, respectively, for MenY).

One month after a second dose of MenABCWY, GMTs in ACWY-naïve participants were 151.3, for MenA (lower than the GMT for this group following Dose 1); 229.1 for MenC; 274.1 for MenW; and 301.5 for MenY which were all lower than the GMTs observed for MenACWY-experienced participants at 1 month following either MenABCWY + saline or MenB + MenACWY-CRM.

Among ACWY-experienced participants, GMTs 1 month following the first dose of MenABCWY were higher than those observed following the second dose for all four serogroups (568.6 and 337.3, respectively, for MenA; 814.9 and 498.7, respectively, for MenC; 1214.9 and 570.9, respectively, for MenW; and 1174.0 and 558.6, respectively, for MenY). ACWY-experienced participants had higher hSBA GMTs for MenA, MenC, MenW, and MenY compared to ACWY-naïve participants regardless of which dose was evaluated.

MenB Component

Seroresponse rates following two doses of MenABCWY were similar to those observed following two doses of MenB + MenACWY-CRM. Recipients achieving a 4-fold rise from baseline in hSBA titer at 1 month after Vaccination 2 were 75.8% and 73.8%, respectively, for PMB80 (A22); 94.7% and 95.0%, respectively, for PMB2001 (A56); 76.1% and 67.4%, respectively, for PMB2948 (B24); and 91.7% and 86.4%, respectively, for PMB2707 (B44). The proportion of MenABCWY and MenB + MenACWY-CRM recipients achieving a composite response at 1 month after Vaccination 2 was 79.9% and 74.3%, respectively.

hSBA GMTs among MenABCWY recipients for the 4 primary MenB test strains were similar to those observed for MenB + MenACWY-CRM recipients. RCDCs show the distribution of titers against all four MenB strains are overlapping or slightly shifted to the right for the MenABCWY group compared to the MenB + MenACWY group.

Stage 2

MenACWY Component, Persistence

During the 48 months following the 2-dose series, proportions of participants with hSBA titers ≥1:8 declined gradually for serogroups A and C and remained relatively high for serogroups W and Y. At 48 months, the percent of ACWY-naïve participants with hSBA titers ≥1:8 ranged from 62.0% to 100.0% for MenABCWY (2 doses) and 38.1% to 95.2% MenB + MenACWY-CRM (1 dose MenACWY-CRM). Among ACWY-experienced participants, the percentage with hSBA titers ≥1:8 at 48 months ranged from 98.7% to 100.0% in MenABCWY recipients compared with 89.7% to 100.0% in MenB+ MenACWY-CRM recipients.

GMTs trended higher for MenABCWY than MenB + MenACWY-CRM through and at 48 months among both ACWY-naïve and -experienced participants.

MenB Component, Persistence

The percentage of MenABCWY recipients with MenB hSBA titers ≥LLOQ declined during the first 12 months following the second dose and remained generally stable through 48 months across the 4 primary MenB test strains, ranging from 18.2% to 36.6%. Similarly, in the MenB + MenACWY-CRM group the proportion of recipients with MenB hSBA titers ≥LLOQ through 48 months following the second dose, ranged from 16.2% to 31.9% across the 4 primary MenB test strains.

MenACWY Component, Stage 2 Dose

The percentage of participants with hSBA Titers ≥1:8 and hSBA GMTs for MenA, MenC, MenW, and MenY following a dose of MenABCWY or MenB + MenACWY-CRM in Stage 2 are shown in Table 13.

Table 13. Participants with hSBA Titers ≥1:8 and GMTs for MenA, MenC, MenW, and MenY – MenABCWY (Groups 1 and 3) and Trumenba + MenACWY-CRM (Groups 2 and 4), Evaluable Immunogenicity Population, Study B1971057 Stage 2

Serogroup Time Point Endpoint	Group 1 ACWY-Naïve MenABCWY	Group 2 ACWY-Naïve MenB + MenACWY-CRM	Group 3 ACWY-Experienced MenABCWY	Group 4 ACWY-Experienced MenB + MenACWY-CRM
MenA	--	--	--	--
1 month after vaccination 2, N[a]	**60**	**37**	**33**	**17**
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	35 (94.6) (81.8,99.3)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**143.7** (114.3, 180.6)	56.1 (33.9, 93)	**315.8** (223.7, 445.9)	236 (136.5, 408)
Before Stage 2 dose, N[a]	60	36	32	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	47 (**78.3**) (65.8,87.9)	22 (**61.1**) (43.5,76.9)	32 (**100**) (89.1,100)	17 (**100**) (80.5,100)
GMT (95% CI[d])	**29.9** (21.2, 42)	**21** (11.6, 37.8)	**125.3** (89.3, 175.8)	**122.9** (62, 243.5)
1 month after Stage 2 dose, N[a]	60	37	33	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**530.1** (427.6, 657)	**1043.4** (728.5, 1494.3)	**451.4** (333.1, 611.6)	**1024** (687.5, 1525.3)
MenC	--	--	--	--
1 month after vaccination 2, N[a]	60	36	70	51
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	33 (91.7) (77.5,98.2)	70 (100) (94.9,100)	51 (100) (93,100)
GMT (95% CI[d])	**191.8** (143.5, 256.3)	50.8 (30.3, 85.2)	**689.1** (531.2, 894)	318.2 (217.8, 464.8)
Before Stage 2 dose, N[a]	60	37	68	51
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	36 (**60**) (46.5,72.4)	14 (**37.8**) (22.5,55.2)	67 (**98.5**) (92.1,100)	45 (**88.2**) (76.1,95.6)
GMT (95% CI[d])	**17.1** (11.5, 25.6)	**12.1** (7, 21)	**130.6** (96.8, 176.3)	**91.1** (57.9, 143.4)
1 month after Stage 2 dose, N[a]	60	37	70	51
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	37 (100) (90.5,100)	70 (100) (94.9,100)	51 (100) (93,100)
GMT (95% CI[d])	**383.6** (286, 514.4)	**641.1** (421.8, 974.3)	**760.8** (593.8, 974.8)	**1272.7** (885.6, 1829)
MenW	--	--	--	--
1 month after vaccination 2, N[a]	60	37	33	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**230.7** (185, 287.7)	84.8 (59.2, 121.4)	**779.3** (496.3, 1223.8)	313.9 (141.8, 694.8)
Before Stage 2 dose, N[a]	59	37	32	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	53 (**89.8**) (79.2,96.2)	26 (**70.3**) (53,84.1)	32 (**100**) (89.1,100)	15 (**88.2**) (63.6,98.5)
GMT (95% CI[d])	**36.4** (26.4, 50.3)	**16** (10.2, 25.1)	**159** (94.8, 266.7)	**92.4** (35.6, 239.4)
1 month after Stage 2 dose, N[a]	60	37	33	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**822.2** (627.1, 1077.9)	**1189.6** (796.8, 1776)	**631.7** (492.2, 810.7)	**943.8** (479.5, 1857.7)

Serogroup Time Point Endpoint	**Group 1 ACWY-Naïve MenABCWY**	**Group 2 ACWY-Naïve MenB + MenACWY-CRM**	**Group 3 ACWY-Experienced MenABCWY**	**Group 4 ACWY-Experienced MenB + MenACWY-CRM**
MenY	--	--	--	--
1 month after vaccination 2, N[a]	60	35	33	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	35 (100) (90,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**297.5** (244, 362.6)	84.4 (54.2, 131.7)	**522.9** (348.7, 784.1)	208.8 (103.8, 420)
Before Stage 2 dose, N[a]	60	37	32	16
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (**100**) (94,100)	35 (**94.6**) (81.8,99.3)	32 (**100**) (89.1,100)	16 (**100**) (79.4,100)
GMT (95% CI[d])	**45.3** (34.8, 58.9)	**27.5** (18.8, 40.4)	**162.4** (105.3, 250.6)	**103.1** (55, 193.2)
1 month after Stage 2 dose, N[a]	60	37	33	17
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI[d])	**1012.2** (793.6, 1291.1)	**1575.5** (1062.3, 2336.7)	**522.9** (404.4, 676)	**943.8** (538.1, 1655.3)

Source: adapted from Tables 14 and 15 in the interim CSR for Protocol B1971057 Stage 2 submitted to STN 125770/0 and Statistical Review
Abbreviations: GMT=geometric mean titer; hSBA=serum bactericidal assay using human complement; LLOQ=lower limit of quantitation; MenA=*Neisseria meningitidis* serogroup A; Stage 2 Evaluable Immunogenicity Population= subjects who were elig ble for the study, received a booster dose as intended, had blood drawn for assay testing within the required time frame at Month 55 (Visit 11), and had a valid and determinate MenB or MenA/C/W/Y assay result, as well as no major protocol violations.
MenC=*N. meningitidis* serogroup C; MenW=*N. meningitidis* serogroup W; MenY=*N. meningitidis* Y
Notes: Groups 1 and 3 received MenABCWY+saline at the first study vaccination, MenABCWY at the second study vaccination, and MenABCWY at the Stage 2 vaccination; Groups 2 and 4 received MenB+MenACWY-CRM at the first study vaccination, Trumenba at the second study vaccination, and MenB+MenACWY-CRM at the Stage 2 vaccination.
LLOQ=1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ were set to 0.5×LLOQ for analysis of GMTs.
[a] N=number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point. These values are used as the denominators for the percentage calculations.
[b] n=Number of participants with hSBA titer ≥LLOQ at the given sampling time point for the given strain.
[c] Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
[d] CIs are back transformed from confidence interval based on the student t distribution for the mean logarithm of the concentrations.

Among MenABCWY recipients, the percentage achieving hSBA titers ≥1:8 for serogroups A, C, W, and Y at 1 month after the Stage 2 dose were 100% in both ACWY-naïve and ACWY-experienced.

Among MenABCWY recipients, hSBA GMTs for serogroups A, C, W, and Y were markedly higher compared to the pre-immunization hSBA GMTs and generally higher than 1 month post-Vaccination 2 GMTs of the 2-dose series except for serogroups W and Y in the ACWY-experienced group, for which GMTs were the same for serogroup Y and slightly lower for serogroup W compared to post-Vaccination 2. GMTs ranged from 383.6 to 1012.2 at 1 month after completing the MenABCWY dose (MenACWY Dose 3) in ACWY-naïve participants and from 451.4 to 760.8 at 1 month after completing the MenABCWY dose (MenACWY Dose 4) in ACWY-experienced participants. For MenB + MenACWY-CRM recipients, 1 month after the Stage 2 dose, GMTs ranged from 641.1 to 1575.5 in ACWY-naïve participants (MenACWY Dose 2) and 943.8 to 1272.7 in ACWY-experienced participants (MenACWY Dose 3).

When comparing across vaccination groups, GMTs for MenABCWY recipients (MenACWY Dose 3) were generally lower than observed for MenB + MenACWY-CRM recipients 1 month after completing the Stage 2 dose in ACWY-naïve participants and ACWY-experienced participants.

MenB Component, Stage 2 Dose

At 1 month after a dose administered 48 months after Dose 2, 95%-100% of MenABCWY recipients achieved hSBA titers ≥LLOQ for the 4 primary MenB test strains. A rise over pre-immunization hSBA GMTs was demonstrated for the 4 primary MenB test strains among MenABCWY recipients. hSBA GMTs 1 month after the Stage 2 vaccination were higher than post-Dose 2 GMTs.

Table 14. Participants with hSBA Titers ≥LLOQ and GMTs for Primary MenB Strains – MenABCWY (Groups 1 and 3 Combined) and Trumenba + MenACWY-CRM (Groups 2 and 4 Combined) – Evaluable Immunogenicity Population, Study B1971057 Stage 2

Primary MenB hSBA Test Strain Time Point Endpoint	**Groups 1 + 3 MenABCWY**	**Groups 2 + 4 MenB + MenACWY-CRM**
PMB80 (A22)	--	--
1 month after vaccination 2, N[a]	129	88
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	122 (94.6) (89.1,97.8)	82 (93.2) (85.7,97.5)
GMT (95% CI[d])	54.8 (47.1, 63.7)	43.5 (36.2, 52.3)
Before Stage 2 vaccination, N[a]	121	83
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	34 (**28.1**) (20.3,37)	26 (31.3) (21.6,42.4)
GMT (95% CI[d])	12 (10.5, 13.8)	11.6 (10.1, 13.4)
1 month after Stage 2 vaccination, N[a]	122	81
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	116 (**95.1**) (89.6,98.2)	76 (93.8) (86.2,98)
GMT (95% CI[d])	85 (70.3, 102.9)	74.7 (60.3, 92.5)
PMB2001 (A56)	--	--
1 month after vaccination 2, N[a]	128	87
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	126 (98.4) (94.5,99.8)	84 (96.6) (90.3,99.3)
GMT (95% CI[d])	161.6 (134.7, 193.8)	123 (97.5, 155.2)
Before Stage 2 vaccination, N[a]	127	86
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	46 (**36.2**) (27.9,45.2)	25 (29.1) (19.8,39.9)
GMT (95% CI[d])	8.9 (7.2, 11)	6.6 (5.4, 8)

Primary MenB hSBA Test Strain **Time Point** **Endpoint**	**Groups 1 + 3** **MenABCWY**	**Groups 2 + 4** **MenB + MenACWY-CRM**
1 month after Stage 2 vaccination, N[a]	124	86
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	124 (**100**) (97.1,100)	85 (98.8) (93.7,100)
GMT (95% CI[d])	321.9 (272.3, 380.7)	223.2 (172, 289.7)
PMB2948 (B24)	--	--
1 month after vaccination 2, N[a]	126	87
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	109 (86.5) (79.3,91.9)	68 (78.2) (68,86.3)
GMT (95% CI[d])	28.8 (23.6, 35.2)	16.9 (13.5, 21.2)
Before Stage 2 vaccination, N[a]	126	86
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	44 (**34.9**) (26.6,43.9)	21 (24.4) (15.8,34.9)
GMT (95% CI[d])	7 (6, 8.1)	5.9 (5, 7.1)
1 month after Stage 2 vaccination, N[a]	123	84
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	117 (**95.1**) (89.7,98.2)	80 (95.2) (88.3,98.7)
GMT (95% CI[d])	60.8 (50.9, 72.7)	40.7 (33.1, 49.9)
PMB2707 (B44)	--	--
1 month after vaccination 2, N[a]	130	86
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	128 (98.5) (94.6,99.8)	82 (95.3) (88.5,98.7)
GMT (95% CI[d])	46.7 (39, 56)	34.1 (27.5, 42.4)
Before Stage 2 vaccination, N[a]	129	87
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	23 (**17.8**) (11.7,25.5)	14 (16.1) (9.1,25.5)
GMT (95% CI[d])	5.1 (4.6, 5.6)	5 (4.4, 5.7)
1 month after Stage 2 vaccination, N[a]	128	86
hSBA ≥ LLOQ, n[b] (%) (95% CI[c])	127 (**99.2**) (95.7,100)	85 (98.8) (93.7,100)
GMT (95% CI[d])	98.2 (81.3, 118.5)	66.1 (53.3, 81.9)

Source: Tables 16 and 17 in the interim CSR for Protocol B1971057 Stage 2 submitted to STN 125770/0 and Statistical Review.
Abbreviations: GMT=geometric mean titer; hSBA=serum bactericidal assay using human complement; LLOQ=lower limit of quantitation; MenB=*Neisseria meningitidis* serogroup B
Groups 1 and 3 received MenABCWY+saline at the first study vaccination, MenABCWY at the second study vaccination, and MenABCWY at the Stage 2 vaccination; Groups 2 and 4 received MenB+MenACWY-CRM at the first study vaccination, Trumenba at the second study vaccination, and MenB+MenACWY-CRM at the Stage 2 vaccination.
LLOQ=1:16 for A22 and 1:8 for A56, B24, and B44. Titers below the LLOQ were set to 0.5×LLOQ for analysis of GMTs.
[a] N=number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point. These values are used as the denominators for the percentage calculations.
[b] n=Number of participants with hSBA titer ≥LLOQ at the given sampling time point for the given strain.
[c] Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.
[d] CIs are back transformed from confidence interval based on the Student's t-distr bution for the mean logarithm of the concentrations.

Reviewer Comment:
The underlying recruitment from Stage 1, and disproportionate loss to follow-up between study groups makes interpretation of the hSBA responses following a third MenABCWY vaccination difficult. Fewer participants were enrolled than were planned, and fewer than 70% completed the 48-month persistence, and Stage 2 through the 1 month post-vaccination follow-up visit. Additionally, among MenACWY vaccine-experienced participants (Groups 3 and 4), over half of the participants had received a monovalent MenC vaccine and were evaluated as experienced only for serogroup C. These factors resulted in sample sizes of fewer than 100 for all study groups for A, C, W and Y hSBA, and fewer than 20 for Group 4. The small sample sizes limit the interpretation of immunogenicity data from Study B1971057 Stage 2. For the Stage 2 MenB responses, all participants were MenB vaccine-naïve upon initial enrollment, so Groups 1 and 3, and Groups 2 and 4 are combined.

6.2.11.2 Subpopulation Analyses

Subgroup analyses of MenB responses following Dose 1 or Dose 2 of MenABCWY in Stage 1 showed no meaningful differences based on sex or Geographic location (US vs. non-US sites). No meaningful interpretation of immunogenicity data by race was possible as the immunogenicity study population was >85% White.

6.2.11.3 Exploratory and Post Hoc Analyses

In post hoc analyses comparing MenABCWY to MenB + MenACWY-CRM for both MenB and MenACWY endpoints, noninferiority criteria as described in Study C3511001 would have been met.

6.2.12 Safety Analyses

6.2.12.1 Methods

Methods for collection of safety data were the same in Phase 1 as for Study C3511001 (see Section 6.1.12.1)

6.2.12.2 Overview of Adverse Events

Reactogenicity and AEs reported were similar to those in Study C3511001. See Section 6.1.12.2.

6.2.12.3 Solicited Adverse Reactions

Solicited local reactions and systemic events within 7 days after vaccination were reported in similar proportions with similar levels of severity to those reported in Study C3511001. See Section 6.1.12.3.

Systemic Events

Four MenABCWY + saline recipients reported systemic events with a duration of >15 days:

- Participant (b) (6) (ACWY-experienced) reported headache on Day 1 after Vaccination 1, which lasted 21 days.
- Participant (b) (6) (ACWY-naïve) reported fatigue and headache on Day 1 after Vaccination 1; both lasted 19 days.
- Participant (b) (6) (ACWY-naïve) reported fatigue on Day 5 after Vaccination 1, which lasted 33 days.
- Participant (b) (6) (ACWY-naïve) reported chills, fatigue, and headache on Day 1 after Vaccination 1, lasting 20 days. Muscle pain was also reported on Day 4 after Vaccination 1, lasting 17 days.

The systemic events for all 4 participants were self-limiting and did not lead to withdrawal from the study. The long durations were queried with the participating sites and confirmed as correct. None of these participants who received Vaccination 2 reported systemic events with a duration >15 days after the second vaccination.

6.2.12.4 Adverse Events

- AE of clinical interest: Severe headache and somnolence nine hours after receiving the first dose, presented to the ER and required IV fluids. Assessed as MenABCWY related by the Applicant and FDA/CBER clinical review team.

- New onset medical conditions: Two MenABCWY participants, one diagnosed with Scoliosis, and one with a varicocele, assessed as unrelated by the Applicant and FDA/CBER clinical review team.
- New onset chronic medical condition: Polycystic ovarian syndrome (140 days after Dose 1). Assessed as unrelated by the Applicant and FDA/CBER clinical review team.

6.2.12.5 Serious Adverse Events

In the MenABCWY study groups:

- Death: The participant died in a road traffic accident on May 1, 2018, 109 days after receiving the second dose of MenABCWY in Stage 1. Assessed by the Applicant and FDA/CBER clinical review team to be unrelated to vaccination.
- SAEs assessed by the Applicant and FDA/CBER clinical review team to be unrelated to vaccination: Cholelithiasis requiring cholecystectomy (83 days following Dose 2); lateral neck cyst (164 days following Dose 2); spontaneous abortion (123 days following Dose 2); suicidal ideation (177 days following Dose 1); Migraine (33 days following Dose 1); finger extensor tendon laceration;
- SAE of clinical interest: Diagnosed with a moderate conversion disorder 17 days after receiving MenABCWY Dose 1. Syncopal episode 12 days after Dose 1, presented to an emergency room with histrionic behavior and concussion-like symptoms. The participant returned to the ER because of unresolved symptoms including difficulty speaking and right hemibody numbness and weakness. Months later the participant presented to the ER for suicidal ideation with symptoms of escalating depression and anxiety. Assessed as unrelated by the Applicant and FDA/CBER clinical review team.
- SAEs during Stage 2, MenABCWY recipients: new onset epilepsy (Study Day 458); spontaneous abortion (Study Day 1296). Both SAEs assessed as unrelated by the Applicant and FDA/CBER clinical review team.

6.2.12.6 Dropouts and/or Discontinuations

In the MenABCWY study groups:

- AEs leading to discontinuation from the study: Three MenABCWY recipients withdrew from Stage 1 due to urticaria (95 days after Dose 1), psychiatric issues (SAE 11 days after Dose 1), and overdose/suicide attempt (SAE, 6 days after Dose 1). Assessed as unrelated by the Applicant and FDA/CBER clinical review team.
- Safety-related withdrawal: Syncope with blood draw, not vaccinated. Assessed as related by the Applicant and FDA/CBER clinical review team.

6.2.13 Study Summary and Conclusions

Study B1971057 was the first-in-human study of MenABCWY. The immune response data and safety data are generally consistent with the results of Study C3511001. Stage 2 examined antibody persistence for four years following two doses of MenABCWY, and the safety and immunogenicity following a dose administered approximately 4 years after the 2-dose series. The open-label recruitment, discordant loss to follow-up, and small sample sizes limit the interpretability of these results. Descriptive data from Study B1971057 Stage 2 data alone do not support use of MenABCWY as a booster dose administered to those who previously completed a 2-dose series with MenABCWY or Trumenba, or who previously received MenACWY.

6.3 Study C3511004

NCT# 04440176
Title: "A Phase 2b, Randomized, Observer-Blinded Trial to Describe the Safety, Tolerability, and Immunogenicity of MenABCWY Administered on 2 Different Dosing Schedules in Healthy Participants ≥11 to <15 Years of Age"

6.3.1 Objectives

Primary Immunogenicity

1. To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 12-month schedule by estimating the percent of participants with hSBA titers ≥LLOQ for 4 primary MenB strains.
2. To describe the immune response for MenB induced by 2 doses of MenABCWY administered on a 0- and 36-month schedule by estimating the percent of participants with hSBA titers ≥LLOQ for 4 primary MenB strains.

Primary Safety

To describe the safety profile of MenABCWY when administered on a 0- and 12-month schedule and on a 0- and 36-month schedule.

Secondary Immunogenicity

1. To describe the immune response for MenA, C, W, and Y induced by 1 and 2 doses of MenABCWY administered on a 0- and 12-month schedule by estimating the percentage of participants with hSBA titers ≥LLOQ for each serogroup strain.
2. To describe the immune response for MenA, C, W, and Y induced by 1 and 2 doses of MenABCWY administered on a 0- and 36-month schedule by estimating the percentage of participants with hSBA titers ≥LLOQ for each serogroup strain.
3. To describe the persistence of the MenB response following 2 doses of MenABCWY administered on a 0- and 12-month schedule by estimating the percentage of participants with hSBA titers ≥LLOQ for 4 primary MenB strains at 12 and 24 months after Dose 2.
4. To describe the persistence of the MenA, C, W, and Y response following 2 doses of MenABCWY administered on a 0- and 12-month schedule by estimating the percent of participants with hSBA titers ≥LLOQ for each serogroup strain at 12 and 24 months after Dose 2.

Exploratory Immunogenicity

To describe the immune response to MenABCWY administered on a 0- and 12-month schedule by estimating the seroresponse and hSBA GMTs.

6.3.2 Design Overview

Study C3511004 is a descriptive study to evaluate extended dosing intervals of a 2-dose series of MenABCWY. In this study, 309 participants 11 to <15 years of age were randomized to receive two doses of MenABCWY administered either 12 or 36 months apart. Participants received MenABCWY Dose 1, and at 12 months, Group 1 received MenABCWY Dose 2 and Group 2 received a saline placebo. Blood was collected from participants in both groups before and 1 month following immunization Dose 1 and at Study Month 13.

The interim study report submitted to this application includes safety and immunogenicity data and analyses through Study Month 13 (referred to as Analysis 1).

6.3.3 Population

- Male or female, 10-<15 years of age at the time of randomization
- ACWY-naïve participants: Participants who have never received a prior dose of a meningococcal vaccine containing ACWY serogroups

Exclusion Criteria were as described for Study C3511001 (see Section 6.1.3).

6.3.4 Study Treatments or Agents Mandated by the Protocol

Table 15. Investigational Product Lot Numbers – Study C3511004 Analysis 1

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
Trumenba (MenB)[b]	Pfizer	DA4348	19-005010
Nimenrix (MenACWY-TT)[b]	Pfizer	DK9946	20-000490
Placebo (0.9% Sodium Chloride)	Pfizer	CW7633	19-004627

Source: Table 4 Study C3511004 Interim Clinical Study Report
a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
b. Trumenba (MenB) solution was used to reconstitute Nimenrix lyophilized powder in order to formulate MenABCWY.

6.3.5 Directions for Use

See Section 6.1.5.

6.3.6 Sites and Centers

This study was conducted at 21 sites in the U.S.

6.3.7 Surveillance/Monitoring

For Analysis 1, nonserious AEs were collected through 1 month after Vaccination 1 and 1 month after Vaccination 2. SAEs, MAEs, NDCMCs were collected through 6 months after Vaccination 1 and 1 month after Vaccination 2.

In Study C3511004, solicited local and systemic reactions were not collected. Participants were observed for 30 minutes following MenABCWY vaccination. AEs were assessed during immunization and blood draw study visits and during a safety telephone call at 6 months following Dose 1. A Study Visit/Telephone Contact AE Checklist was used as a guide, completed at each scheduled study visit/telephone contact after Visit 1, and included in the study source documentation. Hospitalizations, visits to other medical facilities, medication use, and days of school or work missed were collected and recorded only if associated with an AE.
In Study C3511004, solicited local and systemic reactions were not collected. Participants were observed for 30 minutes following MenABCWY vaccination. AEs were assessed during immunization and blood draw study visits and during a safety telephone call at 6 months following Dose 1. A Study Visit/Telephone Contact AE Checklist was used as a guide, completed at each scheduled study visit/telephone contact after Visit 1, and included in the study source documentation. Hospitalizations, visits to other medical facilities, medication use, and days of school or work missed were collected and recorded only if associated with an AE.

6.3.8 Endpoints and Criteria for Study Success

This is a descriptive study with no criteria for study success.

The main analyses to address primary and secondary immunogenicity objectives for Analysis 1 are summarized:

- The MenB immune response induced by 2 doses of MenABCWY was assessed by estimating the percentages of participants achieving an hSBA titer ≥LLOQ for each of the 4 primary MenB test strains at baseline and 1 month after the second dose of MenABCWY for Group 1 (0- and 12-month schedule).
- The immune response induced by 1 dose of MenABCWY was assessed by the percentages of participants achieving hSBA titers ≥LLOQ for each of the ACWY test strains at baseline and 1 month after the first dose of MenABCWY for Groups 1 and 2. The immune response induced by 2 doses of MenABCWY on a 0-, 12-month schedule (Group 1) was assessed by the percentages of participants achieving hSBA titers ≥LLOQ for each of the ACWY test strains at baseline and 1 month after the second dose of MenABCWY.

For the primary safety analyses for Analysis 1, the following safety endpoints are descriptively summarized:

- The percentage of participants reporting at least 1 AE, at least 1 SAE, at least 1 MAE, and at least 1 NDCMC
- The percentage of participants reporting at least 1 immediate AE
- The percentage of participants with missed days of school or work due to AEs

6.3.9 Statistical Considerations & Statistical Analysis Plan

All planned analyses were descriptive. The study sample size of ~300 participants was not based on hypothesis testing criteria.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Table 16. Study C3511004 Population

Population N=309	**Group 1 MenABCWY 0, 12 Months**	**Group 2 MenABCWY 0 Months, Saline 12 Months, MenABCWY 36 Months**
Randomized	155	154
Received Dose at 0 months	149 (96.1%)	151 (98.1%)
Completed Dose 1 vaccine phase	146 (94.2%)	150 (97.4%)
Received Dose at 12 months	121 (78.1%)	130 (84.4%)
Completed Dose 2 vaccine phase	120 (77.4%)	130 (84.4%)

Source: FDA-generated table

6.3.10.1.1 Demographics

Most participants were White (85.4%), 18.4% Hispanic/Latino. The median age at the time of study vaccination was 11.0 years, and 55.4% of participants were male.

6.3.10.1.2 Participant Disposition

Of 309 participants, 9 (2.9%) were withdrawn prior to Vaccination 1, and 50 (16.2%) were withdrawn in the interval from Vaccination 1 through 1 month after Vaccination 2.

- Two (0.6%) randomized participants, both on the 0- and 36-month vaccination schedule, were withdrawn due to AEs, which were reported after the Vaccination 1 follow-up phase and before Vaccination 2. No participant on the 0- and 12-month vaccination schedule was withdrawn due to AEs through 1 month after the second dose of MenABCWY.

- The most common reasons for withdrawal from Vaccination 1 through 1 month after Vaccination 2 were: lost to follow-up; protocol deviation; withdrawal by parent/guardian; and withdrawal by subject. Two participants refused vaccination at visit 4, two participants stated they withdrew because they did not feel well after Vaccination 1. One participant withdrew due to syncope following blood draw at visit 1. Twice as many participants were lost to follow-up in the 0, 12 month immunization group (n=12, 7.7%) compared to the 0, 36 month immunization group (n=6, 3.9%).

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

All immunogenicity analyses for this study were descriptive.

The primary immunogenicity analysis describes the MenB component immunogenicity by the percentage of participants with hSBA titer ≥LLOQ at baseline and at 1 month following Dose (MenABCWY) in study Group 1 only. For each of the MenB primary strains 0.9% to 7.0% of participants had hSBA ≥LLOQ before Dose 1, and 96.6% to 100% had hSBA titers ≥LLOQ at 1 month following Dose 2.

Following two doses of MenABCWY administered 12 months apart, the MenB responses as measured by the endpoints that were primary in Study C3511001 were:

The proportion of participants with a 4-fold rise in hSBA for the MenB primary strains:
- PMB80 (A22) - 106/111 (95.5%)
- PMB2001 (A56) - 115/115 (100%)
- PMB2948 (B24) - 105/113 (92.9%)
- PMB2702 (B44) - 110/116 (96.4%)

The proportion meeting the hSBA composite response (≥LLOQ for all 4 MenB strains):
- Composite - 106/110 (96.4%)

Reviewer Comment:
The MenB seroresponse rate following 2 doses of MenABCWY administered 12 months apart is higher in this study than in Study C3511001, especially for the B24 strain expressing the most common U.S. fHbp type. hSBA GMTs and RCDC were also presented; however, without a comparator group that received MenABCWY at 0 and 6 months, the effect of extended intervals on the MenB responses cannot be assessed. Furthermore, in Study C3511004, the responses to the MenB component were not evaluated after the first dose, which precludes the ability to use immune responses to Dose 1 to assess whether or not study populations and immunogenicity data are similar across studies.

6.3.11.2 Analyses of Secondary Endpoints

The percentage of participants achieving hSBA titers ≥1:8 (LLOQ) for MenA, C, W, and Y before and after MenABCWY Dose 1 and after Dose 2 were 10.7%, 98.6% and 99.1% for MenA; 10.1%, 79.3% and 99.1% for MenC; 15.9%, 98.6%, and 100% for MenW and 36%, 99.3% and 100% for MenY.

6.3.11.3 Subpopulation Analyses

Subgroup analyses of MenB responses following Dose 1 or Dose 2 of MenABCWY showed no meaningful differences based on sex. No meaningful interpretation of immunogenicity data by race was possible as the immunogenicity study population was >85% White.

6.3.11.4 Exploratory and Post Hoc Analyses

Serogroup A, C, W and Y hSBA 4-fold rise and GMTs are shown in Table 17 and Table 18 below.

Table 17. Participants Achieving ≥4-Fold Rise in hSBA Titer at 1 Month After MenABCWY Dose 1 in Groups 1 and 2, and 1 Month After MenABCWY Dose 2 in Group 1 for MenA, MenC, MenW, MenY – Post-Vaccination 1 – Evaluable Population Study C3511004

Serogroup Time Point	Group 1 MenABCWY (0- and 12-Month Schedule)	Group 2 MenABCWY (0- and 36-Month Schedule)
MenA, N[a]; n[b] (%); (95%CI[c])	--	--
1 Month after Dose 1	140; 138 (98.6); (94.9, 99.8)	141; 141 (100); (97.4, 100.0)
1 Month after Dose 2	116; 115 (99.1); (95.3, 100.0)	--
MenC, N[a]; n[b] (%); (95%CI[c])	--	--
1 Month after Dose 1	139; 98 (70.5); (62.2, 77.9)	143; 98 (68.5); (60.2, 76.0)
1 Month after Dose 2	115; 114 (99.1); (95.3, 100.0)	--
MenW, N[a]; n[b] (%); (95%CI[c])	--	--
1 Month after Dose 1	138; 125 (90.6); (84.4, 94.9)	143; 126 (88.1); (81.6, 92.9)
1 Month after Dose 2	113; 112 (99.1); (95.2, 100.0)	--
MenY, N[a]; n[b] (%); (95%CI[c])	--	--
1 Month after Dose 1	136; 118 (86.8); (79.9, 92.0)	141; 122 (86.5); (79.8, 91.7)
1 Month after Dose 2	111; 109 (98.2); (93.6, 99.8)	--

Source: Interim Full Clinical Study Report Protocol C3511004 Tables 20 and 21 pg. 65-66
Abbreviations: hSBA=serum bactericidal assay using human complement; LLOQ=lower limit of quantitation; LOD=limit of detection; MenA, MenC, MenW, and MenY=Neisseria meningitidis serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ=1:8 for all MenA, MenC, MenW, and MenY serogroups.
Note: The 4-fold rise is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer <1:4), a response is defined as an hSBA titer ≥1:16. (2) For participants with a baseline hSBA titer ≥LOD and <LLOQ, a response is defined as an hSBA titer ≥4 times the LLOQ. (3) For participants with a baseline hSBA titer ≥LLOQ, a response is defined as an hSBA titer ≥4 times the baseline titer.
a. N=number of participants with valid and determinate hSBA titers for the specified serogroup at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.
b. n=Number of participants who achieved an hSBA titer ≥4 from baseline for the specified serogroup.
c. Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Table 18. hSBA GMTs for MenA, MenC, MenW, MenY at Baseline, 1 Month After MenABCWY Dose 1 in Groups 1 and 2, and 1 Month After MenABCWY Dose 2 (Group 1) or Saline Placebo (Group 2) – Evaluable Population Study C3511004

Serogroup Time Point	Group 1 MenABCWY (0- and 12-month Schedule)	Group 2 MenABCWY (0- and 36-month Schedule)
MenA, n[a]; GMT[b]; (95% CI[c])	--	--
Before Dose 1	140; 4.7; (4.3, 5.1)	141; 4.5; (4.1, 4.9)
1 Month after Dose 1	140; 133.2; (111.1, 159.6)	144; 147.9; (124.8, 175.2)
13 Months 1 Month after Dose 2 or saline placebo	116; 236.9; (203.7, 275.5)	126; 19.6; (15.7, 24.4)
MenC, n[a]; GMT[b]; (95% CI[c])	--	--
Before Dose 1	139; 4.4; (4.2, 4.7)	144; 4.5; (4.2, 4.9)
1 Month after Vaccination 1	140; 51.5; (36.5, 72.6)	143; 41.8; (30.8, 56.7)
13 Months 1 Month after Dose 2 or saline placebo	116; 140; (114.0, 172.0)	127; 17.9; (14.0, 23.0)

Serogroup **Time Point**	**Group 1 MenABCWY** **(0- and 12-month Schedule)**	**Group 2 MenABCWY** **(0- and 36-month Schedule)**
MenW, n[a]; GMT[b]; (95% CI[c])	--	--
Before Dose 1	138; 4.9; (4.5, 5.3)	143; 4.8; (4.4, 5.2)
1 Month after Vaccination 1	140; 48; (39.2, 58.8)	144; 47.7; (39.4, 57.7)
13 Months 1 Month after Dose 2 or saline placebo	115; 385.7; (327.5, 454.2)	128; 42; (34.8, 50.5)
MenY, n[a]; GMT[b]; (95% CI[c])	--	--
Before Dose 1	136; 6.7; (5.8, 7.6)	142; 6.5; (5.7, 7.6)
1 Month after Vaccination 1	140; 80; (65.8, 97.2)	143; 80.8; (65.5, 99.6)
13 Months 1 Month after Dose 2 or saline placebo	114; 377.8; (315.7, 452.1)	126; 47.3; (38.6, 57.9)

Source: Interim Full Clinical Study Report Protocol C3511004 Tables 18 and 19 pgs. 63-64
Abbreviations: GMT=geometric mean titer; hSBA=serum bactericidal assay using human complement; MenA, MenC, MenW, and MenY=Neisseria meningitidis serogroup A, serogroup C, serogroup W, and serogroup Y.
Note: LLOQ=1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ were set to 0.5 × LLOQ for analysis.
a. n=Number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point.
b. GMTs were calculated using all participants with valid and determinate hSBA titers at the given time point.
c. CIs obtained by exponentiating the limits of CIs for the mean logarithm of the hSBA titers (based on the Student t distribution).

***Reviewer Comment**:*
While the MenA GMT following a second dose administered at 12 months was approximately 2-fold higher than the GMT following the first dose, the GMT following the first dose in this study was approximately half of the GMT observed in Study B1971057. The GMT results from this study are consistent with the previously described studies in which serogroup A hSBA GMTs following a second dose of MenABCWY increase ~2- fold or less compared with hSBA GMTs following the first dose.

6.3.12 Safety Analyses

6.3.12.1 Methods

See Section 6.3.7.

6.3.12.2 Overview of Adverse Events

An e-diary for solicited reactogenicity was not used in this study. AEs, SAEs, MAEs, and NDCMCs reported were similar to those described in Study C3511001. One neuroinflammatory event/MAE (restless leg syndrome) was assessed as possibly related to MenABCWY vaccination. FDA/CBER clinical review team assessed the event to be unrelated to MenABCWY vaccination. Please see Section 8.4.4 for additional information.

6.3.12.3 Solicited Adverse Reactions

Not applicable

6.3.12.4 Adverse Events

In Group 1, at least 1 AE was reported by 45 (30.8%) participants during the Dose 1 vaccination phase and by 19 (15.7%) participants during the Dose 2 vaccination phase, respectively. Related AEs were reported by 28 (19.2%) and 9 (7.4%) participants during the Dose 1 and Dose 2 phases, respectively, and were primarily reactogenicity-type events (injection site pain, pyrexia, fatigue, headache, vomiting, and chills). Severe AEs were reported by 3 (2.1%) participants during the Dose 1 vaccination phase and were attributable to reactogenicity-type events. No severe AEs were reported during the Vaccination 2 vaccination phase.

In Group 1, within 6 months after Dose 1, MAEs and NDCMCs were reported by 36 (24.7%) and 2 (1.4%) participants, respectively. Within the Dose 2 vaccination phase, no NDCMCs were reported and MAEs were reported by 7 (5.8%) participants.

MAEs assessed as related to MenABCWY included participants with local or systemic reactogenicity consistent with events observed in Study C3511001 (see Section 6.1.12.4) including injection site pain, headache, dizziness, myalgias, vomiting, fever, and fatigue. In addition, one participant experienced an MAE of sinus tachycardia (Day 1).

Severe MAE assessed as unrelated to MenABCWY by the Applicant and FDA/CBER clinical review team included depression (Day 72); GE reflux (Day 2); dysmenorrhea (Day 160); orthopedic injuries (Day 51).

None of the NDCMCs were assessed as related to MenABCWY by the Applicant or FDA/CBER clinical review team. One possibly related MAE of restless leg syndrome occurred with an onset of 140 days after Vaccination 1 in a participant in Group 2 and was also identified as a neuroinflammatory event.

6.3.12.5 Serious Adverse Events

One SAE (orbital cellulitis on Day 71) was reported during the period from Visit 1 to one month following Dose 2, and assessed as unrelated to MenABCWY by the study investigator and FDA/CBER clinical review team.

There were no deaths reported in the study.

6.3.12.6 Dropouts and/or Discontinuations

Four participants in Group 2 withdrew from the study due to AEs, two following Dose 1 (MenABCWY) and two following Dose 2 (saline placebo). The AEs were an intentional overdose and three participants with suicidal ideation that were assessed by the study investigator and FDA/CBER clinical review team to be unrelated to vaccine.

6.3.13 Study Summary and Conclusions

Study C3511004 was an open-label descriptive study without either a comparator group that received currently licensed MenACWY and MenB vaccines, or a comparator group that received MenABCWY on a 0- and 6-month schedule. The patterns of seroresponses to serogroups ACWY were generally similar to those observed in Study C3511001, and seroresponse rates were somewhat higher for some serogroup B strains following a second dose administered at 12 months compared to those observed in the two studies where MenABCWY was administered on a 0, 6 month schedule. However, the lack of a comparator group that received two doses at 0 and 6 months precludes an adequate comparison to support a dosing interval longer than 6 months.

MenACWY GMTs in Study C3511004 following Dose 1 differ from those observed in Study B1971057, and MenB hSBA were not evaluated in this study following Dose 1, so the similarity or differences between this study and the studies that support the 0- and 6-month dose interval cannot be assessed.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

An integrated analysis of the immunogenicity for all studies submitted is not applicable because Study C3511004 and Study B1971057 Stage 2 included different numbers of doses administered on different time schedules and regimens. Integrated analyses of immunogenicity results were provided for Studies B1971057 Stage 1 and C3511001. The integrated analyses assessed the immune response measured by hSBA to the *N. meningitis* serogroup B primary strains following two doses of MenABCWY, and by hSBA MenA, MenC, MenW, and MenY responses following both one and two doses of MenABCWY.

7.1.2 Demographics and Baseline Characteristics

Please see Table 1 and Section 6 for descriptions of each study.

7.1.3 Participant Disposition

Please see Section 6 for descriptions of each study.

7.1.4 Analysis of Endpoints following MenABCWY vaccination

Analyses included pooled data for Study B1971057 and Study C3511001 and separate analyses for each study. Similar analyses were described for the subset of U.S. study participants only.

Except as noted below, the seroresponse results between each of the two studies and the pooled data were similar. The immune response data were also similar for U.S. participants compared to the results of the entire study population. The seroresponse data and GMTs were as described in the individual studies. Please see Section 6.

Of note, the 4-fold rise in hSBA titer for serogroups C and W were modestly different between Studies B1971057 and C3511001 following the first MenABCWY dose, with 75.5% and 62.9%, respectively, responding to MenC, and 86.6% and 79.3%, respectively, responding to serogroup W in the ACWY-naïve participants (Study Group 1). No notable differences were present for serogroups A or Y in vaccine-naïve participants or for any serogroup in the MenACWY vaccine-experienced (Study Group 3) groups. The differences for serogroups C and W were less pronounced in the subset of U.S. study participants only. Following the second MenABCWY dose, 4-fold seroresponse rates were similar between both studies for all four serogroups in both vaccine-naïve and vaccine-experienced participants. Response rates ranged from 93% to 97.8%.

The 4-fold hSBA seroresponse rates for MenB primary strains were most different between studies for the B24 strain with 76.1% and 68.1% of participants achieving 4-fold rise in Studies B1971057 and C3511001, respectively. In U.S. participants only, 4-fold rise against strain B24 was observed in 77.0% and 69.6%, respectively. For all participants, composite responses (≥LLOQ for all four primary MenB strains) were observed in 79.9% and 78.3% in Studies B1971057 and C3511001, respectively. The similar composite responses suggest similar evidence of effectiveness across both studies. Overall, similar or lower response rates were observed in the Phase 3 study compared to the Phase 1-2 first-in-human study of MenABCWY,

supporting the conclusions of the review of Study C3511001 with respect to the evaluation of effectiveness.

7.1.5 Immunogenicity Conclusions

Comparison of immunogenicity results from Studies B1971057 and C3511001, and review of the integrated analyses support the conclusions from Study C3511001: In individuals 10 to <25 years of age, MenABCWY administered at 0, 6 months induces immune responses against *N. meningitidis* serogroups A, B, C, W and Y that are noninferior to those induced by licensed MenB and MenACWY-CRM vaccines.

8. INTEGRATED OVERVIEW OF SAFETY

Only the SAEs and NDCMCs, including autoimmune and neuroinflammatory conditions occurring in the three studies (C3511001, B1971057, and C3511004), are presented here.

An integrated summary of all safety parameters was not informative because the designs of B1971057 Stage 2 and C3511004 differed from the designs of Study C3511001 and B1971057 Stage 1. The design of each study is described in Section 6 of this memo.

8.1 Safety Assessment Methods

Studies C3511001 and B1971057 Stage 1

MenABCWY was administered at 0 and 6 months. Information about interim SAEs and NDCMCs was collected at a study visit (immunogenicity subsets) or by telephone (safety subsets) at 1 month after each vaccination. Study staff contacted all participants or parent(s)/legal guardian by telephone to collect information about interim events that occurred from 1 month after vaccination Visit 2 through 6 months after the last vaccination.

Study B1971057 Stage 2

MenABCWY was administered approximately 4 years after completion of 2 doses of MenABCWY or comparator. The interim report contained SAEs and NDCMCs assessed during the interval from 6 months following the second dose (Month 18) through 1 month after the Stage 2 dose (Month 55). Study staff collected the safety information at the vaccination visit and at the 1-month post-vaccination visit.

Study C3511004

MenABCWY was administered at 0 and 12 months (Group 1) or 0 and 36 months (Group 2; saline administered at 12 months). There was no comparator group that did not receive MenABCWY. The interim report contained SAEs and NDCMCs that occurred from vaccination Visit 1 through 6 months post-Vaccination 1 (collected by telephone), and from vaccination Visit 2 (i.e., MenABCWY Dose 2 (Group 1), saline (Group 2) through the 1 month post-Vaccination 2 (collected at the time of the visit).

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of MenABCWY was evaluated in a total of 4546 (2704 MenABCWY, 1802 comparator) individuals 10-25 years of age in 3 studies. A total of 1792 (946 MenABCWY, 846 comparator) participants had a history of prior meningococcal conjugate vaccination. In the two active controlled studies (C3511001, B1971057 Stage 1), 2306 participants received at least 1

dose of MenABCWY and 1706 received a comparator vaccine(s) (vaccination Visit 1: MenB+MenACWY-CRM; vaccination Visit 2: MenB).

Study B1971057 Stage 2 included 144 MenABCWY and 96 comparator participants. In Study C3511004, a total of 294 participants received MenABCWY.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see Table 1 and Section 6 for descriptions of each study.

8.2.3 Categorization of Adverse Events

NDCMCs were defined as disease or medical condition(s), not previously identified, that are expected to be persistent or otherwise long-lasting in their effects. Autoimmune and neuroinflammatory conditions were categorized as NDCMCs.

For all studies, detailed clinical information on participants with reports of suspected autoimmune and neuroinflammatory conditions was actively sought during study conduct prior to study unblinding (where applicable). The Applicant established a broad list of MedDRA preferred terms representing potential autoimmune and neuroinflammatory conditions which includes all confirmed or possible autoimmune conditions recognized by the American Autoimmune Related Diseases Association, and all preferred terms included in MedDRA and the autoimmune disorders High Level Group Term (HLGT). At the time a potential autoimmune or neuroinflammatory condition was reported in the study database, the Applicant assessed the validity of the reported diagnosis for confirmation. All potential autoimmune and neuroinflammatory conditions were presented to an external data monitoring committee for review.

8.3 Safety Results

8.3.1 Deaths

In Study B1971057 Stage 1, one (1) MenABCWY recipient died from a motor vehicle accident that occurred 109 days after Dose 2. No deaths were reported in Study C3511001, B1971057 Stage 2, or C3511004.

8.3.2 Nonfatal Serious Adverse Events

2-dose series (0, 6 months)
Within 30 Days after any vaccination, 6 (0.3%) MenABCWY participants reported 9 SAEs (0.3%) and none of the participants in the comparator group reported an SAE.

During the time period from 1 month after vaccination (Visit 1 or 2) through the respective 6-month follow-up visit, 16 (0.4%) MenABCWY participants reported 17 SAEs and 17 (0.5%) comparator participants reported 19 SAEs. The most commonly reported SAEs were events in MedDRA SOCs of *Injury, poisoning and procedural and Complications* and *Psychiatric disorders*; none of the SAEs reported by MenABCWY participants were assessed as related to vaccination by the study investigator or FDA/CBER clinical review team.

MenABCWY (0, 12 months)
One (1) SAE (cellulitis orbital) was reported within 6 months after MenABCWY Dose 1, and was not assessed related to vaccination by the study investigator or FDA/CBER clinical review team. No SAEs were reported within 1 month after MenABCWY Dose 2.

Vaccination 48 months following the 2-dose series
Within 30 days after vaccination, no participants in the vaccine or comparator group reported an SAE.

8.3.3 Newly Diagnosed Chronic Medical Conditions

2-dose series (0, 6 months)
Within 30 days after any vaccination, 5 (0.6%) MenABCWY participants and 5 (0.3%) participants in the comparator group reported an NDCMC. During the time period from 1 month after vaccination (Visit 1 or 2) through the respective 6-month follow-up visit, 23 (0.6%) MenABCWY participants and 8 (0.3%) comparator participants reported an NDCMC. The most frequently reported NDCMCs were events in MedDRA SOC of *Psychiatric disorders*, namely attention deficit hyperactivity disorder (ADHD). Among the 12 ADHD cases, 9 participants received MenABCWY and 3 participants received control (MenB + MenACWY-CRM or saline). Among the 12 cases, onset of ADHD-related symptoms occurred in 6 MenABCWY participants prior to study enrollment. Among the remaining 6 participants with ADHD but without evidence of onset of symptoms (3 MenABCWY, 3 comparator), 4 participants had either a family history of ADHD or a history of one or more conditions prior to enrollment that commonly co-occur with ADHD, including autism, anxiety, depression, or substance abuse. The remaining 2 participants (1 MenABCWY, 1 comparator) had no apparent history of psychiatric symptoms, risk factors, or associated diagnoses. None of the NDCMCs reported by MenABCWY participants were assessed as related to vaccination by the study investigator or FDA/CBER clinical review team.

MenABCWY (0, 12 months)
NDCMCs were reported by 2 (1.4%) participants within 6 months after MenABCWY Dose 1 (scoliosis, depression), which were not assessed as related to vaccination by the study investigator or FDA/CBER clinical review team.

Vaccination 48 months following the 2-dose series
Within 30 days after vaccination, no participants in the vaccine or comparator groups reported an NDCMC.

8.3.4 Autoimmune and Neuroinflammatory Conditions

Within the category of NDCMCs:

Autoimmune Conditions
Overall (3 studies), an autoimmune condition with confirmed diagnosis was reported for 0 MenABCWY and 7 (0.4%) MenB+MenACWY-CRM participants. None of the autoimmune conditions were assessed by the investigator or FDA/CBER clinical review team to be related to study intervention, due to confirmation of pre-existing conditions or the timing of diagnosis following vaccination.

- Five participants had evidence that the autoimmune conditions existed prior to study enrollment (autoimmune thyroiditis (n=2), Crohn's disease, alopecia areata). A participant diagnosed with Hashimoto's thyroiditis 139 days after MenB+MenACWY had a family history of autoimmune disease (Hashimoto's thyroiditis, rheumatoid arthritis).
- The sixth participant was a female diagnosed with alopecia areata 34 days after MenB Dose 2. She went to a dermatologist for evaluation of hair loss and cystic acne. Physical examination revealed a few scattered alopecic patches on the scalp with preserved follicular ostia, which were resolving with topical clobetasol propionate treatment.

- The seventh participant was a female diagnosed with ulcerative colitis (UC) 43 days after MenB Dose 2. She had no prior medical history of UC. Approximately 5 weeks after vaccination Visit 1 (MenB+MenACWY-CRM), she experienced GI bleeding but did not notify the study site.

Neuroinflammatory Conditions

Overall (3 studies), a neuroinflammatory condition with confirmed diagnosis was reported for 2 (0.07%) MenABCWY participants and 1 (0.06%) MenB+MenACWY-CRM participant. Two participants (1 MenABCWY, 1 MenB+MenACWY-CRM) reported restless leg syndrome:

- The MenABCWY female participant was diagnosed 140 days after Dose 1, and had received concomitant non-study vaccines (Tdap, HPV, VZV, and influenza) during the time period after MenABCWY Dose 1 and 40-112 days prior to the onset of the event. No treatment was required, and the condition resolved approximately 3 months from onset. Ferritin level was within normal limits. The participant had a medical history of obstructive sleep apnea and hyperinsulinemia. The study investigator assessed the event to be possibly related to vaccination (study and non-study) because no other cause was identified. The participant had no reported symptoms of COVID-19 or COVID-19 vaccination prior to the onset of symptoms. FDA/CBER clinical review team assessed this event as not related to MenABCWY due to the long timeframe before onset of symptoms following MenABCWY vaccination.

- The MenB+MenACWY-CRM female participant was diagnosed 57 days after MenB Dose 2. The event was ongoing at the time the study report was written. The study investigator attributed the event to iron deficiency anemia associated with the participant's medical history of menorrhagia. Iron deficiency can cause or worsen restless syndrome. FDA agrees with the study investigator's assessment.

The third participant (MenABCWY) was diagnosed with epilepsy 457 days after MenABCWY Dose 2. The event was assessed by the study investigator and FDA/CBER clinical review team to be unrelated to vaccination.

8.4 Safety Conclusions

Interpretation of safety data in Studies C3511004 and B1971057 Stage 2 was limited by the absence of a comparator group that did not receive MenABCWY (Study C3511004) and by small number of participants (144 MenABCWY recipients in Study B1971057 Stage 2).

Across all studies, none of the SAEs, autoimmune or neuroinflammatory conditions after MenABCWY were assessed as related to vaccination by the study investigator or the FDA/CBER clinical review team. Clinical review of uncommon AEs (SAEs, autoimmune or neuroinflammatory conditions) when MenABCWY was administered as a 2-dose series at 0 and 6 months did not identify any new safety concerns not already identified for Trumenba or MenACWY vaccines.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no clinical studies of MenABCWY in pregnant individuals nor developmental toxicity studies performed with MenABCWY.

In Studies C5311001 and B1971057 combined, inadvertent pregnancy exposures were reported for 18 of 2306 (0.8%) MenABCWY recipients and 18 of 1707 (1.1%) MenB+MenACWY-CRM recipients. Among the 33 pregnancies with an estimated conception date, for 28 pregnancies, vaccination occurred >30 days prior to the estimated date of conception, and for 5 pregnancies (1 MenABCWY [full term live birth], 4 MenB+MenACWY-CRM), the most recent vaccination occurred ≤30 days prior to the estimated conception date. Overall, among the 25 pregnancies with known outcomes: 19 live births (17 full term, 2 preterm), 6 fetal losses (1 elective termination, 4 spontaneous abortions, no information for 1 fetal loss).
By study group:

- MenABCWY: 7 live births (6 full term, 1 premature birth), 4 fetal losses (time between the last MenABCWY vaccination and estimated date of conception was 50, 1143, and 1244 days; 175 days for fetal loss for which cause was unknown.
- MenB+MenACWY-CRM: 12 live births (11 full term, 1 preterm), 2 fetal losses (1 spontaneous abortion, 1 elective termination).

There were no pregnancies reported in Study C3511004.

9.1.2 Use During Lactation

There are no data available to assess the effects of MenABCWY on the breastfed infant or on milk production/excretion.

9.1.3 Pediatric Use and PREA Considerations

For the age group 0 to <1 year, the pediatric study requirement was waived because there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group. In a clinical study, 90% of infants younger than 12 months of age who were vaccinated with a reduced dosage formulation of Trumenba had fever. MenABCWY contains the same MenB component, in the same quantity, as Trumenba; this statement was included in section 8 of the full prescribing information for MenABCWY.

For age group 1 to <10 years, submission of reports for Studies B1971067 and C3511005 were deferred for this BLA because MenABCWY is ready for approval for use in individuals 10-25 years of age before pediatric studies are completed.

The pediatric assessment in individuals 10 to <18 years of age was primarily based on Study C3511001 (see Section 6.1). The safety of MenABCWY was also evaluated in 2 other studies (B1971057 and B1971004); the safety data for MenABCWY were consistent (Study C3511001). The total safety database (3 studies) included 2744 MenABCWY vaccine recipients and 1802 recipients in the comparator group.

9.1.4 Immunocompromised Patients

Individuals with certain complement deficiencies and individuals receiving treatment that inhibits terminal complement activation are at increased risk for invasive disease caused by *N.*

meningitidis serogroups A, B, C, W, and Y, even if they develop antibodies following vaccination with MenABCWY. MenABCWY has not been evaluated in immunocompromised patients.

9.1.5 Geriatric Use

The safety and effectiveness of MenABCWY have not been established in individuals >65 years of age.

10. Overall Conclusions

The safety and immunogenicity data submitted in this BLA support the use of MenABCWY, administered as a 2-dose series (at 0 and 6 months) for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10-25 years of age.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 19. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Six *N. meningitidis* serogroups (A, B, C, W, X and Y) are responsible for the majority of clinical disease, which is commonly meningitis and septicemia. • A timely clinical diagnosis is difficult, and, even with available treatments, 10-20% of individuals with meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, and seizure disorder) and approximately 10% of cases are fatal. • The incidence of invasive meningococcal disease is highest in infants, and second peak occurs in adolescents and young adults.	• Invasive disease due to *N. meningitidis* serogroups A, B, C, W and Y is a serious and potentially life-threatening condition. • Adolescents and young adults are at risk to develop invasive meningococcal disease.
Unmet Medical Need	• Available therapy for prevention of invasive meningococcal disease includes antibiotic chemoprophylaxis; however, disease manifestations are prevented only if individuals at risk are identified in a timely manner. • There are 2 MenB and 3 MenACWY conjugate vaccines that are licensed and available in the U.S.	• MenABCWY would be the first combination vaccine containing five *N. meningitidis* serogroups licensed and available in the U.S.
Clinical Benefit	• Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp present in the outer membrane of *N. meningitidis* serogroup B. Effectiveness was evaluated by measuring antibodies with assays that uses human complement to assess serum bactericidal activity (hSBA). • In study C4591001, noninferiority of hSBA responses was demonstrated for each serogroup after MenABCWY Dose 2 vs. Trumenba (MenB) Dose 2 (four MenB primary strains) and Menveo (MenACWY-CRM) Dose 1 (A,C,W,Y seroresponses).	• The evidence for clinical benefit of a 2-dose MenABCWY regimen (administered at 0 and 6 months) meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 10-25 years of age.
Risk	• The most commonly reported solicited adverse reactions after any dose were pain at the injection site (up to 89.3%), fatigue (up to 52.1%), headache (up to 46.8%), injection site redness (up to 25.9%), muscle pain (up to 25.7%), and injection site swelling (up to 25.0%). • Except for injection site pain (6.5%-7.5%), rates of severe solicited adverse reactions were generally <3.0%. Fever (≥38°C) was 5.9% after	• The most common risks are mild-to-moderate, self-limited injection site and systemic adverse reactions. • No safety concerns were identified that have not already been characterized for Trumenba or U.S.-licensed MenACWY vaccines.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	MenABCWY Dose 1, which was similar to the comparator group receiving MenB+MenACWY-CRM (5.8%) • Across all studies, none of the SAEs, autoimmune or neuroinflammatory conditions after MenABCWY were assessed as related to vaccination by the study investigator or the FDA/CBER clinical review team.	
Risk Management	• The full prescribing information describes the common and uncommon (but potentially serious) risks associated with MenABCWY. The labeling includes a warning statement for severe allergic reactions.	• Risk mitigation strategies for MenABCWY use in individuals 10-25 years of age include communication of risks and benefits through labeling, including patient counseling information, and a pharmacovigilance plan to further evaluate risks. • The Applicant committed to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy.

11.2 Risk-Benefit Summary and Assessment

PENBRAYA contains 5 of the 6 *N. meningitidis* serogroups (A, B, C, W, X, and Y) that cause meningococcal disease globally. *N. meningitidis* can cause invasive disease, which presents as septicemia, meningitis, or both. Adolescents and young adults are one (1) of the age groups in which disease incidence is high compared to the general population.

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to fHbp present in the outer membrane of *N. meningitidis* serogroup B. Effectiveness was evaluated by measuring antibodies with assays that uses human complement to assess serum bactericidal activity (hSBA). In study C4591001, noninferiority of hSBA responses was demonstrated for each serogroup after MenABCWY Dose 2 vs. Trumenba (MenB) Dose 2 (four MenB primary strains) and Menveo (MenACWY-CRM) Dose 1 (A,C,W,Y seroresponses).

The safety of MenACWY was evaluated in a total of 4546 individuals (2704 MenACWY, 1802 comparator) in 3 studies. The most commonly reported solicited adverse reactions after any dose were pain at the injection site (up to 89.3%), fatigue (up to 52.1%), headache (up to 46.8%), injection site redness (up to 25.9%), muscle pain (up to 25.7%), and injection site swelling (up to 25.0%). Except for injection site pain (6.5%-7.5%), rates of severe solicited adverse reactions were generally <3.0%. Fever (≥38°C) was 5.9% after MenABCWY Dose 1, which was similar to the comparator group receiving MenB+MenACWY-CRM (5.8%). Across all studies, none of the SAEs, autoimmune or neuroinflammatory conditions after MenABCWY were assessed as related to vaccination by the study investigator or FDA/CBER clinical review team.

Risk mitigation strategies for MenABCWY use in individuals 10-25 years of age include communication of risks and benefits through labeling, including patient counseling information, and a pharmacovigilance plan to further evaluate risks. The Applicant committed to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy.

11.3 Discussion of Regulatory Options

In the prescribing information for MenABCWY the Applicant proposed to include statements in the Dosage and Administration section of the prescribing information indicating that:

1. A (b) (4) dose of MenABCWY provides protection against disease caused by serogroups A, C, W, and Y.
2. A (b) (4) dose may be administered to individuals at continued risk for meningococcal disease.
3. The interval between the first and second dose of the 2-dose series can be 6 (b) (4) months.

Statements indicating that a (b) (4) dose of MenABCWY prevents disease caused by serogroups A, C, W and Y, either as an initial immunization or as the second dose of MenACWY in individuals who have previously received their first MenACWY conjugate vaccine, were not included in the prescribing information for the following reasons:

- The Dosage and Administration section of labeling provides the information needed for safe and effective use of MenABCWY to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, Y and W. Inclusion of a sentence in Dosage and

Administration that a (b) (4) dose of MenABCWY provides protection against serogroups A, C, W and Y implies that a (b) (4) dose of MenABCWY is an approved dosing regimen and is not consistent with the requirement for a two-dose schedule to provide protection against *N. meningitidis* serogroups A, B, C, W and Y.

- A (b) (4) dose of MenABCWY should not be administered when protection from invasive disease caused by *N. meningitidis* serogroups A, C, W and Y and not serogroup B is intended because administration of this combination vaccine exposes individuals to a reactogenic component that will not provide benefit unless the two-dose series is completed.
- Data were not provided that demonstrated effectiveness of a (b) (4) dose to prevent disease caused by all 5 serogroups to support a (b) (4)-dose regimen of this combination vaccine.

Statements indicating that a (b) (4) dose of MenABCWY is indicated to prevent disease caused by serogroups A, B, C, W and Y for individuals who previously received the two-dose series of MenABCWY at least 4 years prior were not included in the prescribing information for the following reasons:

- Data from Study B1971057 Stage 2 provided to support this use were descriptive.
- The open-label recruitment, discordant loss to follow-up, and small sample sizes limited the interpretability of these results.

An extended interval of 6(b) (4) months for Dose 2 of MenABCWY was not supported for the following reasons:

- A dosing regimen of 2 doses 6 months apart reflects the dosing regimen adequately evaluated in Study C3511001.
- Study C3511004 was an open-label descriptive study that did not include either a comparator group that received currently licensed MenACWY and MenB vaccines, or a comparator group that received MenABCWY on a 0- and 6-month schedule. The lack of a comparator group that received two doses at 0 and 6 months precluded an adequate comparison to support a dosing interval longer than 6 months.
- MenACWY GMTs in Study C3511004 following Dose 1 differed from those observed in Study B1971057, and MenB hSBA were not evaluated in this study following Dose 1, so the similarity or differences between this study and the studies that support the 0- and 6-month dose interval cannot be assessed.

11.4 Recommendations on Regulatory Actions

The clinical review team recommends approval of MenABCWY for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y, administered as a 2-dose series (at 0 and 6 months), for use in individuals 10 through 25 years of age.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed, comments were sent to the Applicant, and all issues were satisfactorily resolved. The clinical data in the final prescribing information were reviewed by the clinical reviewers and found to be consistent with and supported by data in the BLA.

11.6 Recommendations on Postmarketing Actions

In accordance with PREA requirements, the Applicant is required to conduct the following studies:

- Study B1971067 to evaluate the safety and immunogenicity of MenABCWY in individuals 1 to <10 years of age
  - Final protocol submission: November 30, 2023
  - Study completion: November 30, 2026
  - Final report submission: May 31, 2027

- Study C3511005 to evaluate the safety and immunogenicity of MenABCWY in individuals 1 to <10 years of age
  - Final protocol submission: October 31, 2026
  - Study completion: May 31, 2030
  - Final report submission: November 30, 2030

Postmarketing Commitment

The Applicant committed to conduct a pregnancy registry study to evaluate the safety of MenABCWY vaccine exposure during pregnancy

- Final protocol submission: January 31, 2024
- Study completion: April 30, 2032
- Final report submission: April 30, 2033