CBER Integrated Review

Table 1. Application Information

Date Completed:	February 14, 2025
Signatory Product Office	Office of Vaccines Research and Review
Priority Review (Yes/No)	No
BLA Number:	STN 125819/0
Applicant:	GlaxoSmithKline Biologicals
Submission Receipt Date:	February 15, 2024
PDUFA Action Due Date:	February 14, 2025
Proper Name:	Meningococcal Groups A, B, C, W, and Y Vaccine
Proprietary Name:	Penmenvy
Indication(s) and Intended Population(s):	For active immunization to prevent invasive disease caused by *Neisseria meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.
Dosage Form(s) and Route(s) of Administration	Penmenvy (Meningococcal Groups A, B, C, W, and Y Vaccine) for injectable suspension, for intramuscular use.
Dosing Regimen	Administer 2 doses (approximately 0.5 mL each) of Penmenvy intramuscularly 6 months apart
Orphan Designation (Y/N)	N

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Glossary

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
BIMO	bioresearch monitoring
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drugs Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
DRMRR	Division of Review Management and Regulatory Review
enc-hSBA	endogenous complement human serum bactericidal activity
ESFU	extended safety follow-up
FDA	U.S. Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GSK	GlaxoSmithKline Biologics SA
hSBA	human serum bactericidal activity
ICSR	individual case safety report
IMD	invasive meningococcal disease
IND	investigational new drug
LOD	limit of detection
MenABCWY	meningococcal groups A, B, C, W, and Y vaccine
MenACWY	meningococcal groups A, C, Y, and W-135
MenB	meningococcal serogroup B
NHBA	neisserial heparin-binding antigen
OBPV	Office of Biostatistics and Pharmacovigilance
OCBQ	Office of Compliance and Biologics Quality
OMV	outer membrane vesicle
OVRR	Office of Vaccines Research and Review
PDUFA	Prescription Drug User Fee Act
PI	prescribing information
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
RCDC	reverse cumulative distribution curve
REMS	risk evaluation and mitigation strategy
rMenB+OMV NZ	Bexsero meningococcal vaccine
RRR	relative reduction in risk
SAE	serious adverse event
SAP	statistical analysis plan
U.S.	United States
USPI	U.S. Prescribing Information

I. Executive Summary

1. Summary of Regulatory Action

GlaxoSmithKline Biologics SA (GSK) (Applicant) submitted a biologics license application (BLA) for its Meningococcal Groups A, B, C, W and Y Vaccine (MenABCWY) (trade name: Penmenvy) to seek approval for active immunization to prevent invasive disease caused by *Neisseria meningitidis (N. meningitidis*) serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

MenABCWY is an injectable suspension for intramuscular use and is to be given as two doses (approximately 0.5 mL each) 6 months apart. To prepare MenABCWY, one vial of lyophilized meningococcal (groups A, C, Y, and W-135) oligosaccharide diphtheria *Corynebacterium diphtheriae* CRM_{197} conjugate component (Lyophilized MenACWY Component), which contains the same antigens in the same amounts as in Menveo, is reconstituted at the time of use with the liquid meningococcal serogroup B component (MenB Component) in the accompanying prefilled syringe, which contains the same antigens in the same amounts as in Bexsero. Upon reconstitution, MenABCWY is to be administered immediately.

Menveo Regulatory History

Menveo (Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) is indicated for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135. Menveo is approved for use in persons 2 months through 55 years of age. It was initially approved for use in individuals 11 through 55 years of age on February 19, 2010, individuals 2 through 10 years of age on January 28, 2011, and individuals 2 months through 23 months of age on August 1, 2013. For individuals 2 years through 55 years of age (the age group relevant to the desired age range for MenABCWY of 10 through 25 years of age), Menveo is licensed as a single dose with a booster dose administered at least 4 years after the first dose for individuals considered at continued risk for meningococcal disease.

Bexsero Regulatory History

Bexsero (Meningococcal Group B Vaccine containing recombinant proteins neisserial adhesin A [NadA], neisserial heparin-binding antigen [NHBA], and factor H binding protein [fHbp], and outer membrane vesicles [OMV]) is indicated for active immunization to prevent invasive disease caused by *N. meningitidis* serogroup B. Bexsero is approved for use in individuals aged 10 through 25 years.

In 2014, given the public health concerns about meningococcal serogroup B disease in the U.S., FDA agreed to consider licensing Bexsero under the accelerated approval regulations, 21 CFR 601 Subpart E. The Agency determined that the accelerated approval pathway was appropriate, and approval was based on the demonstration of serum bactericidal antibody responses, as

measured by the exogenous complement human serum bactericidal activity (hSBA) assay, against three *N. meningitidis* indicator strains, each expressing one antigen (fHbp, NadA, OMV) in common with the Bexsero components. On January 23, 2015, Bexsero was approved under accelerated approval regulations as a two-dose schedule administered at least one month apart.

This approval under the accelerated approval regulations required adequate and well-controlled postmarketing studies to verify and describe the clinical benefit attributable to Bexsero by demonstrating effectiveness against diverse meningococcal group B strains. Two postmarketing studies were required as a part of this accelerated approval. The first was Study V102_16 to assess the performance of immunologic assays for evaluating the breadth of coverage against diverse *N. meningitidis* serogroup B strains. The second was Study V72_72 of Bexsero among persons 10 years through 25 years of age in the U.S. to confirm effectiveness against a panel of diverse *N. meningitidis* serogroup B strains.

On July 21, 2023, GSK submitted an efficacy supplement to the Bexsero BLA with data from studies V102_16 and V72_72 to fulfill the accelerated approval required studies and request traditional approval of Bexsero. This efficacy supplement also included supplemental safety data from studies V102_15 and V102_15E1. On August 19, 2024, the BLA supplement was approved to verify and describe the clinical benefit of Bexsero for individuals 10 through 25 years of age.

With traditional approval, the Bexsero dosing schedule was revised to two doses administered with a 6-month interval (Bexsero [0, 6 months]), and to include a three-dose schedule of Bexsero administered at 0, 1-2, and 6 months (Bexsero [0, 1-2, 6 months]) based on immunogenicity results from Study V72_72 demonstrating higher serogroup B responses following these schedules as compared with Bexsero (0, 2 months). The choice of dosing schedule depends on the risk of exposure and the individual's susceptibility to *N. meningitidis* serogroup B disease.

MenABCWY Regulatory History

The original BLA for MenABCWY (STN 125819/0) was submitted on February 15, 2024, and included data from 12 clinical studies. Of these, results from Study V72_72 and Study 019 are the primary basis for demonstrating the safety and effectiveness of MenABCWY for the active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

Study V72_72 was a phase 3, randomized, controlled, observer-blind study to demonstrate the effectiveness, immunogenicity, and safety of MenABCWY when administered to healthy adolescents and young adults who were either meningococcal serogroups ACWY-conjugate vaccine (MenACWY) naïve or experienced. All participants were serogroup B vaccine naïve. The study was initiated August 14, 2020, and was completed September 13, 2022. Primary and key secondary immunogenicity objectives in this study demonstrated the effectiveness of the serogroup A, B, C, W, and Y responses following MenABCWY administered according to a 0, 6-month schedule (MenABCWY [0, 6 months]).

Study 019 was a phase 3, randomized, controlled, observer-blind study to demonstrate the effectiveness, immunogenicity, and safety of MenABCWY when administered to healthy adolescents and young adults who were MenACWY-experienced. The study was initiated January 25, 2021, and was completed May 3, 2023.

New BLAs for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are to contain a pediatric assessment unless the Applicant has obtained a waiver or deferral. To fulfill the Pediatric Research Equity Act (PREA) requirements, the Applicant has committed to conduct four postmarketing required studies in infants and children ranging from 6 weeks of age through 9 years of age. Two of the studies are to evaluate the safety and immunogenicity of MenABCWY and the other two are to evaluate the safety and effectiveness of MenABCWY. The Applicant was granted a waiver from conducting pediatric assessment requirements from birth to <6 weeks of age. Additionally, the Applicant agreed to conduct a postmarketing study for assessment of pregnancy and birth outcomes in women exposed to MenABCWY during pregnancy. The USPI will note that data regarding pregnancy risks are not available currently.

The BLA was reviewed by a multidisciplinary team and no disciplines identified issues precluding approval. The signatory authority agrees that the benefit-risk assessment favors approval. For detailed information supporting the basis for the benefit-risk assessment, please refer to the details in this integrated assessment document.

2. Benefit-Risk Assessment

2.1. Benefit/Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• *Neisseria meningitidis (N. meningitidis)* is responsible for endemic and epidemic invasive meningococcal disease (IMD) worldwide with serogroups B, C, W, and Y being responsible for most IMD in the U.S. IMD due to serogroup A occurs primarily in endemic areas outside of the U.S. • IMD usually presents as bacteremia with or without meningitis. Other clinical presentations include pneumonia, arthritis, and pericarditis. • Even with prompt antimicrobial therapy, up to 15% of infected individuals will have a fatal outcome (CDC 2024). Furthermore, up to 20% of survivors will have substantial morbidity including brain damage, deafness, and loss of limbs. • IMD can affect any age group with the highest incidences in children <1 year of age and adolescents.	• IMD due to *N. meningitidis* is a serious disease associated with substantial morbidity and mortality, even with antimicrobial therapy. • *N. meningitidis* serogroups B, C, W, and Y are responsible for cases of IMD in the U.S. Disease due to serogroup A occurs mainly in travelers to, and people residing in (e.g., deployed military members, members of the diplomatic corps), endemic areas outside of the U.S. • Individuals in the age group relevant to this BLA (10 through 25 years of age in the U.S.) are at risk for IMD due *N. meningitidis.*
Current treatment options	• Antimicrobial agents are available for the treatment of IMD but substantial morbidity and mortality may still occur despite treatment. • Chemoprophylaxis may be given; however, its use is limited to those with close contact with IMD cases. • There are 2 vaccines available for use in the U.S for the prevention of IMD due to serogroup B, 2 vaccines for the prevention of IMD due to serogroup A, C, W, and Y, and 1 vaccine for the prevention of IMD due to serogroups A, B, C, W, and Y. • Recommendations for use of the separately administered serogroup B and serogroup ACWY vaccines in individuals at increased risk for developing	• Although antimicrobial therapy is available for the treatment of and chemoprophylaxis against IMD following exposure, vaccines are important public health measures for the prevention of IMD and its associated morbidity and mortality. • MenABCWY will provide an additional option for a combination vaccine to provide protection against IMD due to *N. meningitidis* serogroups A, B, C, W, and Y with fewer injections than the component vaccines potentially leading to increased vaccination rates.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	IMD due to exposure and/or susceptibility are available	
Benefit	*Approach to the assessment of benefit* • For serogroups A, C, W and Y, capsular polysaccharides are conserved across strains and elicit strong immune responses in humans; therefore, demonstration of an adequate serum bactericidal activity (SBA) response against an indicator strain with a representative capsular polysaccharide is considered representative of the effectiveness of the serogroup A, C, W, and Y vaccine components. • For serogroup B, the capsular polysaccharide is poorly immunogenic due to mimicry of human antigens. Therefore, the serogroup B antigenic components of the vaccine are derived from outer membrane proteins and pieces of the outer membrane itself. As these components are less well conserved across serogroup B strains, demonstration of the effectiveness of the serogroup B components of the vaccine requires demonstration of adequate SBA responses against diverse serogroup B strains. *Evidence to support benefit* Evidence of effectiveness of MenABCWY (0, 6m) in individuals 10 through 25 years of age were demonstrated by the following: For serogroup A, C, W, and Y responses: • Statistically non-inferior responses following MenABCWY (0, 6m) as compared to a single dose of Menveo, measured using exogenous complement hSBA (hSBA) assays against 4 indicator strains representing Serogroups A, C, W, and Y in MenACWY-naïve (Study V72_72) and MenACWY-experienced (Study 019) participants. For serogroup B responses: • Endogenous complement hSBA (enc-hSBA) responses demonstrating the breadth of immune responses elicited against a diverse panel of 110 U.S invasive strains of *N. meningitidis* serogroup B in	• The evidence for clinical benefit of the MenABCWY (0, 6m) schedules meets the evidentiary standards for approval (i.e., substantial evidence of effectiveness) for use in individuals 10 through 25 years of age. • Study V72_72 results confirm effectiveness of MenABCWY (0, 6m) against *N. meningitidis* serogroups A, C, W, and Y when administered to MenACWY-naïve individuals. • Post hoc analyses suggest suboptimal serogroup A responses following a single dose of MenABCWY administered to MenACWY conjugate vaccine-naïve individuals. • Study 019 results confirm the effectiveness of MenABCWY (0, 6m) against *N. meningitidis* serogroups A, C, W, and Y when administered to MenACWY-experienced individuals. • There were decreased serogroup B responses observed following MenABCWY as compared with Bexsero (0, 6m); however, primary analyses of the enc-hSBA responses met prespecified statistical success criteria and additional descriptive and post hoc analyses suggest that the impact of the observed differences is small. • Therefore, Study V72_72 results confirm the effectiveness of MenABCWY (0, 6m) against diverse *N. meningitidis* serogroup B strains associated with IMD in the U.S. • The choice of the appropriate meningococcal vaccine regimen (combination MenABCWY versus Bexsero and Menveo individual component vaccines administered according to the schedules intended for those at increased risk of IMD) may depend on an individual's risk of *N. meningitidis* exposure and their susceptibility to IMD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Study V72_72 including demonstration of statistical non-inferiority of the percentage of samples with enc-hSBA activity following MenABCWY (0, 6m) compared with Bexsero (0, 6m). • Statistically non-inferior hSBA responses against the factor H binding protein (fHbp) and neisserial adhesion protein A (NadA) indicator strains following MenABCWY (0, 6 months) as compared with Bexsero (0, 6 months). *Uncertainties related to the evaluation of benefit* • Point estimates of the serogroup B responses following MenABCWY were lower compared with Bexsero (0, 6 months) and Bexsero (0, 2, 6 months). • Analyses of the hSBA responses against the neisserial heparin-binding antigen (NHBA) and outer membrane vesicle (OMV) indicator strains following MenABCWY (0, 6 months) compared with Bexsero (0, 6 months) did not meet pre-specified statistical success criteria. • Post hoc exploratory analyses demonstrated decreased responses to the serogroup A component following a single dose of MenABCWY as compared with Menveo in MenACWY-naïve participants.	
Risk and risk management	• The most frequently reported adverse reactions (ARs) following MenABCWY in participants who were mostly MenACWY vaccine naïve (87%) and occurring in ≥5% of participants were injection site pain (Dose 1: 92%; Dose 2: 88%), fatigue (51%, 42%), headache (42%, 36%), myalgia (15%, 12%) nausea (15%, 10%), injection site erythema (13%, 12%), injection site swelling (13%, 12%), induration (9%, 8%), and arthralgia (8%, 7%) (Study V72_72). • The most frequently reported ARs following MenABCWY in participants who were MenACWY conjugate vaccine-experienced and occurring in ≥5% of participants were Injection site pain (Dose 1: 80%, Dose 2: 74%), fatigue (40%, 33%), headache (41%,	• Injection site pain, fatigue, headache, myalgia, nausea, injection site erythema, and injection site swelling were the most frequently reported adverse reactions following MenABCWY. • The reactogenicity of MenABCWY was generally similar for individuals who were either MenACWY vaccine-experienced or -naïve. • The local reactogenicity of MenABCWY was similar to Bexsero and greater than Menveo (particularly pain which was of greater intensity following MenABCWY as compared to Menveo). • The systemic reactogenicity of MenABCWY was generally similar to Bexsero and Menveo.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	33%), myalgia (15%, 13%), nausea (15%, 12%), injection site erythema (5%, 6%), arthralgia (7%, 6%), and injection site swelling (4%, 6%) (Study 019). • Most ARs following MenABCWY were of Grade 1 or Grade 2 intensity. Overall, the rates of Grade 3 ARs were approximately 4% to 10% for local ARs (Table 26 and Table 29) and 3% to 5% for systemic ARs (Table 27 and Table 30). • Similar percentages of participants reported local and systemic ARs of similar severity after MenABCWY and Bexsero. • Greater percentages of participants reported solicited local ARs after MenABCWY as compared with Menveo (particularly pain). • Pain of Grade 3 intensity was more common (> 5% difference in percentages of participants) following MenABCWY as compared with Menveo. • Similar results following MenABCWY were demonstrated in the other trials submitted with the BLA in which ARs were reported. • There were two serious adverse events (SAEs) that were considered related to MenABCWY vaccination by the study investigator: a case of connective tissue disorder with petechiae occurring after Dose 1 and Dose 2 of MenABCWY as well as after a dose of hepatitis A vaccine; and a case of seizures 9 hours after Dose 1 of MenABCWY. See Section 7.6.3.3 for additional details.	• Results of analyses of unsolicited AEs (including serious adverse events [SAEs] and adverse events of special interest [AESIs]) did not identify substantial safety concerns. • There were no safety concerns identified in the studies submitted to the BLA that suggest the risks of MenABCWY outweigh its potential benefits.

Source: FDA-generated table
Abbreviations: IMD=invasive meningococcal disease; U.S.=United States; m=months of age; ARs=adverse reactions; AEs=adverse events; AESIs=adverse events of special interest; SAEs=serious adverse events; BLA=Biologics License Application

Invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroups A, B, C, W, and Y results in substantial morbidity and mortality even with prompt antimicrobial treatment due to the rapidity of disease progression. In the U.S., most IMD is caused by serogroups B, C, W, and Y. Serogroup A is responsible for IMD in U.S. travelers to endemic areas. While there are antimicrobial agents available for the treatment of and chemoprophylaxis against IMD, vaccination is an important public health measure for the prevention of IMD and the associated sequelae. There are 2 vaccines licensed and available for use in the U.S for the prevention of IMD due to *N. meningitidis* serogroup B, 2 vaccines for the prevention of IMD due to serogroups A, C, W, and Y, and 1 vaccine for the prevention of IMD due to serogroups A, B, C, W, and Y.

With this Biologics License Application (BLA), the Applicant has provided data from 2 key trials (Studies V72_72 and 019) and 10 supportive trials (Studies V102P1, V102_02, V102_02E1, V102_02E2, V102_03, V102_03E1, V102_15, V102_15E1, V102_16, and V102_16E1) to demonstrate the safety and effectiveness of MenABCWY for the prevention of IMD due to *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age.

For serogroups A, C, W and Y, capsular polysaccharides are conserved across strains and elicit strong immune responses in humans; therefore, demonstration of an adequate serum bactericidal activity (SBA) response against an indicator strain with a representative capsular polysaccharide is considered representative of the effectiveness of the serogroup A, C, W, and Y vaccine components. For serogroup B, the capsular polysaccharide is poorly immunogenic due to molecular mimicry of human antigens. Therefore, the serogroup B antigenic components of the vaccine are derived from outer membrane proteins and pieces of the outer membrane itself. As these components are less well conserved across serogroup B strains, demonstration of the effectiveness of the serogroup B components of the vaccine requires demonstration of adequate SBA responses against a broad range of serogroup B strains.

Study V72_72 was conducted to demonstrate the clinical benefit of 2 doses of MenABCWY administered 6 months apart (MenABCWY [0, 6 months]) against serogroups A, C, W, and Y in participants who were MenACWY vaccine-naïve and against serogroup B in participants who were serogroup B vaccine-naïve. Co-primary immunogenicity endpoints in this study measured the serum bactericidal activity (SBA) against indicator strains representative of serogroups A, C, W, and Y with assays that used human complement from sources exogenous to study participants (hSBA) and measured the SBA responses against a diverse panel of 110 *N. meningitidis* serogroup B strains with an assay that used the complement activity preserved in the samples study participant samples (enc-hSBA). These 110 strains were selected from 442 strains collected by the Centers for Disease Control and Prevention (CDC) from U.S. IMD cases between 2000 and 2008.

The primary comparator regimen for the serogroup A, C, W, and Y responses was a single dose of Menveo and for the serogroup B responses was Bexsero (0, 6 months). Immunogenicity endpoints were determined at 1 month following the single dose of Menveo and 1 month following the 2nd dose of MenABCWY (0, 6 months) or Bexsero (0, 6 months).

Primary analyses of the serogroup A, C, W, and Y hSBA responses demonstrated statistical non-inferiority following MenABCWY (0, 6 months) as compared with a single dose of Menveo and

statistical non-inferiority of the percent of samples with enc-hSBA activity against the 110-strain serogroup B panel following MenABCWY (0, 6 months) as compared with Bexsero (0, 6 months). Responder and test-based analyses of the enc-hSBA responses following MenABCWY (0, 6 months) met statistical success criteria. Point estimates of enc-hSBA responses following MenABCWY were lower as compared with Bexsero (0, 6 months) and Bexsero (0, 2, 6 months).

Secondary endpoints evaluated the hSBA responses against indicator strains representative of each of the 4 serogroup B antigens in MenABCWY (factor H binding protein [fHbp], neisserial adhesion protein A [NadA], neisserial heparin-binding antigen [NHBA], and the outer membrane vesicle [OMV]) measured using the hSBA assay. Analyses of the hSBA responses against the fHbp and NadA indicator strains met statistical non-inferiority criteria following MenABCWY (0, 6 months) as compared with Bexsero (0, 6 months). Analyses of the hSBA responses against the NHBA and OMV indicator strains did not meet statistical non-inferiority criteria.

Overall, the immunogenicity data, including descriptive and post hoc analyses support the effectiveness of MenABCWY for the prevention of invasive serogroup B disease.

Study 019 was conducted to demonstrate the clinical benefit of MenABCWY (0, 6 months) against serogroups A, C, W, and Y in participants who were MenACWY vaccine-experienced. Responses against indicator strains representative of serogroups A, C, W, and Y were measured using the same hSBA assay used in Study V72_72. Primary analyses of these responses demonstrated statistical non-inferiority following MenABCWY (0, 6 months) as compared with a single dose of Menveo.

Across all studies submitted to the BLA, injection site pain was the most common adverse reaction following MenABCWY (74% to 92% of recipients). Fatigue, headache, myalgia, nausea, injection site erythema, and injection site swelling were also frequently reported adverse reactions following MenABCWY. The local reactogenicity of MenABCWY was similar to that of Bexsero and greater than that following Menveo, particularly pain which was also of greater intensity following MenABCWY as compared with Menveo. The systemic reactogenicity of MenABCWY was generally similar to Bexsero and Menveo.

Results of analyses of unsolicited adverse events (AEs, including serious adverse events [SAEs] and adverse events of special interest [AESIs]) did not identify safety concerns that suggest the risks of MenABCWY outweigh its potential benefits.

The totality of these data supports the safety and effectiveness of MenABCWY (0, 6 months) for the prevention of IMD caused by *N. meningitidis* serogroup A, B, C, W, and Y for individuals 10 through 25 years of age who are either MenACWY conjugate vaccine naïve or experienced. The choice of the appropriate meningococcal vaccine regimen (combination MenABCWY versus component vaccines administered according to the schedules intended for those at increased risk of IMD) may depend on an individual's risk of *N. meningitidis* exposure and their susceptibility to IMD.

2.2. Conclusions Regarding Benefit-Risk

The data submitted with the BLA support the safety and effectiveness of MenABCWY administered as a 2-dose schedule with a 6-month interval between doses for the prevention of IMD caused by *N. meningitidis* serogroups A, B, C, W, and Y for individuals 10 through 25 years of age.

The clinical reviewers recommend approval of MenABCWY for the prevention of IMD caused by *N. meningitidis* serogroup A, B, C, W, and Y for individuals 10 through 25 years of age.

The prescribing information (PI) was reviewed and specific comments on the labeling were provided by CBER to the Applicant who made the requested revisions. All issues were satisfactorily resolved.

The proposed pharmacovigilance plan (PVP), version 1.0, dated Jan 10, 2024, is adequate to monitor postmarketing safety for MenABCWY with routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement (PMR) study. Safety in pregnancy and lactation will be characterized in the planned postmarketing commitment (PMC) study.

II. Interdisciplinary Assessment

3. Introduction

N. meningitidis is a leading cause of bacterial meningitis and sepsis worldwide that may occur as sporadic cases, localized outbreaks, or widespread epidemics. Meningococcal infections affect individuals of all ages, including healthy young adults. Despite prompt antibiotic treatment (CDC 2024), 10-15% of infected individuals have a fatal outcome and up to 10-20% of survivors have substantial morbidity including brain damage, deafness, and loss of limbs.

On February 15, 2024, the Applicant submitted a new BLA for a vaccine with the proposed proper name of Meningococcal Groups A, B, C, W, and Y Vaccine and the proposed proprietary name of Penmenvy. The indication proposed for Penmenvy was for prevention of invasive disease caused by *N. meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

Data from 12 clinical studies were included in the BLA: two key trials (Study V72_72 and MenABCWY-019 [hereafter Study 019]) and supportive trials Studies V102P1, V102_02, V102_02E1, V102_02E2, V102_03, V102_03E1, V102_15, V102_15E1, V102_16, and V102_16E1 to demonstrate the safety and effectiveness of MenABCWY for the prevention of invasive meningococcal disease.

Study V72_72 provided the key immunogenicity data evaluating the *N. meningitidis* serogroup B responses following MenABCWY (0, 6 months) as compared with the serogroup B responses following Bexsero (0, 6 months). The V72_72 trial design, endpoints, and prespecified criteria for enc-hSBA and hSBA were developed based on results from studies V102_15 and V102_16 and their respective extension studies. Study endpoints were determined using assays which measured:

1. the serum bactericidal activity (SBA) against a diverse panel of 110 serogroup B strains associated with invasive disease in the U.S. (enc-hSBA) and
2. the SBA against four serogroup B indicator strains representing each of the serogroup B components found in MenABCWY (hSBA).

Evaluation of the antibody responses to diverse serogroup B strains (measured by enc-hSBA) and the strength or magnitude of the immune response to the serogroup B vaccine components (measured by hSBA) are important for characterizing the effectiveness of MenABCWY against *N. meningitidis* serogroup B.

Primary analyses of the serogroup B enc-hSBA results met statistical success criteria. Secondary analyses of the serogroup B hSBA results met statistical success criteria for two of the indicator strains (fHbp and NadA) and did not meet statistical success criteria for two of the indicator strains (NHBA and OMV).

The effectiveness of MenABCWY against serogroups A, C, W, and Y was evaluated in MenACWY vaccine-naïve participants in Study V72_72 and MenACWY vaccine-experienced participants in Study 019. The serum bactericidal antibody responses were measured using hSBA assay against serogroups A, C, W and Y. The serum bactericidal antibody responses were measured using an hSBA assay against serogroups A, C, W and Y. The non-inferiority criteria for the percentages of participants achieving a seroresponse against each of the four serogroups A, C, W, and Y were met at one month after Dose 2 of MenABCWY compared with a single dose of Menveo in MenACWY vaccine-naïve participants and in MenACWY vaccine-experienced participants.

3.1. Key Review Issues

3.1.1. Key Review Issues Relevant to the Evaluation of Benefit

The review team identified the following the key review issues relevant to the evaluation of benefit. In-depth assessment of these issues relating can be found in Section 6.3.

3.1.1.1. enc-hSBA and hSBA Responses Against *N. meningitidis* Serogroup B Following MenABCWY (0, 6 Months)

Although primary analyses met the pre-specified statistical success criteria, the review team has identified that the point estimates of the enc-hSBA responses were lower following MenABCWY (0, 6 months) as compared with the responses following Bexsero (0, 6 months). These enc-hSBA responses were also lower following MenABCWY (0, 6 months) as compared with Bexsero (0, 2, 6 months). Bexsero (0, 2, 6 months) was not a pre-specified comparator regimen.

Analyses of hSBA responses against the NHBA and OMV indicator strains demonstrated lower responses following MenABCWY (0, 6 months) as compared with Bexsero (0, 6 months). These analyses failed to meet the pre-specified statistical non-inferiority criteria.

3.1.1.2. Post hoc Exploratory Analyses of the Exogenous Human Complement SBA Responses in MenACWY-Naïve Participants Against the *N. meningitidis* Serogroup A Indicator Strain Following a Single Dose of MenABCWY as Compared to Menveo

The review team has identified that post hoc exploratory analyses of the hSBA responses against the Serogroup A indicator strain demonstrated lower responses following Dose 1 of MenABCWY as compared with Menveo when administered to participants who were MenACWY-naïve.

3.1.2. Key Review Issues Relevant to the Evaluation of Risk

There were no key review issues identified during the evaluation of risk.

3.2. Approach to the Clinical Review

STN 125819/0 included safety and effectiveness data from 12 clinical trials (Table 3). Of these, Study V72_72 and Study 019 provided the primary evidence of safety and effectiveness of MenABCWY for the prevention of invasive meningococcal disease in individuals 10 through 25 years of age.

Table 3. Clinical Trials Submitted to Support Effectiveness and Safety of MenABCWY

Study (NCT #)	Countries (% U.S. Participants)	Participant Age Range (y)	Final Formulationa MenABCWY N	Final Formulation & Schedule MenABCWY (0, 6 months) b N
V72_72 (NCT04502693)	Australia, Canada, Czech Republic, Estonia, Finland, Turkey, U.S. (34%)	10-25	1657	1657
MenABCWY_019 (NCT04707391)	Argentina, Australia, Canada, U.S. (58%)	15-25	626	626
V102_15[c]/E1[d] (NCT02212457) (NCT02946385)	Finland, Poland	10-21	825 (V102_15) 99 (V102_15E1)	134 (V102_15) 0 (V102_15e1)
V102_16[c]/E1[d] (NCT02140762) (NCT02285777)	U.S. (100%)	10-19	152 (V102_16) 0 (V102_16E1)	0 (V102_16) 0 (V102_16E1)
V102_03[c] /E1[d] (NCT01272180) (NCT01992536)	Poland, U.S. (69%)	10-25	71 (V102_03) 83 (V102_03E1)	0 (V102_03) 0 (V102_03E1)
V102_02 [c] /E1[d]/E2[d] (NCT01210885) (NCT01367158) (NCT02451514)	Chile, Columbia, Panama	11-18	83 (V102_02) 0 (V102_02E1) 96 (V102_02E2)	0 (V102_02) 0 (V102_02E1) 0 (V102_02E2)
V102P1	Switzerland	--	25	0

Source: FDA-generated table adapted from relevant CSRs; STN125819/0
Abbreviations: N= number of participants; NCT #=National Clinical Trial number; U.S.=United States; y=years
a. Participants with available data who received the final formulation of MenABCWY (irrespective of schedule).
b. Participants with available data who received the final formulation of MenABCWY according to the 2-dose, 6-month interval schedule
c. Participants included in the counts for the parent studies (V102_15, V102_16, V102_03, and V102_02) were not included in the counts for the respective extension studies, even if they received additional doses of the final formulation of MenABCWY in the extension study
d. Participants included in the counts for the extension studies (V102_15E1, V102_16E1, V102_03E1, and V102_02E1 and E2) did not receive doses of the final formulation MenABCWY in the respective parent studies.

The following amendments to STN125819 were reviewed in support of this application.

Table 4. Amendments to BLA 125819/0

Amendment Number	Date Submitted	Description
1	March 14, 2024	Shell tables for Study V72_72 CRFs and Datasets for Studies V103, V102_02/E1, V102P1
2	March 28, 2024	Erratum for CSR for Study 019
3	April 30, 2024	Revised immunogenicity results to reflect updated assay values
4	May 3, 2024	Responses to E-diary IR 3 dated April 22, 2024
5	May 8, 2024	Responses to E-diary IR 4 dated April 24, 2024
8	May 24, 2024	Shell tables for Study 019, V102_15/E1, V102_16/E1 requested in IR 6 dated May 6, 2024
9	June 5, 2024	Responses to E-diary IR 7 dated May 22, 2024
11	June 27, 2024	Pediatric study plan revisions requested in May 15, 2024 email
12	July 5, 2024	Responses to dataset IR 10 dated June 20, 2024
16	July 26, 2024	Responses to dataset IR 10 dated June 20, 2024
19	August 5, 2024	Shell tables for V102_02/E1/E2, V102_03/E1 requested in IR 14 dated July 5, 2024
24	August 29, 2024	Responses to mid-cycle communication
29	October 1, 2024	Response to mid-cycle communication regarding immunogenicity results for Study V72_72
30	October 4, 2024	Response to mid-cycle communication regarding immunogenicity results for Study V72_72
31	October 8, 2024	Response to IR 21 regarding AEs across studies dated September 26, 2024
33	October 15, 2024	Response to IR 22 regarding AEs in Studies V72_72 and 019 dated September 30, 2024
35	October 29, 2024	Response to IR 23 for immunogenicity datasets for Studies V72_72 and 019 dated October 3, 2024
39	November 12, 2024	Revised USPI in response to October 2024 Mid-Cycle follow-up meeting and October 31, 2024, post-meeting request for revised draft USPI
42	November 13, 2024	Revised AE tables for Study 019 requested in IR 28 dated November 4, 2024
43	November 14, 2024	Response to IR 27 regarding planned post-approval pregnancy study and additional SAE narratives dated October 31, 2024
45	November 18, 2024	Response to IR 29 regarding pediatric study plan dated November 12, 2024
46	November 25, 2024	Response to IR 31 regarding pediatric study plan dated November 21, 2024
47	November 26, 2024	Response to IR 30 regarding AEs across studies dated November 19, 2024
52	December 9, 2024	Response to IRs 32 and 37 regarding pregnancy outcomes and pediatric study plan dated November 25, 2024 and December 4, 2024
54	December 10, 2024	Response to IR 33 regarding planned post-approval pregnancy study and pharmacovigilance plan dated November 26, 2024
56	December 24, 2024	Response to IR 39 regarding planned post-approval pregnancy study and pharmacovigilance plan dated December 18, 2024
57	January 6, 2025	Response to IR 40 regarding pregnancy outcomes dated December 30, 2024

Amendment Number	Date Submitted	Description
59	January 13, 2025	Response to IR 41 regarding AEs dated January 10, 2025
60	January 14, 2025	Response to IR 43 regarding AEs dated January 14, 2025
62	January 21, 2025	Response to IRs 41 and 42 regarding AEs dated January 10, 2025 and January 13, 2025
63	January 21, 2025	Response to IR 44 regarding distribution data of Bexsero and Menveo dated January 14, 2025
64	January 21, 2025	Revised carton and container labels in response to IR 45 sent January 15, 2025
67	January 23, 2025	Revised USPI in response to IR 47 sent January 17, 2025
68	February 3, 2025	Response to dataset IR 48 dated January 29, 2025
69	February 5, 2025	Response to IR 49 regarding AEs and USPI correspondence dated January 31, 2025
70	February 6, 2025	Revised carton and container labels in response to IR 50 sent February 4, 2025
72	February 10, 2025	Revised USPI in response to IR 52 sent February 6, 2025
74	February 10, 2025	Response to IR 54 regarding AEs dated February 7, 2025
75	February 11, 2025	Response to IR 55 regarding financial disclosures dated February 8, 2025
76	February 12, 2025	Revised USPI in response to IR 56 sent February 11, 2025
77	February 13, 2025	Revised USPI in response to IR57 sent February 12, 2025
78	February 13, 2025	Revised USPI in response to IR 58 sent February 13, 2025

Source: FDA-generated table.
Abbreviations: AE=adverse event; CRF= Case report form; CSR=Clinical Study Report; E-diary=electronic diary; IR=information request, SAE= serious adverse event; USPI=United States Prescribing Information
Note: Only amendments relevant to the clinical review are included in the table above.

For the above listed amendments, the following modules were reviewed as applicable:

- Module 1 Administrative Information and PI
- Module 5 Clinical Study Reports

The information submitted with the initial application and listed amendments were satisfactory for the evaluation of the safety and effectiveness of MenABCWY. Salient information provided with the initial application and subsequent amendments were incorporated into this memorandum.

4. Patient Experience Data

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

To measure immunogenicity of the combined MenABCWY product, the Applicant performed a series of nonclinical studies in (b) (4) mice. In the studies, the Applicant administered vaccines of varying meningococcal serogroup B antigen compositions under varying dosing regimens. Additional supportive immunogenicity assessments were conducted in (b) (4) rabbits in conjunction with MenABCWY toxicology studies. A list of the study reports is shown below, followed by a table summarizing the studies:

- 253501-02, entitled “Immunogenicity evaluation of MenACWY (lyophilized) vaccine re-suspended with Bexsero (liquid) Vaccine”

- 270832-01, entitled "Immunogenicity evaluation of Meningococcal ACWY (lyophilized) vaccine reconstituted with either one or two doses of rMenB (liquid) tetravalent vaccine"
- 278172-01, entitled "Immunogenicity evaluation of lyophilized MenACWY vaccine reconstituted with one or two doses of rMenB or one dose of rMen + OMV or one dose of rMenB + ¼ OMV liquid vaccines"
- UBA00045, entitled "MenABCWY Vaccine: Intramuscular Local Tolerance Study in Rabbits"
- 495244, entitled "MenABCWY vaccine: Five dose intramuscular toxicity study in (b) (4) , followed by a two week recovery period"
- AB04984, MenABCWY vaccine – Intramuscular dose-range-finding developmental toxicity study in the rabbit (pilot study)"
- AB20847, entitled "MenABCWY vaccine – A 5-dose pivotal intramuscular Female Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity study"

Table 6. Nonclinical Studies, MenABCWY Vaccine

Study	Animal Model	Route of Immunization	Dosing Schedule (Days)
253501-02	Mouse	Intraperitoneal	0, 21
270832-01	Mouse	Intraperitoneal	0, 21, 35
278172-01	Mouse	Intraperitoneal	0, 21, 35
UBA00045	Rabbit	Intramuscular	0, 11
495244	Rabbit	Intramuscular	0, 14, 28, 42, 56
AB04984	Rabbit	Intramuscular	0, 14, 28, 42, 56
AB20847	Rabbit	Intramuscular	0, 14, 28, 42, 56

Source: FDA-generated table

In general, dose-ranging studies showed that immunization of animals with higher concentrations of serogroup B antigens, particularly the OMV antigen, boosted anti-serogroup B seroresponses as tested in IgG ELISAs; the Applicant did not provide data assessing the effects of different concentrations of MenACWY conjugates as tested in the same study. Administration of three versus two vaccine doses resulted in production of elevated anti- serogroup B and anti-serogroup A, C, W, and Y antibody levels in mice and rabbits. Immunization of mice with admixtures of the recombinant MenB and MenACWY vaccine components elicited lower anti-serogroup A, C, W, and Y IgG titers relative to mice immunized with the MenACWY component alone, suggesting potential immune interference. Similarly, a trend towards decreased anti-serogroups A, C, W, and Y titers was noted for female, but not male, rabbits administered the MenABCWY vaccine versus a formulation containing the MenACWY component and recombinant serogroup B antigens. In contrast, mice vaccinated with similar formulations demonstrated elevated anti-serogroup A, C, W, and Y antibody titers for those given an OMV component versus those given the recombinant serogroup B antigens alone. The root cause of the differences observed in anti-serogroup A, C, W, and Y antibody responses when animals were administered admixtures of the various serogroup B antigens is unclear but may be due in part to variation in vaccine formulations (i.e., antigen concentrations, batches, and site of manufacture).

Despite differences among total IgG levels in the immunized groups, bactericidal titers against representative serogroup B (b) (4) , NZ98/254, and H44/76) and serogroups A, C, W, and Y (b) (4), C11, 240070, and 860800) test strains were largely unaffected by serogroup B

antigen dose or the vaccine regimen administered. In a notable exception, bactericidal activity against the serogroup A, C, W, and Y strains was boosted in animals administered serogroup B antigens alone post-3rd dose versus post-2nd dose. In contrast, no bactericidal activity was observed when anti-serogroup A, C, W, and Y capsular antibodies were incubated with serogroup B test strains. These data suggest that vaccination with multiple serogroup B antigen doses enhances elicitation of cross-reactive antibodies that bind to homologous antigens expressed by the serogroup A, C, W, Y test strains.

Reviewer Comment: Although the submitted ELISA data suggest possible immune interference of recombinant serogroup B vaccine components in the elicitation of anti-serogroup A, C, W, and Y IgG seroresponses, no differences in functional antibody responses were observed. However, the results of the bactericidal assays are complicated by testing of samples with baby rabbit complement as opposed to the human complement that was used for testing of clinical samples in Phase 3 studies. Because human complement contains matrix factors that can bind meningococci and impede bactericidal activity, use of baby rabbit complement produces comparatively elevated titers that may obfuscate immunologically meaningful differences among vaccinated groups. Although the Applicant's use of baby rabbit complement precludes a direct comparison to the clinical immunogenicity results, the data from both the bactericidal assays and the ELISAs support the immunogenicity of serogroup B and serogroups A, C, W, and Y vaccine components in the combined MenABCWY product.

6. Evidence of Benefit (Assessment of Effectiveness)

6.1. Dose and Dose Responsiveness

Safety and immunogenicity data from the phase 1 and 2/2b clinical studies V102P1, V102_02, V102_02E1, V102_02E2, V102_03, V102_03E1, V102_15 and V102_15E1 supported the selection of the formulation, dose, and schedule of MenABCWY (see Section 7.6). Formulations with and without OMV and different doses of each of the antigenic components administered with different dosing schedules were evaluated. As a result of these studies, MenABCWY administered as a 2-dose series with a 6-month interval between doses was selected as the formulation and dosing schedule for evaluation in the Phase 3 study.

6.2. Clinical Studies/Trials Intended to Demonstrate Benefit

6.2.1. Study V72_72

6.2.1.1. Design, Study V72_72

Study V72_72 was a phase 3, randomized, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity, and safety of Bexsero and MenABCWY vaccines. A total of 3657 healthy adolescents and young adults 10 through 25 years of age from seven

countries were enrolled and 3651 were randomized (5:5:3:3:3:1 ratio) to one of the six parallel study groups (Table 7):

- Bexsero (0, 2, 6 months) group: participants to receive 3 doses of Bexsero at Day 1, Day 61 and Day 181 (0, 2, 6-month schedule). These participants were to receive 1 dose of Menveo vaccine at Day 211*. Data from this group was assessed at 1 month after the second Bexsero vaccination administered at Day 61 (Visit 3) and assessed at 1 month after the third Bexsero vaccination at Day 181 (Visit 5), in the same group.
- Bexsero (0, 6 months) group: participants to receive 2 doses of Bexsero at Day 1 and Day 181 and 1 dose of Menveo vaccine at Day 61 (Bexsero, 0, 6-month schedule). These participants were to receive 1 dose of placebo at Day 211*.
- MenABCWY-1**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Days 1 and 181 with Lot 1 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- MenABCWY-2**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- MenABCWY-3**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- Menveo group: participants to receive 1 dose of Menveo vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of Bexsero at Day 181 and Day 211*.

Reviewer Comment:

1. *Menveo doses and Bexsero doses were given to participants in the Bexsero groups and Menveo group, respectively, to complete the Advisory Committee on Immunization Practices (ACIP)-recommended meningococcal vaccine series. To maintain study blinding, participants in the Bexsero (0, 6 months) group and MenABCWY groups received doses of placebo. These study doses were not associated with any study objectives/ endpoints (safety assessment conducted after 1 dose of Bexsero in the Menveo group at Day 181 was to maintain the blind of the study); however, available safety data following these Bexsero and Menveo doses are described in Section 7.6
2. **(1) A Bexsero lot was used for the pre-filled syringe component of the MenABCWY vaccine; (2) The groups MenABCWY-1, MenABCWY-2, MenABCWY-3 will be pooled into a single group, MenABCWY (pooled lots) (except for analysis of lot-to-lot consistency), if lot-to-lot consistency criteria are met. The pooled group will be referred to as the MenABCWY group throughout the memo.

Table 7. Dosing Regimens, Study V72_72

Group	Dose 1 (Month 0)	Dose 2 (Month 2)	Dose 3 (Month 6)	Dose 4 (Month 7)
MenABCWY (all lots)	MenABCWY	Saline placebo	MenABCWY	Saline placebo
Bexsero (0, 2, 6m)	Bexsero	Bexsero	Bexsero	Menveo
Bexsero (0, 6m)	Bexsero	Menveo	Bexsero	Saline placebo
Menveo (control)	Menveo	Saline placebo	Bexsero	Bexsero

Source: FDA generated table adapted from STN 125819/0 Study72_72 protocol Section 5.2

The randomization algorithm used a minimization procedure accounting for region (U.S. or ex-U.S.), age category (10 through 17 years of age or 18 through 25 years of age), and previous ACWY vaccination (experienced or naïve).

Primary effectiveness and immunogenicity objectives are listed below. Only the results for MenABCWY-related objectives (*) are included and reviewed in this memo while the Bexsero-related results were reviewed under BLA 125546/1058.

- **Test-based analysis of Bexsero:** To demonstrate the effectiveness of the Bexsero vaccine against a randomly selected panel of endemic U.S. *N. meningitidis* serogroup B invasive disease strains as measured by bactericidal activity using enc-HSBA at 1 month after the 3-dose (0, 2, 6 months) and 2-dose (0, 6 months; 0, 2 months) vaccination series when compared with 1 month after Menveo vaccination.
- **Responder-based analysis of Bexsero:** To demonstrate the effectiveness of the Bexsero vaccine by assessing the percentages of participants whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the 3-dose (0, 2, 6 months) and 2-dose (0, 6 months; 0, 2 months) vaccination series of the Bexsero.
- ***Lot-to-lot consistency of MenABCWY vaccine:** To demonstrate lot-to-lot consistency of the immune responses of 3 lots of the MenACWY component of the MenABCWY vaccine, as measured by hSBA GMTs directed against serogroups A, C, W, and Y at 1 month after last vaccination (0, 6 months).
- ***Immunological non-inferiority of MenABCWY vaccine versus Menveo vaccine:** To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared with Menveo as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the last MenABCWY vaccination (0, 6 months) and 1 month after the Menveo vaccination. (This objective was evaluated only in participants without a previous MenACWY vaccination (naive)).
- ***Test-based analysis of MenABCWY (defined in Section 6.2.1.3):** To demonstrate the effectiveness of the MenABCWY vaccine against a randomly selected panel of endemic U.S. *N. meningitidis* serogroup B invasive disease strains as measured by enc-hSBA at 1 month after the last MenABCWY vaccination (0, 6 months) when compared with 1 month after the Menveo vaccination.
- ***Non-inferiority of MenABCWY vaccine versus Bexsero vaccine:** To demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine (0, 6-month schedule) compared with the Bexsero vaccine (0, 6 months)* in terms of percentage of samples with bactericidal serum activity using enc-hSBA against a randomly selected panel of endemic U.S. *N. meningitidis* serogroup B invasive disease strains.

- ***Responder-based analysis of MenABCWY:** To demonstrate the effectiveness of MenABCWY vaccine by assessing the percentages of participants whose sera kill ≥70% of strains tested using enc-hSBA at 1 month after the last vaccination of MenABCWY (0, 6 months).

Secondary objectives include:

- To demonstrate the immunological non-inferiority of the MenABCWY vaccine compared with the Bexsero vaccine as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroup B indicator strains at 1 month after the last MenABCWY vaccination (0, 6-month schedule) and 1 month after the Bexsero (0, 6-month schedule).

  **Reviewer Comment: ***The pre-defined strategy for selecting the Bexsero schedule to be used as the comparator for MenABCWY included evaluations following the second dose in the Bexsero (0, 2, 6 months) group, the second dose in the Bexsero (0, 6 months) group, and the third dose in the Bexsero (0, 2, 6 months) group. Following the traditional approval of Bexsero as either a two-dose schedule administered at 0 and 6 months or a three-dose schedule administered at 0, 1-2, 6 months, the primary and secondary analyses evaluating the non-inferiority of the meningococcal serogroup B hSBA responses following MenABCWY (0, 6 months) vaccinations were compared with those elicited following Bexsero (0, 6 months).

Blood samples were planned to be taken from all participants at specified time points (Visit 1, Visit 2, Visit 4, and Visit 6). The primary immunogenicity endpoints evaluated immunogenicity of the MenABCWY vaccine against serogroup B with the serum bactericidal assay with endogenous human complement (enc-hSBA) and serogroups A, C, W, and Y with the serum bactericidal assay using exogenous source of human complement (hSBA). For enc-hSBA, each participants' serum was tested against approximately 35 strains out of a panel of 110 Serogroup B strains. The key secondary endpoint evaluated immunogenicity of the MenABCWY vaccine against serogroup B with hSBA. Depending on the endpoint, vaccine group, and the serogroup being evaluated, primary and secondary endpoints used a random subset of immunological read-outs.

Additional design details are described in Section 15.1.

6.2.1.2. Eligibility Criteria, Study V72_72

Study V72_72 enrolled healthy individuals 10 through 25 years of age without known or suspected prior meningococcal disease, exposure to meningococcal disease, or previous meningococcal B vaccination (see section 15.1.2).

6.2.1.3. Statistical Analysis Plan, Study V72_72

The primary effectiveness analyses tested a family of hypotheses for Bexsero and MenABCWY vaccines each. The overall alpha for V72_72 is two-sided 0.05 and was split equally between the two families of hypotheses for Bexsero and MenABCWY vaccine. Within each family, the

hypotheses were tested hierarchically. That is, if the first null hypothesis was rejected, then the testing would continue with the second hypothesis at same alpha. Same for 3rd, 4th, and so forth. Whenever a null hypothesis was not rejected, then the testing would stop. Since all null hypotheses for the Bexsero vaccine were rejected (results reviewed under BLA 125546/1058), the 0.025 (two-sided) alpha was propagated to the family of hypotheses for the MenABCWY vaccine; therefore, each MenABCWY vaccine hypothesis was tested at α=0.05 (two-sided). Of the five MenABCWY primary objectives, the statistical analyses of the first four were based on the Per-Protocol Set (PPS), and the last was based on the Full Analysis Set (FAS). The key secondary objective used the PPS. The FAS consists of all participants who received at least 1 dose of the study treatment and have post-vaccination immunogenicity data. The FAS is analyzed as randomized. The PPS consists of all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the PPS.

The lot-to-lot consistency of the A, C, W, and Y components of the MenABCWY vaccine was analyzed first. GMT ratios, observed at 1 month after the last vaccination of MenABCWY for the ABCWY lot groups, and corresponding 95% confidence intervals (CIs) were calculated by exponentiating the difference of the least square means of the log transformed hSBA titers and the lower and upper limits of the 95% CIs on the difference obtained from the Analysis of Variance (ANOVA) model with terms for vaccine lot and randomization factors (i.e., region (U.S. or ex-U.S.), age category (10 through 17 years of age or 18 through 25 years of age), and previous ACWY vaccination (experienced or naive)). The null hypothesis of at least one of the pairs of lots being outside the equivalence interval would be rejected if the two-sided 95% CI for the ratio of hSBA GMTs of antibodies against each serogroup A, C, W, and Y was within the [0.5, 2.0] equivalence interval for each pair of lots.

The second immunogenicity analysis was non-inferiority of MenABCWY vaccine versus Menveo vaccine in terms of percentage of participants with 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y. The percentage of participants with 4-fold rise in hSBA titers against serogroups A, C, W, and Y and the corresponding exact two-sided 95% CIs based on Clopper-Pearson method were calculated for the MenABCWY (pooled lots) group and the Menveo group (Clopper, 1934). The 95% CIs for the difference in percentages between MenABCWY (pooled lots) and Menveo group were constructed using the method of Miettinen and Nurminen (Miettinen, 1985). This analysis was restricted to participants without previous MenACWY vaccination (naive). The null hypothesis of the group difference $\leq$ -10% would be rejected if the lower limit (LL) of the 2-sided 95% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titers was above -10% for each serogroup.

The third immunogenicity analysis (Test-based Analysis) is based on relative reduction in risk (RRR) for MenABCWY vaccine versus Menveo to evaluate serogroup B immunogenicity. RRR represents the relative reduction in risk of enc-hSBA tests without bactericidal activity against meningococcal serogroup B strains following MenABCWY vaccination as compared with Menveo, defined as 1- RR=(1- percentage of samples without bactericidal serum activity measured by enc-hSBA at a 1:4 dilution in the MenABCWY group / percentage of samples without bactericidal serum activity at 1:4 dilution in the Menveo group) x 100%. The RRR was estimated using a generalized linear model, in which vaccine group, serogroup B strains, and randomization factors were included as independent variables. A repeated statement was used to estimate the variance of the RR to account for correlation within subject's responses to different

strains (approximately 35 strain results/subject). If the lower limit of the two-sided 95% CI for RRR was > 65%, the null hypothesis of RRR ≤65% would be rejected.

> **Reviewer Comment:** The statistical analysis plan specifies, "If the statistical model does not converge due to (one of) the factor(s), a model without this/these factor(s) will be fitted instead." When the fully specified model is fit in SAS, the model does not converge. Instead, the final model used by the Applicant removes serogroup B strains as a fixed effect and contains vaccine group, randomization factors (region (U.S. or ex-U.S.), age category (10 through 17 years of age or 18 through 25 years of age), and previous MenACWY vaccination (experienced or naive) variables as independent variables.

The fourth immunogenicity analysis was non-inferiority of MenABCWY vaccine versus Bexsero vaccine in terms of risk for *N. meningitidis* serogroup B bactericidal serum activity using enc-hSBA. The 95% CIs for the difference in percentages of samples with bactericidal activity measured by enc-hSBA at 1:4 dilution between MenABCWY (pooled lots) and selected Bexsero group (fully licensed Bexsero [0, 6 months]) were constructed using the method of Miettinen and Nurminen (Miettinen, 1985). The null hypothesis of group difference ≤ -5% would be rejected if the lower limit (LL) of the 2-sided 95% CI for the group difference in percentages of samples with bactericidal serum activity at 1:4 dilution is above -5%.

The last primary immunogenicity analysis tested for the percentages of responders, defined as participants with at least 70% of the strains killed in sera using enc-hSBA, observed at 1 month after the last vaccination of MenABCWY for the MenABCWY group (pooled). The 95% confidence intervals were based on the Clopper-Pearson method. If the lower limit of the two-sided 95% CI for πB was >65%, the null hypothesis of πB ≤65% would be rejected.

> **Reviewer Comment:** A responder was defined as "a subject with at least 70% of the strains killed in sera." As a clarification, it should be noted that the condition of 70% or more strains killed refers to 70% or more of the tested strains (approximately 35 strains/subject). For example, ~25 strains need to be killed to be deemed a responder with 35 tested strains.

The key secondary endpoint analysis compared the MenABCWY vaccine with the Bexsero (0, 6 months) group using percentages of participants with 4-fold rise in hSBA titers against *N. meningitidis* serogroup B indicator strains (M14459, 96217, M13520 and NZ98/254 for fHbp, NadA, NHBA and OMV antigens, respectively). The 95% CIs for the difference in percentages between ABCWY group (pooled lots) and Bexsero (0, 6 months) group were constructed using the method of Miettinen and Nurminen. The non-inferiority criterion of each indicator strain is the LL of the 2-sided 95% CI for the difference in percentages of participants achieving a 4-fold rise in hSBA titers is above -10%. The per-protocol analysis set was used for the indicator strain analysis.

For additional analysis descriptions and details, including definitions of four-fold rise, please refer to Section 15.1.

6.2.1.4. Results of Immunogenicity Analyses, Study V72_72

Participant Disposition

A total of 3651 participants were randomized, of which 3638 participants received at least one dose of a study treatment, and 1657 participants received at least one dose of MenABCWY. Overall, 91.6% of exposed participants were included in the Full Analysis Set, and 82.3% of exposed participants were included in the Per-Protocol Analysis Set.

Table 8 summarizes subject disposition in study V72_72. Overall, 82.5%, 82.8%, 81.8%, and 83.1% of exposed participants from the Bexsero (0, 2, 6 months) group, Bexsero (0, 6 months) group, MenABCWY group, and Menveo group met criteria for the per-protocol set, respectively.

Table 8. Subject Disposition, All Enrolled Participants, Study V72_72

Disposition	Bexsero (0, 2, 6m) n (%)	Bexsero (0, 6m) n (%)	MenABCWY n (%)	Menveo n (%)	Overall n (%)
Enrolled	900	908	1666	177	3657**
Study blinding/unblinding procedures	0	0	1 (0.1)	0	1 (0.0)
Eliminated (Study treatment not administered per protocol)	3 (0.3)	1 (0.1)	8 (0.5)	0 (0)	18 (0.5)**
Withdrawal	0	0	0	0	0
Exposed	897	907	1657	177	3638
Eliminated (Missed assessment)	58 (6.5)	92 (10.1)	150 (9.1)	5 (2.8)	305 (8.4)
Withdrawal	0	0	0	0	0
Full Analysis Set*	839 (93.5)	815 (89.9)	1507 (90.9)	172 (97.2)	3333 (91.6)
Eliminations	70 (8.3)	64 (7.9)	137 (9.1)	17 (9.9)	288 (8.6)
Assessment not properly performed	0	0	2 (0.1)	0	2 (0.1)
Biological sample specimen procedures	2 (0.2)	0	1 (0.1)	0	3 (0.1)
Eligibility criteria not met	2 (0.2)	1 (0.1)	7 (0.5)	1 (0.6)	11 (0.3)
Medication, excluded by the protocol, was administered	0	1 (0.1)	0	1 (0.6)	2 (0.1)
Missed assessment	8 (1.0)	3 (0.4)	6 (0.4)	0	17 (0.5)
Missed visit/phone contact (safety calls)	4 (0.5)	2 (0.2)	5 (0.3)	0	11 (0.3)
Other	0	1 (0.1)	1 (0.1)	0	2 (0.1)
Other deviations related to wrong study treatment/administration/dose	4 (0.5)	2 (0.2)	8 (0.5)	0	14 (0.4)
Out of window treatment administration	29 (3.5)	28 (3.4)	53 (3.5)	6 (3.5)	116 (3.5)
Out of window assessment for immunogenicity	18 (2.1)	25 (3.1)	50 (3.3)	8 (4.7)	101 (3.0)
Randomization procedures	0	1 (0.1)	1 (0.1)	0	2 (0.1)
Study treatment not administered per protocol	3 (0.4)	0	2 (0.1)	1 (0.6)	6 (0.2)
Vaccine, excluded by the protocol, was administered	0	0	1 (0.1)	0	1 (0.0)
Withdrawals	29 (3.5)	0	14 (0.9)	8 (4.7)	51 (1.5)
Adverse event requiring expedited reporting	1 (0.1)	0	0	1 (0.6)	2 (0.1)
Consent withdrawal, not due to an adverse event and/or a serious adverse event	13 (1.5)	0	7 (0.5)	3 (1.7)	23 (0.7)
Lost to follow-up	11 (1.3)	0	5 (0.3)	2 (1.2)	18 (0.5)
Migrated / moved from the study area	2 (0.2)	0	1 (0.1)	1 (0.6)	4 (0.1)
Protocol deviation	1 (0.1)	0	1 (0.1)	1 (0.6)	3 (0.1)
Unsolicited non-serious adverse event	1 (0.1)	0	0	0	1 (0.0)
Per-Protocol Set*	740 (82.5)	751 (82.8)	1356 (81.8)	147 (83.1)	2994 (82.3)

Disposition	Bexsero (0, 2, 6m) n (%)	Bexsero (0, 6m) n (%)	MenABCWY n (%)	Menveo n (%)	Overall n (%)
Solicited Safety Set	890	900	1650	178[a]	3618
Unsolicited Safety Set	893	900	1648	178 [a]	3619

Source: Adapted from Table 14.1.1.1, Table 14.1.1.2, Table 14.1.1.3, and Table 14.3.1.1 of V72_72 CSR.
Notes: Bexsero (0, 2, 6m) Group: participants received 3 doses of Bexsero at 0, 2, and 6 months; Bexsero (0, 6m) Group: participants received 2 doses of Bexsero at 0 and 6 months with Menveo at month 2; ABCWY Group: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; Menveo group: participants received 1 dose of Menveo at month 0, placebo at month 2, and 1 dose of Bexsero at Month 6.
n: number of participants fulfilling criteria in the first column.
*: percent with exposed participants as the denominator.
**: includes 6 participants who were not randomized.
Solicited Safety Set: No solicited safety follow up was captured for 7, 6, 7, and 0 participants in the Bexsero (0, 2, 6m), Bexsero (0, 6m), ABCWY, and Menveo groups, respectively.
Unsolicited Safety Set: No unsolicited safety follow up was captured for 4, 6, 9, and 0 participants in the Bexsero (0, 2, 6m), Bexsero (0, 6m), ABCWY, and Menveo groups, respectively.
a. One subject in the Bexsero (0, 6m) group received Menveo at Visit 1 and is analyzed as part of the Menveo group for the safety set.

Baseline Demographics

Baseline demographic information for the Exposed Set is presented in Table 9. Overall, 53% of participants were female; median age was 16 years; 89% were White; and 5% identified as Hispanic or Latino. The distributions of baseline demographic characteristics appear similar across treatment groups in the Exposed Set. The demographic characteristics of the Enrolled Set, Full Analysis Set, and Per-Protocol Set were similar to the Exposed Set.

Table 9. Demographic and Baseline Characteristics, Exposed Set, Study V72_72

Characteristic	Bexsero (0, 2, 6m) n (%) N=897	Bexsero (0, 6m) n (%) N=906	MenABCWY n (%) N=1657	Menveo n (%) N=178[a]	Overall n (%) N=3638
Age (in years) at first vaccination	-	-	-	-	-
Mean (standard deviation)	16.5 (4.7)	16.5 (4.7)	16.5 (4.7)	16.9 (4.6)	16.5 (4.7)
Median (minimum, maximum)	16.0 (10, 26)	16.0 (9, 26)	16.0 (9, 26)	16.0 (10, 25)	16.0 (9, 26)
Age subgroups at randomization	-	-	-	-	-
≥10 to <18 years	533 (59.4)	541 (59.7)	986 (59.5)	103 (57.9)	2163 (59.5)
≥18 to <26 years	364 (40.6)	365 (40.3)	671 (40.5)	75 (42.1)	1475 (40.5)
Sex	-	-	-	-	-
Male	433 (48.3)	460 (50.8)	724 (43.7)	78 (43.8)	1695 (46.6)
Female	464 (51.7)	446 (49.2)	933 (56.3)	100 (56.2)	1943 (53.4)
Race	-	-	-	-	-
White	796 (88.7)	791 (87.3)	1492 (90.0)	162 (91.0)	3241 (89.1)
Asian	43 (4.8)	60 (6.6)	71 (4.3)	9 (5.1)	183 (5.0)
Black or African American	33 (3.7)	29 (3.2)	59 (3.6)	6 (3.4)	127 (3.5)
American Indian or Alaska Native	5 (0.6)	5 (0.6)	3 (0.2)	0 (0.0)	13 (0.4)
Native Hawaiian or Other Pacific Islander	3 (0.3)	1 (0.1)	3 (0.2)	0 (0.0)	7 (0.2)
Other	17 (1.9)	20 (2.2)	29 (1.8)	1 (0.6)	67 (1.8)
Ethnic origin	-	-	-	-	-
Hispanic or Latino	54 (6.0)	41 (4.5)	92 (5.6)	6 (3.4)	193 (5.3)
Not Hispanic or Latino	840 (93.6)	852 (94.0)	1546 (93.3)	172 (96.6)	3410 (93.7)
Not reported	3 (0.3)	13 (1.4)	19 (1.1)	0 (0.0)	35 (1.0)
Region	-	-	-	-	-
United States	272 (30.3)	270 (29.8)	491 (29.6)	52 (29.2)	1085 (29.8)
Ex-U.S.	625 (69.7)	636 (70.2)	1166 (70.4)	126 (70.8)	2553 (70.2)
Country	-	-	-	-	-
Australia	72 (8.0)	66 (7.3)	146 (8.8)	11 (6.2)	295 (8.1)
Canada	51 (5.7)	63 (7.0)	108 (6.5)	7 (3.9)	229 (6.3)
Czech Republic	179 (20.0)	189 (20.9)	344 (20.8)	38 (21.3)	750 (20.6)
Estonia	28 (3.1)	40 (4.4)	54 (3.3)	5 (2.8)	127 (3.5)
Finland	214 (23.9)	191 (21.1)	365 (22.0)	49 (27.5)	819 (22.5)
Turkey	81 (9.0)	87 (9.6)	149 (9.0)	16 (9.0)	333 (9.2)
United States	272 (30.3)	270 (29.8)	491 (29.6)	52 (29.2)	1085 (29.8)

Characteristic	Bexsero (0, 2, 6m) n (%) N=897	Bexsero (0, 6m) n (%) N=906	MenABCWY n (%) N=1657	Menveo n (%) N=178[a]	Overall n (%) N=3638
Height (in cm)	--	--	--	--	--
Mean (standard deviation)	164.7 (13.3)	164.4 (13.4)	164.6 (13.0)	165.7 (11.3)	164.6 (13.1)
Median (minimum, maximum)	165.1 (115, 202)	165.0 (117, 201)	165.1 (117, 198)	166.0 (138, 200)	165.0 (115, 202)
Weight (in kg)	897	906	1656	178	3637
Mean (standard deviation)	63.8 (20.4)	63.3 (20.6)	63.2 (20.2)	62.5 (18.9)	63.3 (20.3)
Median (minimum, maximum)	62.2 (25, 167)	61.1 (22, 150)	61.0 (26, 218)	59.9 (29, 134)	61.1 (22, 218)
BMI (in kg/m^2)	897	906	1656	178	3637
Mean (standard deviation)	23.1 (5.7)	23.0 (5.7)	23.0 (5.6)	22.4 (5.3)	23.0 (5.7)
Median (minimum, maximum)	21.9 (12, 52)	21.9 (13, 56)	22.0 (13, 67)	21.1 (14, 43)	21.9 (12, 67)
Baseline ACWY vaccination	--	--	--	--	--
Yes	122 (13.6)	119 (13.1)	215 (13.0)	22 (12.4)	478 (13.1)

Source: Adapted from Table 14.1.3.2 of the V72_72 CSR.
Bexsero (0, 2, 6m) Group: participants received 3 doses of Bexsero (at 0, 2, and 6 months); Bexsero (0, 6m) Group: participants received 2 doses of Bexsero (at 0 and 6 months) with Menveo (at 2 months); ABCWY Group: participants received 2 doses of MenABCWY vaccine (0, 6m) and 1 dose of placebo (2m); Menveo group: participants received 1 dose of Menveo (0m), placebo (2m), and 1 dose of Bexsero (6m).
[a]One subject in the Bexsero (0, 6m) group received Menveo at Visit 1 and is analyzed as part of the Menveo group for the exposed set.

Reviewer Comment:

1. Reported ages are based on an imputed birthday of day 15 of the participant birth month. This resulted in a calculated age less than age 10 years or greater than 25 years of age for certain participants.

2. There were no notable imbalances in the demographics between study groups that would impact interpretation of study results.

Primary Immunogenicity/Effectiveness Objectives

Lot-to-lot consistency of MenABCWY vaccine – ACWY component

Table 10 contains the results for the lot-to-lot consistency analysis. For each of the three lots of MenABCWY vaccine, geometric mean titers from 1 month after 2 doses and their corresponding 95% confidence intervals are presented for serogroups A, C, W, and Y. Geometric mean ratios (GMRs) for each pair of lots (i.e. Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) and their corresponding 95% confidence intervals are also presented.

Each of the three 95% CIs for pairwise GMRs of the four serogroups (i.e., 12 CIs total) was contained in the interval [0.5, 2.0], meeting the lot-to-lot consistency criteria.

Table 10. Lot to Lot Consistency Analysis of MenABCWY, Geometric Mean Titers (GMT) and GMT Ratios (GMRs) for Serogroups A, C, W, and Y, Per-Protocol Set, Study V72_72

Serogroup	MenABCWY Lot 1 N=	MenABCWY Lot 1 GMT (95% CI)	MenABCWY Lot 2 N=	MenABCWY Lot 2 GMT (95% CI)	MenABCWY Lot 3 N=	MenABCWY Lot 3 GMT (95% CI)	MenABCWY Lot 1/ MenABCWY Lot 2 GMR (95% CI)	MenABCWY Lot 1/ MenABCWY Lot 3 GMR (95% CI)	MenABCWY Lot 2/ MenABCWY Lot 3 GMR (95% CI)
A	448	341.0 (303.1, 383.7)	443	353.9 (314.6, 398.0)	454	395.8 (351.7, 445.4)	0.96 (0.84, 1.10)	0.86 (0.75, 0.98)	0.89 (0.78, 1.02)
C	448	1036.8 (877.7, 1224.7)	449	1130.7 (958.4, 1334.0)	456	888.4 (752.1, 1049.3)	0.92 (0.76, 1.11)	1.17 (0.97, 1.41)	1.27 (1.05, 1.54)
W	452	564.5 (497.9, 639.9)	449	635.5 (561.0, 719.9)	458	640.1 (564.6, 725.6)	0.89 (0.77, 1.02)	0.88 (0.77, 1.02)	0.99 (0.86, 1.14)
Y	451	536.7 (464.5, 620.2)	449	623.9 (540.4, 720.2)	457	644.3 (557.6, 744.6)	0.86 (0.73, 1.01)	0.83 (0.71, 0.98)	0.97 (0.82, 1.14)

Source: Adapted from Table 14.2.2.7 Submitted to Amendment 3 of BLA 125819/0.
Notes: MenABCWY Lot 1: Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 with Lot 1 of the MenACWY component of the vaccine;
MenABCWY Lot 2: Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 with Lot 2 of the MenACWY component of the vaccine; and,
MenABCWY Lot 3: Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 with Lot 3 of the MenACWY component of the vaccine.
N: number of participants with hSBA immunogenicity data.
GMT (95% CI*): Geometric mean titer and 95% confidence interval obtained by exponentiating the least squares means and the lower and upper limits of the 95% CI of the log transformed titers from an Analysis of Variance with factors for vaccine lot and randomization factors (i.e. region [U.S./ex-U.S.], age category [10-17 years of age/18-25 years of age], previous MenACWY vaccination [yes/no]).
GMR (95% CI**): Geometric mean ratio and 95% confidence interval obtained by exponentiating difference of the least squares means and the lower and upper limits of the 95% CI of the difference of the means from an Analysis of Variance on log transformed titers with factors for vaccine lot and randomization factors (i.e. region [U.S./ex-U.S.], age category [10-17 years of age/18-25 years of age], previous MenACWY vaccination [yes/no]).
Indicator strains: Serogroup A (3125); Serogroup C (C11); Serogroup W (240070); Serogroup Y (860800)

Non-inferiority Analyses (MenABCWY versus Menveo) of percentage of participants with 4-fold rise in hSBA titers against N. meningitidis serogroups A, C, W and Y

Table 11 summarizes the proportions of ACWY-naïve participants whose hSBA titers increased ≥4-fold from baseline to 1 month after 2 doses of MenABCWY (0, 6-month ABCWY vaccine schedule) or 1 month after a single dose of Menveo (ACWY vaccine schedule). Group differences in overall proportions of participants achieving a 4-fold rise in hSBA titers are also presented. All 4 serogroups A, C, W, and Y met the criterion to establish non-inferiority of the immune responses to each regimen. The lower limits of the two-sided 95% confidence intervals for the overall differences were above the threshold of -10% at 5.79%, 38.14%, 26.88%, and 19.38% for A, C, W, and Y, respectively.

Table 11. Proportions and Percent Difference of ACWY-Naïve Participants Achieving ≥4-Fold Rise in hSBA Titer 1 Month After Two Doses of ABCWY or a Single Dose of ACWY for A, C, W, and Y Serogroups, Per Protocol Set, Study V72_72

Serogroup	MenABCWY n/N (%) (95% CI)	Menveo n/N (%) (95% CI)	MenABCWY-Menveo % Difference (95% CI)
A	1133/1170 (96.8) (95.7, 97.8)	95/111 (85.6) (77.6, 91.5)	11.25 (5.79, 19.03)
C	1156/1189 (97.2) (96.1, 98.1)	57/114 (50.0) (40.5, 59.5)	47.22 (38.14, 56.30)
W	1150/1185 (97.0) (95.9, 97.9)	71/115 (61.7) (52.2, 70.6)	35.31 (26.88, 44.49)
Y	1157/1196 (96.7) (95.6, 97.7)	83/119 (69.7) (60.7, 77.8)	26.99 (19.38, 35.81)

Source: Adapted from Table 14.2.2.8 Submitted to Amendment 3 of BLA 125819/0. n: number of participants meeting 4-fold rise definition N: number of participants with immunogenicity data at baseline and post-vaccination in the per-protocol set
Notes: ABCWY: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY.
Menveo: participants received 1 dose of Menveo at Month 0, 1 dose of placebo at Month 2, and 1 dose of Bexsero at Month 6 with serum taken 1 month after the single dose of Menveo.
Four-fold rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a prevaccination hSBA titer ≥LOD and <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall results include participants meeting any 1 of the 3 definitions.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=5 for MenA (3125), 4 for MenC (C11), MenW (240070), and MenY (860800). LLOQ=12 for MenA (3125); 8 for MenC (C11); 8 for MenW (240070); 10 for MenY (860800).

> **Reviewer Comment:** The hSBA responses, including those elicited against the serogroup C, W, and Y indicator strains appear higher following MenABCWY (0, 6 months) compared with the hSBA responses following a single dose of Menveo.

Test-based analysis of MenABCWY for Serogroup B using Relative Reduction in Risk

Table 12 shows the results of the test-based RRR analysis using the enc-hSBA for MenABCWY for serogroup B.

Table 12. Test-Based Analysis of enc-hSBA Activity Against Serogroup B Following Vaccination With MenABCWY or Menveo, Per Protocol Set, Study V72_72

Treatment Group	Series Dose	Tested Schedule	# of Participants with Tested Serum (N_p)	% of enc-hSBA Tests Without Bactericidal Serum Activity % (n/N1)*	Reduction in Risk of a Test Without Bactericidal Serum Activity† % (95% CI)
MenABCWY	MenABCWY Dose 2	MenABCWY 0, 6m	754	17.4 (4493/25715)	77.9 (76.6, 79.2)
Menveo	Menveo Dose 1	Control	133	79.0 (3456/4374)	--

Source: Adapted from Table 14.2.2.9 of V72_72 Clinical Study Report.
Notes: Enc-hSBA: endogenous complement human serum bactericidal assay.
Blood samples taken 1 month after dose.
MenABCWY Group: participants received 1 dose of MenABCWY vaccine at Day 1, 1 dose of placebo at Day 61, 1 dose of MenABCWY vaccine at Day 181, and 1 dose of placebo at Day 211. Lots were pooled.
Menveo group: participants received 1 dose of Menveo at Day 1, 1 dose of placebo at Day 61 and 2 doses of Bexsero at Day 181 and Day 211.
n: number of endogenous hSBA tests without bactericidal serum activity.
N_p: number of participants from the per-protocol analysis set.
N1: number of endogenous hSBA samples tested.
*: Estimate from model least-square means.
†: reduction in risk relative to Menveo.
95% CI: 95% two-sided confidence interval.
Reduction in risk: Defined as 1 - risk ratio=(1- percentage of samples without bactericidal serum activity measured by enc-hSBA in the MenACBWY group / percentage of samples without bactericidal serum activity in the Menveo group) x 100%. The risk ratio and corresponding confidence intervals are estimated using a generalized linear model where treatment group, randomization factors (region (U.S. or ex-U.S.), age category (10-17 years of age or 18-25 years of age), and previous ACWY vaccination (experienced or naive)) were modeled as fixed effects. A repeated statement was used to estimate the variance of the RR including correlation within subject's responses to different strains (approximately 35 strain results/subject).

As shown in Table 12, the lower limit of the two-sided 95% confidence interval of Reduction in Risk of a Test without Bactericidal Serum Activity for MenABCWY compared with Menveo was above the threshold of 65% at 76.6%, meeting the success criterion.

Reviewer Comment:

1. Given that the immunogenicity samples were tested on a random subset, an analysis of demographic data was conducted by the statistical reviewer. In general, the distribution of demographic characteristics was similar in the subset as compared to the FAS. In addition, at baseline the A, C, W, and Y hSBA GMTs between the B subset and the subset not chosen for B analysis were similar.

2. Since a subset of approximately 35 randomly selected strains were tested for each subject (out of 110 strains) for the primary endpoints, the statistical reviewer examined the distributions of tested strains. Strains with high levels of killing in the ABCWY groups did not appear to be disproportionately tested among the Menveo group. It appears that the strains selected for each subject are reasonably random as described in the statistical analysis plan (SAP).

Test-based non-inferiority of MenABCWY vaccine versus Bexsero vaccine in terms of risk differences for N. meningitidis serogroup B bactericidal serum activity

Table 13 shows the results of the test-based non-inferiority analysis using the enc-hSBA for the 0, 6-month MenABCWY vaccine compared with the 0, 6-month Bexsero vaccine.

Table 13. Test-Based Non-Inferiority of MenABCWY Vaccine Versus Bexsero Vaccine in Terms of Risk Differences for *N. meningitidis* Serogroup B Bactericidal Serum Activity Using enc-hSBA Activity Against Serogroup B Following Vaccination, Per Protocol Set, Study V72_72

Treatment Group	Series Dose	Tested Schedule	# of Participants with Tested Serum (N_p)	Number of enc-hSBA Tests with Bactericidal Serum Activity n/N1	% of enc-hSBA Tests with Bactericidal Serum Activity % (95% CI)	Diff % (95% CI)
MenABCWY	Dose 2	MenABCWY 0, 6m	754	21222/25715	82.5 (82.1, 83.0)	-3.02 (-3.65, -2.39)
Bexsero (0, 6m)	Dose 2	Bexsero 0, 6m	799	22365/26142	85.6 (85.1, 86.0)	--

Source: Adapted from Table 14.2.2.10.9 of V72_72 Clinical Study Report.
Notes: Enc-hSBA: endogenous complement human serum bactericidal assay.
Blood samples taken 1 month after dose.
MenABCWY Group: participants received 1 dose of MenABCWY vaccine at Day 1, 1 dose of placebo at Day 61, 1 dose of MenABCWY vaccine at Day 181, and 1 dose of placebo at Day 211. Lots were pooled.
Bexsero Group: participants received 2 doses of Bexsero at Day 1 and Day 181 and 1 dose of Menveo at Day 61 (Bexsero, 0, 6m schedule). These participants received 1 dose of placebo at Day 211.
N_p: number of participants from the per-protocol analysis set.
n: number of endogenous hSBA tests with bactericidal serum activity.
N1: number of endogenous hSBA samples tested.
95% CI: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.

Reviewer Comment: Results of this analysis met the pre-specified statistical criterion and support the effectiveness of MenABCWY against a broad panel of clinically relevant serogroup B strains.

Responder-based analysis of enc-hSBA activity against serogroup B following vaccination with MenABCWY

Table 14 shows the results of the responder-based analysis using the enc-hSBA for MenABCWY.

Table 14. Responder-Based Analysis of enc-hSBA Activity Against Serogroup B Following Vaccination With MenABCWY, Full Analysis Set, Study V72_72

Treatment Group	Series Dose	Tested Schedule	# of Responders (n_f)	# of Participants with Tested Serum (N_f)	% Responders (95% CI)
MenABCWY	MenABCWY Dose 2	MenABCWY 0, 6m	687	817	84.1 (81.4, 86.5)

Source: Adapted from 14.2.2.11 of V72_72 Clinical Study Report.
Notes: Enc-hSBA: endogenous complement human serum bactericidal assay.
Blood samples taken 1 month after dose.
MenABCWY Group: participants received 1 dose of MenABCWY vaccine at Day 1, 1 dose of placebo at Day 61, 1 dose of MenABCWY vaccine at Day 181, and 1 dose of placebo at Day 211. Lots were pooled.
n_f: number of participants whose sera kill ≥70% of the strains tested using enc-hSBA.
N_f: number of participants from the full analysis set.
% Responders: percentages of participants whose sera kill ≥70% of the strains tested using enc-hSBA.
95% CI: 95% two-sided confidence interval. 95% CI is calculated using the Clopper-Pearson method.
Reject null hypothesis if lower limit of the 95% CI is > 65%.

The percentage of responders, defined as participants whose sera killed ≥70% of the strains tested using enc-hSBA at 1 month after the second dose of MenABCWY, was 84.1%. The lower limit of the two-sided 95% confidence interval for MenABCWY was above the threshold of 65% at 81.4%, meeting the success criterion.

Key Secondary Immunogenicity/Effectiveness Objectives

Immune Response Against N. meningitidis Serogroup B Indicator Strains Using Exogenous hSBA Testing

Table 15 summarizes the proportions of participants whose hSBA titers increased ≥4-fold from baseline to 1 month after 2 doses of Bexsero (0, 6-month schedule) or 1 month after 2 doses of MenABCWY (0, 6-month schedule). Group differences in overall proportions of participants achieving a 4-fold rise in hSBA titers and 95% CIs are also presented with pre-specified statistical non-inferiority criteria. Two of the 4 test strains (i.e., fHBP and NadA) met the non-inferiority criterion to compare the immunogenicity results between the two vaccines while the other 2 test strains (i.e. NHBA and OMV) did not. The lower limits of the two-sided 95% confidence intervals for the overall differences were above the threshold of -10% at -9.55% and -5.76% for fHBP and NadA, respectively. The lower limits of the two-sided 95% confidence intervals for the overall differences were below the threshold of -10% at -12.9% and -21.5% for NHBA and OMV, respectively.

Table 15. Proportions of Participants Achieving ≥4-Fold Rise in hSBA Titer 1 Month After Two Doses of MenABCWY or Two Doses of Bexsero for Serogroup B Indicator Strains, Per Protocol Set, Study V72_72

Antigen	MenABCWY n/N (%) (95% CI)	Bexsero n/N (%) (95% CI)	MenABCWY-Bexsero % Difference (95% CI)
fHbp	494/675 (73.2) (69.7, 76.5)	511/654 (78.1) (72.8, 81.2)	-4.95 (-9.55, -0.33)
NadA	622/671 (92.7) (90.5, 94.5)	628/655 (95.9) (94.1, 97.3)	-3.18 (-5.76, -0.69)
NHBA	419/678 (61.8) (58.0, 65.5)	459/659 (69.7) (66.0, 73.1)	-7.85 (-12.90, -2.76)
OMV	271/642 (42.2) (38.4, 46.1)	364/624 (58.3) (54.4, 62.2)	-16.12 (-21.50, -10.64)

Source: Adapted from Table 1 Submitted to Amendment 30 of BLA 125819/0.
Notes: MenABCWY: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY as post-vaccination.
Bexsero: participants received 2 doses of Bexsero at Months 0 and 6 and 1 dose of Menveo at Month 2 with serum taken 1 month after the second dose of Bexsero as post-vaccination.
n: number of participants meeting 4-fold rise definition N: number of participants with immunogenicity data at baseline and post-vaccination in the per-protocol set; fHbp=factor H binding protein, NadA=neisserial adhesin A, OMV=outer membrane vesicle, NHBA=neisserial heparin-binding antigen.
Rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a prevaccination hSBA titer ≥LOD and <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall results include participants meeting any 1 of the 3 definitions.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=4 for fHbp (M14459); 6 for NadA (96217); 4 for OMV (NZ98/254); 4 for NHBA (M13520). LLOQ=5 for fHbp (M14459); 14 for NadA (96217); 6 for OMV (NZ98/254); 6 for NHBA (M13520).

Reviewer Comment:

The statistical reviewer verified analysis results of primary endpoints and secondary endpoints presented above in Tables Table 10, Table 11, Table 12, Table 13, Table 14, and Table 15 based on the SDTM datasets submitted to BLA 125819 Amendment 3. Amendment 3 provided updated seroresponse results based on the FDA agreed upon i) limit of detection (LOD) for the serogroup A assay of 5 (compared with originally submitted files using an LOD of 4) and ii) LODs and LLOQs for Serogroup B antigen assays.

Additional analyses relevant to the review are included in Section 16.

6.2.2. Study 019

6.2.2.1. Design, Study 019

Study 019 was a phase 3, randomized, controlled, observer-blind, multi-center study to evaluate safety and immunogenicity of the MenABCWY vaccine when administered in healthy adolescents and young adults previously vaccinated with a dose of MenACWY conjugate vaccine at least 4 years prior to study enrollment. A total of 1250 healthy adolescents and young

adults 15 through 25 years of age in four countries were enrolled and randomized (1:1 ratio) to one of the two parallel study groups:

- ABCWY group: participants to receive 2 doses of MenABCWY vaccine 6 months apart at Visit 1 (Day 1) and Visit 3 (Day 181) (0, 6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
- Menveo group: participants to receive 1 dose of Menveo at Visit 1 (Day 1) (single dose) and 2 doses of Bexsero at Visit 3 (Day 181) and Visit 4 (Day 211).

The randomization algorithm used a minimization procedure accounting for country (Argentina, Australia, Canada, and the U.S.). Eligible participants must have received a previous vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY; *Menveo* or *Menactra*) at least 4 years prior to study start.

The co-primary immunogenicity objectives are listed below.

- **Immunological non-inferiority of MenABCWY versus MenACWY for Serogroups A, C, W, and Y (Family 1: Post-Dose 2):** To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared with Menveo given to healthy participants, previously vaccinated with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the second MenABCWY vaccination (0 ,6 months) and 1 month after the MenACWY vaccination (single dose).
- **Immunological non-inferiority of MenABCWY versus MenACWY for Serogroups A, C, W, and Y (Family 2: Post-Dose 1):** To demonstrate the immunological non-inferiority of the MenABCWY vaccine, compared with Menveo given to healthy participants, previously vaccinated with a MenACWY vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the *first* MenABCWY vaccination (0, 6 months) and 1 month after the MenACWY vaccination (single dose).

Table 16. Dosing Regimens in Study 019

Group	Month 0	Month 6	Month 7
MenABCWY	MenABCWY	MenABCWY	Saline placebo
Menveo (control group)	Menveo	Bexsero	Bexsero

Source: FDA generated table adapted from STN 125819/0 Study MenABCWY-019 Section 5.2.

Blood samples were planned to be taken from all participants at specified time points (Visit 1, Visit 2, and Visit 4). The co-primary immunogenicity endpoints evaluated immunogenicity of the MenABCWY vaccine against serogroups A, C, W, and Y with the serum bactericidal assay using exogenous source of human complement (hSBA). The first co-primary immunogenicity endpoint used a random subset of immunological read-outs.

Additional design details are described in Section 15.2.

6.2.2.2. Eligibility Criteria, Study 019

Study 019 enrolled healthy individuals 15 through 25 years of age with history of vaccination with 1 dose of MenACWY vaccine (Menveo or Menactra) at the age of 10 years or older and at

least 4 years prior to study enrollment and who did not have history of known or suspected meningococcal disease (see section 15.2.2).

6.2.2.3. Statistical Analysis Plan, Study 019

Primary immunogenicity hypotheses were ranked into two families, family 1 (post-dose 2 of MenABCWY vaccine) and family 2 (post-dose 1 of MenABCWY vaccine). Fixed sequential testing with full alpha propagation in these pre-ordered hypothesis families was applied. Family 1 was tested first and family 2 was only tested if the null hypothesis in family 1 was rejected. Both analyses were based on the per-protocol analysis set (PPS), defined as all participants who received at least 1 dose of the study intervention to which they were randomized and had post-vaccination data minus participants with protocol deviations that led to exclusion from the PPS, as defined prior to analysis.

The first immunogenicity analysis evaluated non-inferiority of MenABCWY vaccine versus Menveo in terms of percentage of participants with 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W and Y. The 95% confidence intervals (CIs) for the difference in percentage of participants with 4-fold rise in hSBA titers against serogroups A, C, W, and Y between the ABCWY group [1 month after the second vaccination of MenABCWY (Day 211, Month 7) relative to baseline (Day 1, Month 0)] and Menveo group [1 month after the single vaccination (Day 31, Month 1) of MenACWY relative to baseline (Day 1, Month 0)] were constructed using the method of Miettinen and Nurminen (Miettinen, 1985). The null hypothesis of the group difference ≤ -10% would be rejected if the lower limit (LL) of the 2-sided 95% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titers was above -10% for each serogroup A, C, W, and Y.

The second immunogenicity analysis evaluated non-inferiority of MenABCWY vaccine versus Menveo in terms of percentage of participants with a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y. The 95% CIs for the difference in percentage of participants with a 4-fold rise in hSBA titers against serogroups A, C, W, and Y between the ABCWY group [1 month after the first vaccination of MenABCWY (Day 31, Month 1) relative to baseline (Day 1, Month 0)] and Menveo group [1 month after the single vaccination (Day 31, Month 1) of MenACWY relative to baseline (Day 1, Month 0)] were constructed using the method of Miettinen and Nurminen (Miettinen, 1985). The null hypothesis of the group difference ≤-10% would be rejected if the lower limit (LL) of the 2-sided 95% CI for the group difference in percentages of participants achieving a 4-fold rise in hSBA titers was above -10% for each serogroup A, C, W, and Y.

For additional analysis descriptions, please refer to Section 15.2.

6.2.2.4. Results of Analyses, Study 019

Participant Disposition

A total of 1250 participants were randomized, of which 1247 participants received at least one dose of a study treatment, and 626 participants received at least one dose of MenABCWY, with

97.9% of randomized participants (and of exposed participants) included in the Full Analysis Set.

Table 17 summarizes subject disposition in Study 019. Criteria for the per-protocol set at Visit 2 were met by 92.2% and 89.0% of exposed participants from the ABCWY group and Menveo group, respectively. All 626 participants in the ABCWY group were included in the Solicited Safety Set for the MenABCWY-related safety analyses.

Table 17. Disposition of All Enrolled Participants by Treatment Group, Study019

Disposition	MenABCWY n (%)	Menveo n (%)	Overall n (%)
Enrolled	626	624	1250
Did not receive at least one dose of study intervention	0	3 (0.5)	3 (0.2)
Exposed	626 (100)	621 (99.5)	1247 (99.8)
Did not have post-vaccination immunogenicity data	13 (2.1)	26 (4.2)	39 (3.1)
Did not receive at least one dose of study intervention	0	3 (0.5)	3 (0.2)
Full Analysis Set*	613 (97.9)	595 (95.8)	1208 (96.9)
Per-Protocol Set at Visit 2*	577 (92.2)	553 (89.0)	1130 (90.4)
Per-Protocol Set at Visit 4*	275 (43.9)	-	275 (22.0)
Solicited Safety Set	626	621	1247
Unsolicited Safety Set	626	621	1247

Source: Adapted from Table 14.1.1.1 and Table 14.1.1.2 of MenABCWY-019 CSR submitted to BLA 125819/0 and Amendment 3.
Notes: ABCWY Group: 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0, 6m schedule) and 1 dose of placebo at Visit 4 (Day 211); Menveo group: 1 dose of Menveo at Visit 1 (Day 1) (single dose) and 2 doses of Bexsero at Visit 3 (Day 181) and Visit 4 (Day 211).
n: number of participants fulfilling criteria in the first column
*: percent with exposed participants as the denominator

Baseline Demographics

Baseline demographic information for the Exposed Set is presented in Table 18. Overall, 53% of participants were female; median age was 16 years; 75% were white; and 30% identified as Hispanic or Latino. The distributions of baseline demographic characteristics appear similar across treatment groups in the Exposed Set. The demographic characteristics of the Enrolled Set, Full Analysis Set, and Per-Protocol Set were similar to the Exposed Set.

Table 18. Demographic and Baseline Characteristics, Exposed Set, Study 019

Demographic and Baseline Characteristics	MenABCWY N=626 n (%)	Menveo N=621 n (%)	Overall N=1247 n (%)
Age (in years) at first vaccination	--	--	--
Mean (standard deviation)	17.2 (2.5)	17.2 (2.6)	17.2 (2.6)
Median (minimum, maximum)	16 (15, 25)	16 (15, 25)	16 (15, 25)
Age subgroups at randomization	--	--	--
≥15 to <18 years	450 (71.9)	441 (71.0)	891 (71.5)
≥18 to <26 years	176 (28.1)	180 (29.0)	356 (28.5)
Sex	--	--	--
Male	283 (45.2)	297 (47.8)	580 (46.5)
Female	343 (54.8)	324 (52.2)	667 (53.5)
Race	--	--	--
White	474 (75.7)	464 (74.7)	938 (75.2)

Demographic and Baseline Characteristics	MenABCWY N=626 n (%)	Menveo N=621 n (%)	Overall N=1247 n (%)
Asian	22 (3.5)	33 (5.3)	55 (4.4)
Black or African American	94 (15.0)	86 (13.8)	180 (14.4)
American Indian or Alaska Native	1 (0.2)	1 (0.2)	2 (0.2)
Native Hawaiian or Other Pacific Islander	2 (0.3)	6 (1.0)	8 (0.6)
Other	33 (5.3)	31 (5.0)	64 (5.1)
Ethnicity	--	--	--
Hispanic or Latino	179 (28.6)	192 (30.9)	371 (29.8)
Not Hispanic or Latino	447 (71.4)	429 (69.1)	876 (70.2)
Region	--	--	--
United States	366 (58.5)	363 (58.5)	729 (58.5)
Non-U.S.	260 (41.5)	258 (41.5)	518 (41.5)
Country	--	--	--
Argentina	116 (18.5)	116 (18.7)	232 (18.6)
Australia	119 (19.0)	118 (19.0)	237 (19.0)
Canada	25 (4.0)	24 (3.9)	49 (3.9)
United States	366 (58.5)	363 (58.5)	729 (58.5)
Height (in cm)	--	--	--
Mean (standard deviation)	168.6 (9.8)	169.3 (9.4)	169 (9.6)
Median (minimum, maximum)	167.9 (145, 204)	169 (143, 196)	168.3 (143, 204)
Weight (in kg)	--	--	--
Mean (standard deviation)	71.6 (20.2)	71.8	71.7
Median (minimum, maximum)	67.1 (40, 159)	67 (41, 201)	67 (40, 201)
BMI (in kg/m^2)	--	--	--
Mean (standard deviation)	25.1 (6.3)	25 (6.5)	25.1 (6.4)
Median (minimum, maximum)	23.4 (15.1, 52.6)	23.5 (16.9, 63.5)	23.5 (14.9, 63.5)

Source: Adapted from Table 14.1.3.2 of the MenABCWY-019 CSR.
Notes: ABCWY Group: 2 doses of the MenABCWY vaccine at Visit 1 (Day 1) and Visit 3 (Day 181) (0, 6m schedule) and 1 dose of placebo at Visit 4 (Day 211); Menveo group: 1 dose of Menveo at Visit 1 (Day 1) (single dose) and 2 doses of Bexsero at Visit 3 (Day 181) and Visit 4 (Day 211).
Abbreviations: n: number of participants fulfilling criteria in the first column; N: number of enrolled participants; cm: centimeters; kg= kilogram; m= meter; BMI: body mass index

Reviewer Comment: There were no notable imbalances in the demographics between study groups that would impact interpretation of study results.

Primary Immunogenicity/Effectiveness Objectives

Immunological non-Inferiority of MenABCWY versus MenACWY for Serogroups A, C, W, and Y (Family 1: Post-Dose 2)

Table 19 summarizes the proportions of participants whose hSBA titers increased ≥4-fold from baseline to 1 month after 2 doses of MenABCWY at months 0 and 6 (ABCWY Family 1) or 1 month after 1 dose of MenACWY (ACWY). Group differences in overall proportions of participants achieving a 4-fold rise in hSBA titers and 95% CIs are also presented. All 4 serogroups A, C, W, and Y met the criterion to establish non-inferiority of the immune responses for the MenABCWY vaccine (after 2 doses of MenABCWY) versus the Menveo (after a single dose of MenACWY) in ACWY-experienced participants. The lower limits of the two-sided 95% confidence intervals for the overall difference were above the threshold of -10% at -3.82%, -4.14%, -2.73%, and -3.93% for serogroups A, C, W, and Y, respectively.

Table 19. Proportions of ACWY-Experienced Participants Achieving ≥4-Fold Rise in hSBA Titer 1 Month After Two Doses of MenABCWY or a Single Dose of MenACWY for A, C, W, and Y Strains, Per Protocol Set, Family 1, Study 019

Serogroup	MenABCWY n/N (%) (95% CI)	Menveo n/N (%) (95% CI)	ABCWY-Menveo % Difference (95% CI)
A	161/168 (95.8) (91.60, 98.31)	477/501 (95.2) (92.96, 96.91)	0.6 (-3.82, 3.77)
C	171/181 (94.5) (90.07, 97.32)	513/546 (94) (91.62, 95.80)	0.5 (-4.14, 3.98)
W	173/181 (95.6) (91.48, 98.07)	511/544 (93.9) (91.59, 95.79)	1.6 (-2.73, 4.89)
Y	171/180 (95) (90.72, 97.69)	507/537 (94.4) (92.12, 96.20)	0.6 (-3.93, 3.91)

Source: Adapted from Table 14.2.2.1 Submitted to Amendment 3 of BLA 125819/0. n: number of participants meeting 4-fold rise definition N: number of participants with immunogenicity data at baseline and post-vaccination in the per-protocol set.
Notes: ABCWY group: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY.
Menveo group: participants received 1 dose of Menveo at Month 0, 1 dose of placebo at Month 2, and 1 dose of Bexsero at Month 6 with serum taken 1 month after the single dose of Menveo.
Rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the limit of detection (LOD) for participants with a pre-vaccination hSBA titer < LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥LOD but <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall results include participants meeting any 1 of the 3 definitions.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=5 for MenA, 4 for MenC, MenW, and MenY. LLOQ=12 for MenA; 8 for MenC; 8 for MenW; 10 for MenY.

> **Reviewer Comment:** A random subset of 250 participants in the ABCWY group and 20 participants in the Menveo group at Visit 4 was planned to be tested for immunogenicity to test the Family 1 null hypotheses. The statistical reviewer examined demographic distributions and baseline GMTs of Family 1 and Family 2 (both per-protocol analysis set analyses). In general, demographic data as well as baseline A, C, W, and Y hSBA GMTs, in the random subset of Family 1 were similar to those of the per-protocol set of Family 2. Demographic data for both families were also similar to the FAS demographics.

Immunological non-inferiority of MenABCWY versus MenACWY for Serogroups A, C, W, and Y (Family 2: Post-Dose 1)

Table 20 summarizes the proportions of participants whose hSBA titers increased ≥4-fold from baseline to 1 month after a single dose of MenABCWY at Month 0 (ABCWY Family 2) or 1 month after 1 dose of MenACWY (ACWY). Group differences in overall proportions for participants achieving a 4-fold rise in hSBA titers and 95% CIs are also presented.

Table 20. Proportions of ACWY-Experienced Participants Achieving ≥4-Fold Rise in hSBA Titer 1 Month After a Single Dose of MenABCWY or a Single Dose of MenACWY for A, C, W, and Y Strains, Per Protocol Set, Family 2, Study 019

Serogroup	MenABCWY n/N (%) (95% CI)	Menveo n/N (%) (95% CI)	ABCWY-Menveo % Difference (95% CI)
A	473/509 (92.9) (90.34, 95.00)	477/501 (95.2) (92.96, 96.91)	-2.3 (-5.30, 0.65)
C	536/570 (94.0) (91.76, 95.83)	513/546 (94.0) (91.62, 95.80)	0.1 (-2.76, 2.94)
W	533/565 (94.3) (92.10, 96.09)	511/544 (93.9) (91.59, 95.79)	0.4 (-2.41, 3.25)
Y	531/567 (93.7) (91.32, 95.51)	507/537 (94.4) (92.12, 96.20)	-0.8 (-3.62, 2.09)

Source: Adapted from Table 14.2.2.2 Submitted to Amendment 3 of BLA 125819/0.
Notes: ABCWY group: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the first dose of MenABCWY.
Menveo group: participants received 1 dose of Menveo at Month 0, 1 dose of placebo at Month 2, and 1 dose of Bexsero at Month 6 with serum taken 1 month after the single dose of Menveo.
Rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the limit of detection (LOD) for participants with a pre-vaccination hSBA titer < LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥LOD but <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall results include participants meeting any 1 of the 3 definitions.
Abbreviations: n: number of participants meeting 4-fold rise definition N: number of participants with immunogenicity data at baseline and post-vaccination in the per-protocol set. CI: confidence interval.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=5 for MenA (3125), 4 for MenC (C11), MenW (240070), and MenY (860800). LLOQ=12 for MenA (3125); 8 for MenC (C11); 8 for MenW (240070); 10 for MenY (860800).

Table 20 shows that all 4 serogroups A, C, W, and Y met the criterion to establish non-inferiority of the immune responses for the MenABCWY vaccine (after 1 dose of MenABCWY) versus the Menveo (after a single dose) in ACWY-experienced participants. The lower limits of the two-sided 95% confidence intervals for the overall difference were above the threshold of -10% at -5.30%, -2.76%, -2.41%, and -3.62% for serogroups A, C, W, and Y, respectively.

Reviewer Comment:

1. The statistical reviewer verified the analysis results of the primary endpoints for the primary hypotheses reported in Table 19 (Family 1) and Table 20 (Family 2) based on the SDTM datasets.
2. Study 019 results presented in this subsection (6.2.2.4) are based on SDTM files submitted to Amendment 3 of BLA 125819/0. Amendment 3 provided updated assay results based on the FDA agreed upon LOD for serogroup A of 5 compared with originally submitted files using an LOD of 4. Additionally, the SDTM files of Amendment 3 correct an incorrect exclusion of a subject from the per protocol set.

6.3. Key Review Issues Relevant to the Evaluation of Benefit

The review team concluded that the results of Studies V72_72 and 019 support the proposed indication. The review team confirmed the findings of the primary analyses including:

1. demonstration of breadth of coverage against a diverse panel of 110 U.S. invasive serogroup B strains based on the responder-based and test-based analyses of the enc-hSBA responses;
2. demonstration of non-inferiority of MenABCWY (0, 6 months) compared with Bexsero (0, 6 months) with respect to the percent of enc-hSBA samples with bactericidal activity; and
3. demonstration of the non-inferiority of the serogroup A, C, W, and Y hSBA responses following MenABCWY (0, 6 months) as compared with a single dose of Menveo in MenACWY-naïve and MenACWY-experienced participants.

The review issues relevant to the evaluation of benefit focus on:

1. enc-hSBA and hSBA responses against *N. meningitidis* serogroup B following MenABCWY
2. the responses against serogroup A following a single dose of MenABCWY administered to participants who were MenACWY-naïve.

6.3.1. enc-hSBA and hSBA Responses Against *N. meningitidis* Serogroup B Following MenABCWY (0, 6 months)

Background

Study V72_72 evaluated the effectiveness of MenABCWY (0, 6 months) against *N. meningitidis* serogroup B in participants who were serogroup B vaccine naïve.

Primary immunogenicity endpoints evaluated the breadth of SBA responses against a panel of 110 serogroup B strains with an assay that used participant samples with preserved endogenous complement activity (enc-hSBA) and tested at the 4-fold dilution correlated with protection against invasive meningococcal disease (Goldschneider 1969). The 110 serogroup B strains were randomly selected from a library of isolates known to cause invasive disease in the U.S. There were 3 pre-specified analyses of these enc-hSBA results: a responder-based analysis, a test-based analysis, and an analysis of non-inferiority of the difference in % of samples with bactericidal activity following MenABCWY as compared to Bexsero (0, 6 months).

Secondary immunogenicity endpoints evaluated the SBA responses against test strains representative of each of the serogroup B antigenic components (fHbp, NadA, NHBA, OMV) using an exogenous human complement SBA assay (hSBA). Pre-specified statistical hypotheses for these endpoints evaluated the difference in the percentage of participants with a 4-fold rise in hSBA titers against each test strain between the MenABCWY (0, 6 months) group and the Bexsero (0, 6 months) group.

As discussed in Section 6.2.1.4, MenABCWY met the prespecified statistical criteria for analyses of the primary immunogenicity endpoints measuring the breadth of coverage against a diverse panel of clinically relevant *N. meningitidis* serogroup B strains including the demonstration of non-inferiority as compared with Bexsero (0, 6 months) for the percentage of samples with bactericidal activity. However, the point estimates of the enc-hSBA responses following MenABCWY (0, 6 months) were lower as compared with Bexsero (0, 6 months) and Bexsero (0, 2, 6 months) for the responder-based analysis (84%, 90%, and 93% for MenABCWY, Bexsero

[0, 6 months] and Bexsero [0, 2, 6 months], respectively) and the test-based RRR analysis (78%, 82%, and 83%, respectively). Similar patterns of results were also observed in subgroup analyses of enc-hSBA responses in U.S. participants (see Section 16.1.2)

Additional descriptive analyses and post hoc analyses included response rates for hSBA indicator strains (including the composite endpoint), individual strains of the panel of 110 enc-hSBA strains by clonal complex and antigen type, and reverse cumulative distribution (RCD) curves.

Results

The results of the responder-based analysis and the analysis of the percent of samples with enc-hSBA activity are shown in Table 21 and Table 22 following MenABCWY, Bexsero (0, 6 months), and Bexsero (0, 2, 6 months). The 95% confidence intervals are presented descriptively for the Bexsero schedules to allow for comparison with the results following MenABCWY.

Table 21. Percentage of Participants Whose Sera Killed ≥70% of Meningococcal Serogroup B Strains Tested[a] (Responder-Based) Following MenABCWY and Bexsero, Full Analysis Set[b], Study V72_72

Group[c]	N	% Responders[d] (95% CI)
MenABCWY	817	84.1 (81.4[e], 86.5)
Bexsero (0, 6 months)	813	89.8 (87.5, 91.8)
Bexsero (0, 2, 6 months)	790	93.4 (91.5, 95.0)

Source: PENMENVY (Meningococcal Groups A, B, C, W and Y Vaccine) package insert. GlaxoSmithKline Biologics SA.
N=Number of participants with available immunogenicity data, CI=Confidence interval.
[a] Each participant's serum was tested using the enc-hSBA assay for bactericidal activity (yes/no) against a maximum of 35 strains randomly selected from the 110strain panel.
[b] Full Analysis Set includes all participants who received at least 1 dose of the study treatment and have postvaccination immunogenicity data.
[c] enc-hSBA response was measured one month after Dose 2 of MenABCWY, one month after Dose 2 of Bexsero (0, 6m), or one month after Dose 3 of Bexsero (0, 2, 6m).
[d] % Responders is defined as percentages of participants whose serum kills ≥70% of strains tested using the enc-hSBA assay.
[e] Predefined criterion (lower limit of the 2-sided 95% CI >65%) met. CI calculated using Clopper-Pearson method.

Table 22. Percentages of Tests[a] with Bactericidal Activity Against Meningococcal Serogroup B Strains (Test-Based) Following MenABCWY, Bexsero, and Menveo, Per Protocol Set[b], Study V72_72

Group[c]	Number of Participants	% of Tests with Bactericidal Activity (n/N)
MenABCWY	754	82.5 (21,222 / 25,715)
Bexsero (0, 6 months)	764	85.6 (22,365 / 26,142)
Bexsero (0, 2, 6 months)	747	86.7 (22,184 / 25,596)
Menveo	133	21.0 (918 / 4,374)

Source: PENMENVY (Meningococcal Groups A, B, C, W and Y Vaccine) package insert. GlaxoSmithKline Biologics SA.
n=Number of tests with bactericidal activity, N=Total number of tests.
[a] Each test qualitatively assessed (yes/no) the bactericidal activity of one participant's serum using the enc-hSBA assay against one of the 110 U.S. meningococcal serogroup B strains. Each participant's serum was tested against a maximum of 35 strains randomly selected from the 110strain panel.
[b] Per Protocol Set includes all participants in the Full Analysis Set minus participants with protocol deviations that lead to exclusion from the Per Protocol Set.

[c] enc-hSBA responses were measured one month after Dose 2 of MenABCWY, one month after Dose 2 of Bexsero (0, 6m), one month after Dose 3 of Bexsero (0, 2, 6m), or one month after a single dose of Menveo.

MenABCWY also met prespecified statistical non-inferiority criteria for the secondary endpoints measuring hSBA activity against the fHbp and NadA test strains. MenABCWY failed to meet the pre-specified non-inferiority criteria for hSBA responses against the NHBA and OMV test strains. These data are shown in Table 23.

Table 23. Secondary Analyses: Percentages of Participants With Four-fold Rise[a] in hSBA Titers Against Four Serogroup B Indicator Strains, and Composite Response, Per Protocol Set, Ages 10 through 25 Years, All Study Sites, Study V72_72

Indicator Strain (Antigen)	MenABCWY (0, 6 months) % (CI[b]) N=642 - 678	Bexsero (0, 6 months) % (CI[b]) N=624 - 659	Bexsero (0, 2, 6 months) % (CI[b]) N=600 - 647
M14459 (fHbp)	73.2 (69.7, 76.5)	78.1 (74.8 81.2)	81.1 (77.8, 84.1)
96217 (NadA)	92.7 (90.5, 94.5)	95.9 (94.1, 97.3)	98.8 (97.6, 99.5)
NZ98/254 (OMV)	42.2 (38.4, 46.1)	58.3 (54.4, 62.2)	56.4 (52.3, 60.4)
M13520 (NHBA)	61.8 (58.0, 65.5)	69.7 (66.0, 73.1)	66.4 (62.6, 70.0)
Composite hSBA response[c,d]	70.0 (66.5, 73.4)	80.1 (76.9, 83.0)	81.5 (78.3, 84.4)

Source: Adapted from STN 125819/0 Table 14.2.2.19, Additional tables – IR 4Oct24, Table 1.
Abbreviations: %=percent of participants with four-fold response CI=95% confidence interval N=number of participants range with available hSBA data in the per protocol set, hSBA=Serum bactericidal activity measured using human complement, CI=confidence interval, fHbp=factor H binding protein, NadA=neisserial adhesin A, OMV=outer membrane vesicle, NHBA=neisserial heparin-binding antigen, LLOQ=lower limit of quantitation, LOD=limit of detection.
a. Response is 4-fold rise defined as:
- a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD,
- a post-vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titre ≥LOD and <LLOQ, and
- a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ

b. 95% CI is an exact CI based on Clopper-Pearson method.
c. Composite hSBA Responses are the proportions of participants with hSBA ≥LLOQ for all 4 Meningococcal B indicator strains evaluated in the FAS.
d. LOD=3 for fHbp (M14459); 6 for NadA (96217); 4 for OMV (NZ98/254); 4 for NHBA (M13520). LLOQ=5 for fHbp (M14459); 15 for NadA (96217); 6 for OMV (NZ98/254); 4 for NHBA (M13520).

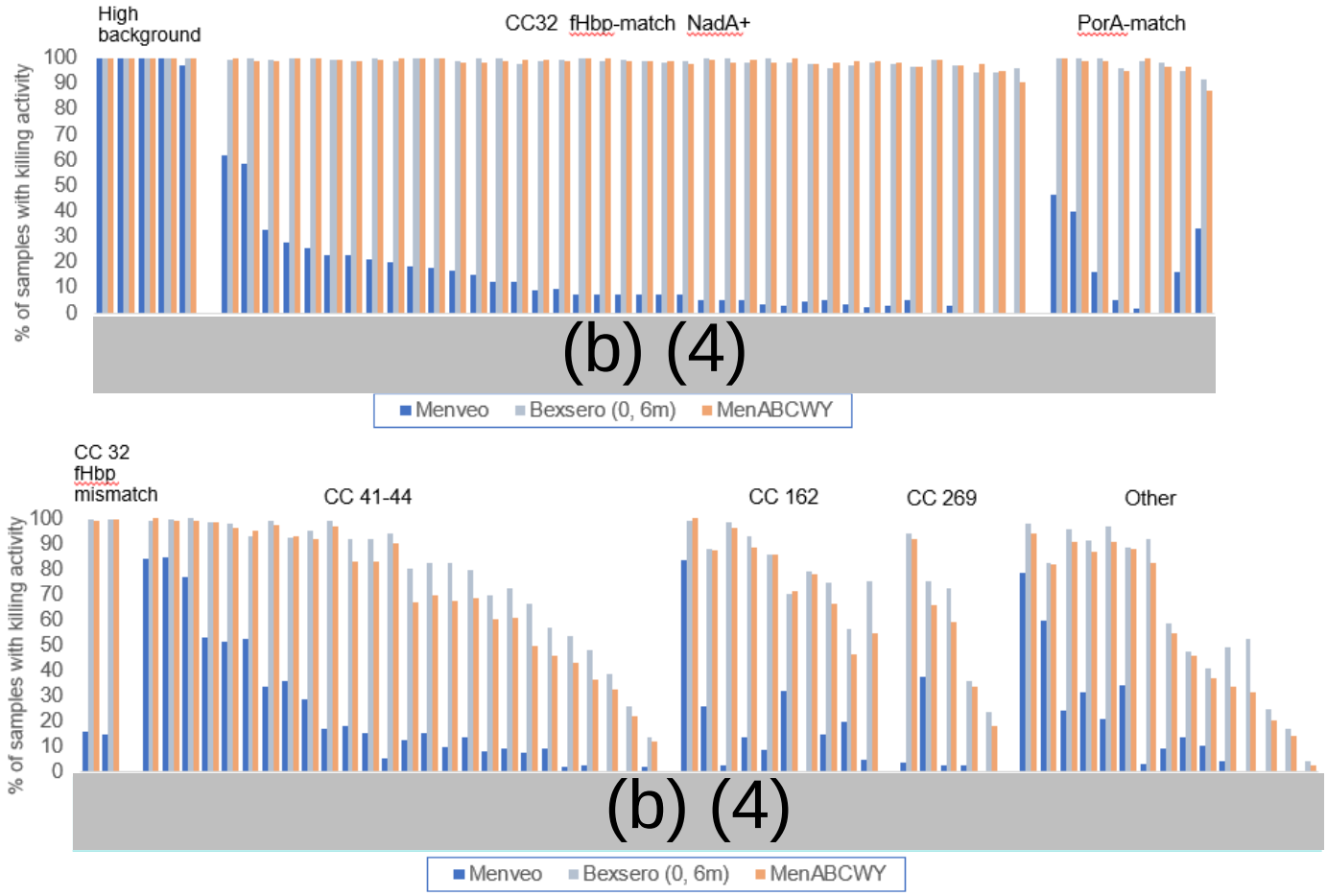
While analyses of the primary endpoints successfully met the statistical success criteria, differences were observed in comparison to Bexsero. To assess the importance of the observed differences, additional post hoc analyses were reviewed including individual strain enc-hSBA data and RCD curves of indicator strain hSBA titers.

The percent of samples positive for enc-hSBA differed by individual strain, by groups of strains characterized by clonal complex (CC)[1], and by vaccine antigen sequence types. For 41 of 42 strains belonging to the most prevalent hypervirulent clonal complex type, CC-32, the proportion of sera with killing activity was high (>95%) for both MenABCWY and Bexsero vaccination

[1] Additional information regarding *Neisseria species* clonal complexes and antigenic sequence types can be found at the following website (accessed 2/13/2025): https://pubmlst.org/organisms/neisseria-spp

groups. Among other clonal complex and antigen types, the percent of sera with bactericidal activity was more variable, between individual strains, for example ranging from <20% to >95% for clonal complex CC41-44 strains, and vaccine group differences were noted for some strains. However, no patterns of vaccine group differences were associated with groups of *N. meningitidis* disease strains (isolates) based on either clonal complex type or PorA, NadA, NHBA, or fHbp antigen type (Figure 1 and Section 16.1.3).

Figure 1. Enc-hSBA Against 110 Serogroup B *N. meningitidis* Isolates Grouped by Clonal Complex



Source: FDA generated table adapted from STN 125819/0 Study V72_72 Clinical Study Report Tables 14.2.2.13 and (b) (4) *MenB SER enc hSBA 110 strains MQR01*' Appendix 3
Notes: Study V72_72 enc-hSBA results by individual isolates in the 110 strain *N. meningitidis* serogroup B panel. Strains are grouped by clonal complex and antigen sequence type. Sera were collected 1 month following MenABCWY (0, 6 months), Bexsero (0, 6 months), or a single dose of Menveo.

RCD curves of hSBA titers against serogroup B indicator strains showed a shift towards lower titers for MenABCWY compared with Bexsero (0, 6 months) across the range of titers above the LLOQ (see Section 16.1.6). The differences were small for all strains and present at or below the LLOQ only for the OMV strain.

Conclusion

MenABCWY includes four different serogroup B antigenic components that elicit independent antibody responses. Protection against invasive meningococcal disease may result from responses to single antigenic components or be the result of cooperative killing due to antibody responses to multiple antigenic components. Cooperative contributions from antibodies to multiple antigens are not assessed by indicator strain hSBA because the strains are selected to match only one vaccine antigen. Enc-hSBA may result from antibodies to single or multiple antigens.

In study V72_72, MenABCWY elicited robust immune responses to the serogroup B antigens as measured by both enc-hSBA and indicator strain hSBA. Importantly, all 3 primary analyses of the enc-hSBA results, including the evaluation of statistical non-inferiority of the enc-hSBA responses following MenABCWY (0, 6 months) as compared with Bexsero (0, 6 months), demonstrated the effectiveness of MenABCWY against a diverse panel of clinically relevant serogroup B strains.

However, the enc-hSBA responses were diminished in comparison to Bexsero (0, 6 months), and two secondary hSBA endpoints were not met. In addition to primary and secondary prespecified endpoints, descriptive and post hoc analyses were considered to assess the potential clinical impact of the observed differences. Overall, the results support that MenABCWY induces an effective immune response against the range of clonal complex and strain types tested, mitigating the clinical significance of 2 failed secondary endpoints.

The totality of immunogenicity data supports the effectiveness of MenABCWY for the prevention of invasive serogroup B disease. The MenABCWY prescribing information will describe the decreased enc-hSBA responses and hSBA responses against the serogroup B NHBA and OMV indicator strains following MenABCWY as compared with Bexsero (0, 6 months).

6.3.2. Post hoc Exploratory Analyses of the hSBA Responses in MenACWY-Naïve Participants Against the *N. meningitidis* Serogroup A Indicator Strain Following a Single Dose of MenABCWY as Compared to Menveo

Background

Primary immunogenicity objectives in Study V72_72 also evaluated the effectiveness of MenABCWY (0, 6 months) against *N. meningitidis* serogroups A, C, W, and Y in participants who were MenACWY vaccine-naïve prior to study enrollment. The serogroup A, C, W, and Y responses were measured with an hSBA assay using 4 indicator strains, one representative of each serogroup. Primary immunogenicity analyses evaluated the percentages of participants with 4-fold rises in hSBA titers against each of the indicator strains at one month following the second dose of MenABCWY (0, 6 months) as compared with a single dose of Menveo. Descriptive post hoc analyses evaluated the serogroup A, C, W, and Y responses in a non-randomly selected

subset of MenACWY-naïve participants (N=113 - 131) following Dose 1 of MenABCWY as compared with Menveo.

Results

MenABCWY met the prespecified statistical non-inferiority criteria for all primary immunogenicity analyses evaluating the hSBA responses against the serogroup A, C, W, and Y indicator strains following the second dose of MenABCWY (0, 6 months) as compared with a single dose of Menveo.

For the post hoc descriptive analyses evaluating serogroup A, C, W, and Y responses, the proportion of participants demonstrating a 4-fold rise in hSBA titers against the serogroup A indicator strain was lower following a single dose of MenABCWY as compared with a single dose of Menveo (Table 24). The proportions of participants demonstrating a 4-fold rise in hSBA responses against the serogroup C, W, and Y indicator strains following a single dose of MenABCWY were similar following the first dose of MenABCWY as compared with a single dose of Menveo.

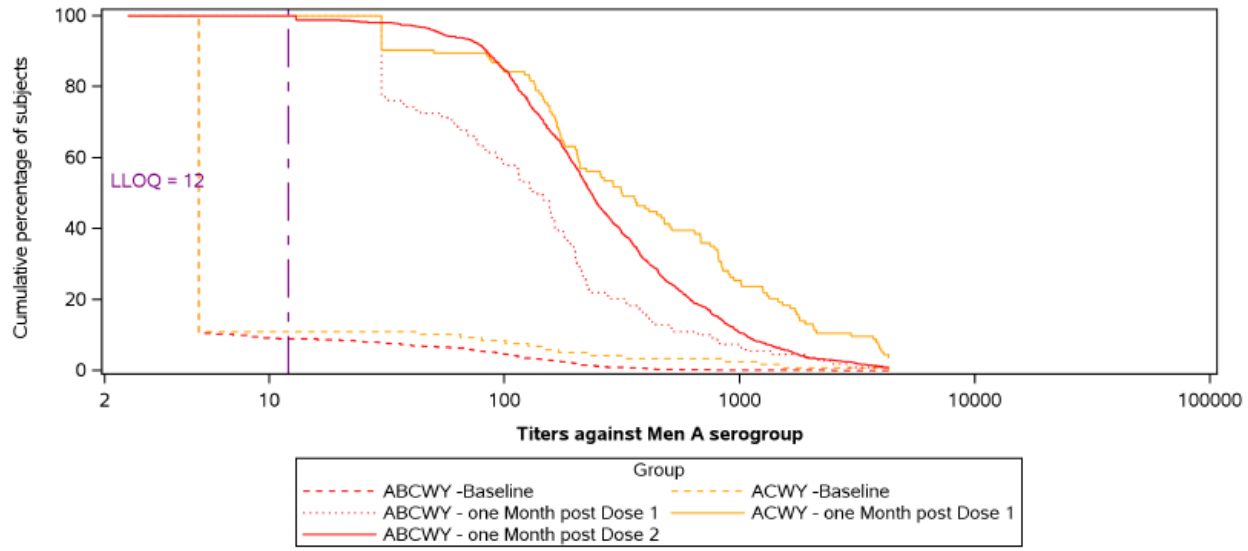
Table 24. Percentages of Participants With 4-Fold Rise in hSBA Titers Following Dose 1 of MenABCWY as Compared to a Single Dose of Menveo, FAS, Study V72_72

Serogroup	Study V72_72 MenABCWY Dose 1 N=113 - 131 % (CI)	Study V72_72 Menveo Dose 1 N=113 - 121 % (CI)	Difference MenABCWY-Menveo % (CI)
A	75.2 (66.2, 82.9)	85.8 (78.0, 91.7)	-10.6 (-21.0, -0.3)
C	64.5 (55.4, 72.9)	50.9 (41.4, 60.3)	13.7 (1.1, 25.8)
W	72.6 (63.8, 80.2)	62.4 (53.0, 71.2)	10.2 (-1.7, 21.9)
Y	74.8 (66.5, 82.0)	70.2 (61.3, 78.2)	4.6 (-6.5, 15.6)

Source: Adapted from Table 14.2.2.16.1 Submitted to Amendment 3 of BLA 125819/0. FDA statistical reviewer generated the values in the 'Difference MenABCWY-Menveo' column
Notes: ABCWY: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY.
Menveo: participants received 1 dose of Menveo at Month 0, 1 dose of placebo at Month 2, and 1 dose of Bexsero at Month 6 with serum taken 1 month after the single dose of Menveo.
Rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a prevaccination hSBA titer ≥LOD and <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall results include participants meeting any 1 of the 3 definitions.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=5 for MenA (3125), 4 for MenC (C11), MenW (240070), and MenY (860800). LLOQ=12 for MenA (3125); 8 for MenC (C11); 8 for MenW (240070); 10 for MenY (860800).

Figure 2 displays the reverse cumulative distribution (RCD) curves of the hSBA titers against the meningococcal serogroup A test strain at baseline and following Doses 1 and 2 of MenABCWY (0, 6 months) or a single dose of Menveo administered to MenACWY-naïve participants. The post-Dose 2 MenABCWY curve and the post-dose Menveo curve are generally similar while the post-Dose 1 MenABCWY curve shifted towards lower titers. This suggests comparable meningococcal serogroup A responses following Dose 2 of MenABCWY (0, 6 months) and lower responses following dose 1 of MenABCWY (0, 6 months) as compared with a single dose of Menveo in MenACWY-naïve participants.

Figure 2. Reverse Cumulative Distribution of hSBA Titers Against Serogroup A, Per Protocol Set

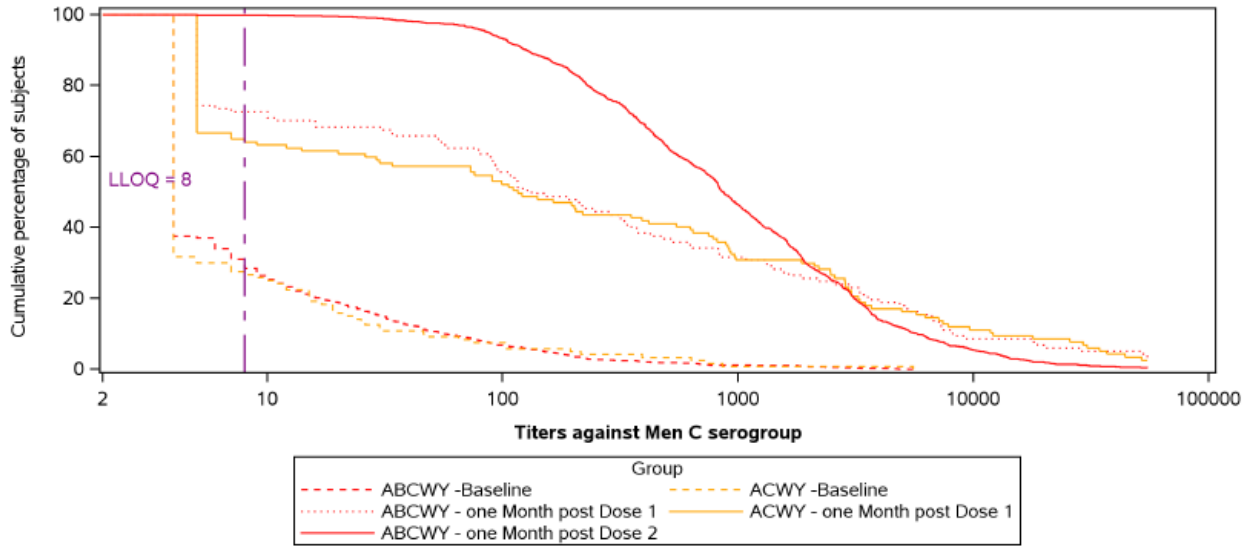


Source: STN 125819/0 IR response received October 4, 2024. Figure 3.
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY=Participants received 1 dose of Menveo vaccine

> **Reviewer Comment:** The RCD curves of the hSBA titers against the serogroup A indicator strain suggests a suboptimal serogroup A response following Dose 1 of MenABCWY (0, 6 months) administered to MenACWY-naïve individuals compared with the serogroup A responses following both doses of MenABCWY (0, 6 months)

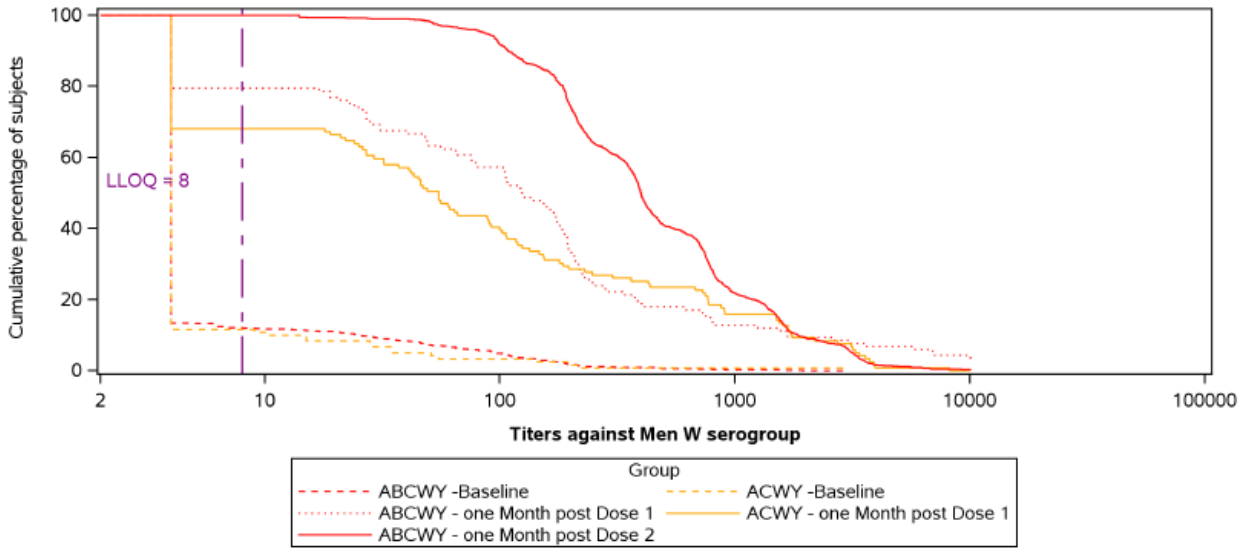
Figure 3 Figure 4 and Figure 5 display the RCD curves of the hSBA titers against the meningococcal serogroup C, W, and Y indicator strains at baseline and following Doses 1 and 2 of MenABCWY (0, 6 months) or a single dose of Menveo administered to MenACWY-naïve participants. The post-dose 1 MenABCWY curves and the post-Menveo curves are generally similar while the post-dose 2 MenABCWY curves are shifted to the right for all 3 serogroups. This suggests comparable Meningococcal serogroup C, W, and Y responses following Dose 1 of MenABCWY (0, 6 months) as compared with a single dose of Menveo and higher responses following Dose 2 of MenABCWY (0, 6 months) in MenACWY-naïve participants.

Figure 3. Reverse Cumulative Distribution of hSBA Titers Against Serogroup C, Per Protocol Set



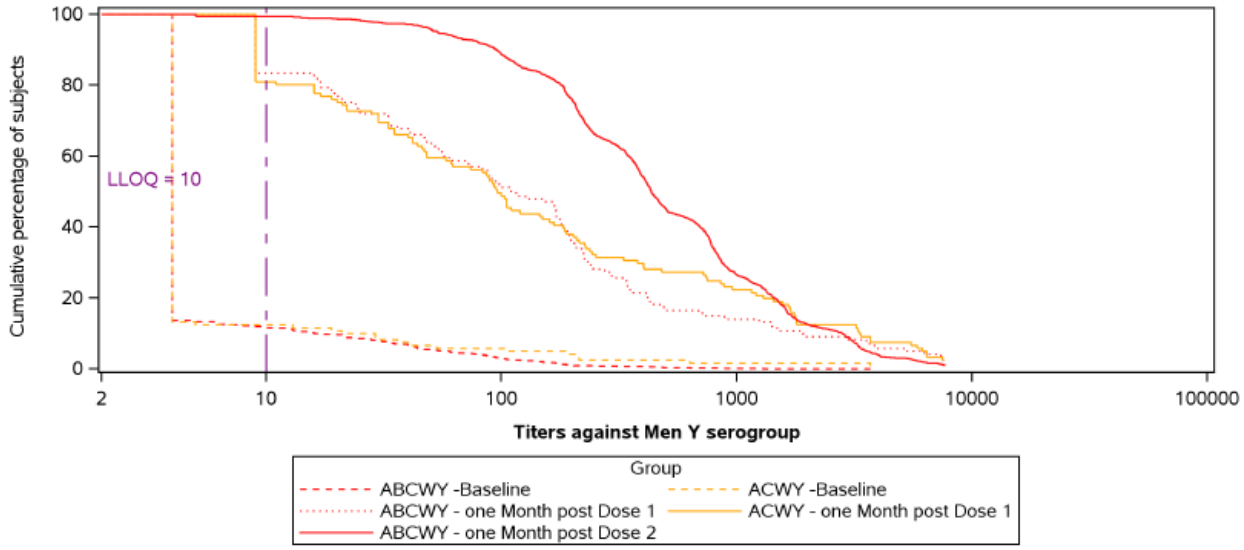
Source: STN 125819/0 IR response received October 4, 2024. Figure 3
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY=Participants received 1 dose of Menveo vaccine

Figure 4. Reverse Cumulative Distribution of hSBA Titers Against Serogroup W, Per Protocol Set



Source: STN 125819/0 IR response received October 4, 2024. Figure 3
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY=Participants received 1 dose of Menveo vaccine

Figure 5. Reverse Cumulative Distribution of hSBA Titers Against Serogroup Y, Per Protocol Set



Source: STN 125819/0 IR response received October 4, 2024. Figure 3
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY=Participants received 1 dose of Menveo vaccine

Reviewer Comment: The RCD curves of the hSBA titers against the serogroup C, W, and Y indicator strains suggest higher responses following Dose 2 of MenABCWY (0, 6 months) compared with a single dose of Menveo.

Conclusion

The totality of immunogenicity data supports the effectiveness of 2 doses of MenABCWY (0, 6 months) for the prevention of invasive serogroup A, C, W, and Y disease including potentially improved protection against invasive meningococcal disease due to serogroups C, W, and Y in MenACWY-naïve individuals. The post hoc descriptive analyses in a subset of MenACWY-naïve participants suggest suboptimal responses against serogroup A following a single dose of MenABCWY and supports the importance of receiving both doses of the MenABCWY (0, 6 months) series to achieve better protection against invasive serogroup A disease for those who are MenACWY-naïve.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Overall, the nonclinical safety assessment for MenABCWY was considered acceptable to support licensing from a toxicology perspective.

7.2. Potential Risks or Safety Concerns Based on Drug Class/Related Products or Other Drug-Specific Factors

The proposed MenABCWY vaccine contains the same antigens in the same amounts as the commercial Menveo, in a lyophilized form, and the serogroup B liquid component is the same formulation as the commercial Bexsero. Thus, safety evaluations and risk management plans for Menveo and Bexsero are considered relevant to the proposed MenABCWY vaccine and are discussed more in depth below in Section 7.3.

Additionally, because of the age ranges for which MenABCWY is indicated (10 through 25 years), syncope is a potential safety concern. The CDC states that although syncope can be triggered by many types of medical procedures including vaccination, post-vaccine syncope is most commonly reported after three types of vaccines given to adolescents: human papillomavirus (HPV) vaccines, tetanus, diphtheria, and acellular pertussis vaccines (Tdap) and quadrivalent meningococcal conjugate vaccines (MCV4) including Menveo (CDC 2024). Because the ingredients in these vaccines are different, fainting is thought more likely to be due to the vaccination process and not to the vaccines themselves.

7.3. Potential Safety Concerns Identified Through Postmarketing Experience

7.3.1. Applicant's Analysis

The Applicant did not provide an analysis of postmarketing safety data, as MenABCWY is not yet authorized in any country and no postmarketing safety data for the combined products are currently available.

7.3.2. FDA Analysis

Although there are no postmarketing safety data for combined MenABCWY, there are extensive data for Bexsero and Menveo (see Section 7.2).

From Menveo's initial marketing authorization to October 31, 2024, (b) (4) doses worldwide and (b) (4) doses in the U.S. (including Puerto Rico) have been distributed (STN 125819/0.63).

From Bexsero's initial marketing authorization approval to October 31, 2024, (b) (4) doses worldwide and (b) (4) doses in the U.S. (including Puerto Rico) have been distributed (STN 125819/0.63).

7.3.2.1. Notable Regulatory History Related to Safety

Menveo

- October 6, 2016: Package insert updated to include postmarketing information on Bell's Palsy.

Bexsero

- October 12, 2017: Package insert revised to include extensive limb swelling and injection nodules in Section 6.3 Postmarketing Experience.
- January 6, 2022: Package Insert revised to include language pertaining to "Lymphadenopathy" in Section 6.3 Postmarketing Experience.

7.3.2.2. VAERS Reports

Menveo

A query in Business Objects was conducted on Dec 3, 2024, for reports from licensure Feb 19, 2010 through Dec 1, 2024 for all Vaccine Adverse Event Reporting System (VAERS) reports of Menveo with age 10 years through 25 years. The query resulted in 7,121 total reports, of which 6,827 (95.9%) were domestic. Among all events, 780 (11.0%) were serious and 7 (0.1%) involved a fatality. The deaths were associated with meningococcal infection (3 cases), other infections (measles, influenza B), malignancy (pontine glioma tumor), and a death from unknown cause.

The top 10 associated MedDRA preferred terms (PTs) were no adverse event, injection site erythema, injection site swelling, erythema, dizziness, syncope, headache, injection site pain, injection site warmth, and pyrexia.

The most recent internal routine pharmacovigilance internal surveillance report (August 1, 2023 – July 31, 2024) identified a continued large number of reports (>100) of "product preparation error" or "product preparation issue" and noted the approval in 2022 of a new single vial presentation.

> **Reviewer Comment:** Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was due to the product. The top 10 PTs were all labeled or related to labeled AEs (for example, "dizziness" is not labeled but "syncope" is). The PTs identified in the internal surveillance report related to product preparation represented a known issue around reconstitution errors with the two-vial presentation. MenABCWY will have a different presentation.

Bexsero

A query in Business Objects was conducted on Dec 3, 2024, for reports from licensure Jan 23, 2015 through Dec 1, 2024 for all VAERS reports of Bexsero with age 10 years through 25 years.

The query resulted in 4,767 total reports, of which 4,547 (95.4%) were domestic. Among all events, 452 (9.5%) were serious and 5 (0.1%) involved a fatality (4 domestic and 1 foreign). The deaths were associated with meningococcal infection in a person with paroxysmal nocturnal hemoglobinuria; seizure in a person with history of epilepsy and a positive THC tox screen; a history of congenital heart disease and probable cardiac arrhythmia due to long QT syndrome; seizure associated with Hashimoto's thyroiditis, and one death of unclear cause.

The 10 most frequent PTs were injection site pain, headache, pyrexia, pain in extremity, dizziness, nausea, injection site erythema, pain, injection site swelling, syncope. Notable among the top 100 PTs was 'seizure,' discussed further below.

> **Reviewer Comment:** The majority of top PTs were labeled AEs, related to labeled AEs, confounded by indication, or represented non-specific events.

Because seizure and arthritis are both included in Bexsero's recent risk management plan (see Section 7.7.2) and "seizure" is among the top 100 PTs represented among spontaneously reported events, additional analyses were conducted for events of "seizure" and "arthritis."

Seizure

A query in Business Objects (QQ_CLL) was conducted for reports of seizure, using all PTs under the SMQ (Narrow search) "Generalised convulsive seizures following immunisation" from date of licensure Feb 23, 2015 through Dec 1, 2024. This search resulted in 1,255 reports, of which 100 (8.0%) were domestic.

Of note, Bexsero is approved in the United States only for those 10 through 25 years of age; however, it is approved in the European Union for individuals ≥2 months and is included in routine infant immunization programs in multiple European Union countries (Marshall 2023). When reports were limited to those 10 through 25 years of age, there were 110 reports. Among these, 57 involved concomitant vaccination with other vaccines. Forty-four reports (40%) were classified as serious/OMIC. All serious cases and domestic OMIC cases were reviewed and found to be associated with a history of seizure, likely alternate explanations (syncope, anaphylaxis, psychogenic non-epileptic seizures), or underlying conditions that are associated with seizure.

> **Reviewer Comment:** Febrile seizures are not uncommon in younger children (CDC, 2021). However, review of the seizure reports in the 10 through 25 age group revealed that these cases were only rarely associated with fever, and the number of the seizure reports were relatively few in the age range compared to overall use of the vaccine. Most serious/OMIC cases were associated with a known history of seizure or other underlying pathology or were associated with syncope. Concomitant vaccine use also complicates attribution of an event to a particular vaccine.

Arthritis

A query in Business Objects was conducted for reports of arthritis in persons 10 to 25 years of age, using all PTs under the SMQ (Narrow search) "arthritis" from date of licensure January 23, 2015 through December 1, 2024. There were 11 reports returned from this query, 9 of which were domestic. Of the 11 total reports, 5 were serious. Review of narratives of these cases

revealed most events of arthritis to be associated with pre-existing or other confounding conditions (including migraine, localized injection site reactions, and allergic reactions). Cases without a clear alternate explanation and onset within 30 days after vaccination included an 11-year-old female with no reported medical history who developed knee swelling less than a week after receiving Bexsero and was diagnosed with reactive arthritis, a 17-year-old female with a family history of rheumatoid arthritis who 14 days after vaccination developed swollen joints, fatigue, and eye swelling and was tested for rheumatoid arthritis with the resulting titer coming back as "mild," and a 17-year-old male vaccinated with Bexsero who developed 25 days after vaccination extensive arthritis and arthralgias affecting small and large joints of all four extremities and numerous sites along the vertebrae.

> **Reviewer Comment:** Arthritis is known to occur in children and adolescents with an estimated prevalence of 305 per 100,000, with prevalence increasing with age (Lites, 2023). Many of the reported cases were associated with pre-existing or confounding conditions. Review of these cases does not change the current risk characterization; arthritis is being monitored through routine surveillance and an additional follow-up form.

7.3.2.3. Data Mining

Menveo

Data mining for Menveo was conducted using the Empirica Signal [Signals tab "VAERS Summary Table"] limited to U.S. teens (9 to 18.9 years) with data lock point 11/29/2024. The PTs with an EB05>2 included: "Product preparation error," "Single component of a two-component product administered," "Product preparation issue," "Product reconstitution quality issue," "Wrong technique in product usage process," "Incorrect product formulation administered," and "Incorrect dose administered."

These PTs can be grouped as primarily related to product preparation and administration, many related to the known issue of reconstitution errors. As noted above in the section of VAERS report review, Menveo is supplied as either one vial that does not need reconstitution or two vials that require the combination of the MenCYW-135 liquid conjugate component and the MenA lyophilized conjugate component, which has led to reconstitution errors. MenABCWY will have a different presentation.

Bexsero

Data mining for Menveo was conducted using the Empirica Signal [Signals tab "VAERS Summary Table"] limited to U.S. teens (9 to 18.9 years) with data lock point 11/29/2024. The PTs with an EB05>2 included: "Injected limb mobility decreased," "Injection site pain," "Pain in extremity," and "Chills."

The PTs are all labeled AEs, related to labeled AES, or represented non-specific events. The Bexsero label was revised October 12, 2017 to include extensive limb swelling and injection nodules. The proposed MenABCWY (Penmenvy) label includes the same language.

7.4. FDA Approach to the Clinical Safety Review

The safety review includes data from 12 clinical studies, 2 key trials (Studies V72_72 and 019) and 10 supportive studies (V102_16, V102_16E1, V102_15, V102_15E1, V102_03, V102_03E1, V102_02, V102_02E1, V102_02E2, and V102P1).

Solicited local adverse events and solicited systemic adverse reactions were reviewed by study. Solicited local and systemic ARs from the key studies are discussed in this review memo. The patterns of solicited ARs in the supportive studies were similar to those reported in the two key studies, V72_72 and 019. Unsolicited adverse events, serious adverse events (SAEs), deaths, adverse events of special interest (AESIs), medically attended adverse events (MAAEs), adverse events leading to premature withdrawal were analyzed by study for the key studies and with the integrated analyses for the 12 supportive studies.

> **Reviewer Comment:** There were no issues identified with safety data submitted for each study that would preclude substantive review of safety findings.

7.5. Adequacy of the Clinical Safety Database

The safety database includes a total of 3718 participants who received at least one dose of the final formulation of MenABCWY. Participants in the supportive studies may have received MenABCWY administered 6 months apart (0, 6 months), the dosing schedule that the Applicant is seeking with this application. In the 2 key trials, Studies V72_72 and 019, unsolicited adverse events (AEs) were collected for 30 days after vaccination. Serious AEs (SAEs), medically attended AEs (MAAEs), adverse events of special interest (AESIs), and AEs leading to withdrawal were collected through the end of the study (5 months following final vaccination).

Seven of the 10 supportive studies collected unsolicited AEs through at least 1 month following vaccination. Three of the studies (V102_02, V102_02E1, and V102P1) collected unsolicited AEs through 7 days following the vaccination. The 10 supportive studies collected SAEs, and AEs leading to withdrawal through at least 1 month following the final study vaccination (range 1 to 12 months). Four of the 9 studies did not differentiate MAAEs from other AE categories (Studies V102P1, V102_02, V102_02E1 and V102_03).

In Studies V72_72 and 019, the eDiary served as the primary mechanism for capture of solicited local and systemic adverse events for seven days following each vaccination. Three significant quality issues (SQIs) related to the eDiary were reported for each study, respectively. While most SQIs did not have a material impact on the safety data, there was one SQI in the V72_72 study (SQI-1394080) which impacted greater than 5% of the participants. A sensitivity analysis was performed by the Applicant to ensure that the SQI did not compromise the data integrity, and we concur with the Applicant that the SQIs did not affect the overall safety reporting through the eDiary. Furthermore, the overall eDiary compliance data submitted by the Applicant were acceptable for both studies. The eDiary compliance ranged from 82.5% to 83.5% in the V72_72 study and ranged from 79.9% to 90.7% for the first vaccination and 63.4 to 75.8% for the second vaccination when analyzed by days in Study 019. In addition, the compliance rates were not significantly different across study arms for both studies. Overall, the eDiary data in Studies V72_72 and 019 indicate no significant eDiary safety data reporting quality issues.

Reviewer Comment: The safety database was adequate for a sufficient safety assessment of MenABCWY for the indication of prevention of invasive disease caused by *N. meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

7.6.1. Safety Results, Study V72_72

A total of 1,657 participants received MENABCWY (0, 6 months), 1804 participants received Bexsero (N=907 as Bexsero [0, 6 months] and N=897 as Bexsero [0, 2, 6 months]) and 178 participants received a single dose of Menveo. Participants in the Bexsero (0, 6 months) group received a dose of Menveo at month 2. Participants in the Bexsero (0, 2, 6 months) group received a dose of Menveo at month 7. Participants in the Menveo group received doses of Bexsero at months 6 and 7.

As of the data cutoff date (October 10, 2022), safety data were available through 30 days after the last dose for 95.3% of participants in the MenABCWY (0, 6 months) group, 91.4% of participants in the Bexsero (0, 6 months) group, and 90.8% of participants in the Bexsero (0, 2, 6 months) group. These safety databases were considered adequate to evaluate the safety of MENABCWY (0, 6 months) in individuals 10 through 25 years of age in conjunction with the safety data from the other clinical studies provided with the BLA submission.

7.6.1.1. Overall Adverse Event Summary, Study V72_72

Table 25 provides an overview of reported safety events following any dose of MenABCWY, Bexsero, or Menveo. As participants in the Bexsero groups received a dose of Menveo and the Menveo group received doses of Bexsero, safety data is presented following any dose. Overall, the rates and severities of adverse events and adverse reactions following MenABCWY were similar to those reported following Bexsero. Solicited ARs and unsolicited AEs were more common following MenABCWY as compared to Menveo. The severities of ARs were similar following MenABCWY and Bexsero and were higher than following Menveo. The severities of unsolicited AEs were similar following all 3 vaccines. Serious adverse events, AEs leading to study discontinuation, and AESIs occurred with similar frequencies following MenABCWY, Bexsero, and Menveo.

Table 25. Proportions of Participants Reporting at Least One Adverse Event Following Vaccination, By Vaccine Type, 10-25 Years of Age, Safety Sets, Study V72_72

AE Type: Monitoring Period[d]	MenABCWY Any Dose[a] N=1657 % (n/N1)	Bexsero Any Dose[b] N=1971 % (n/N1)	Menveo Any Dose[c] N=1031 % (n/N1)
Immediate: 30 minutes	15.9 (263/1657)	15.8 (312/1971)	7.4 (76/1031)
Immediate Unsolicited AE	0.2 (4/1657)	0.4 (7/1971)	0
Solicited local reactions[e] at the injection site: Day 1-7	94.8 (1564/1650)	93.3 (1827/1958)	29.8 (307/1029)
Grade 3 or above	14.9 (246/1650)	16.4 (321/1958)	1.7 (18/1029)

AE Type: Monitoring Period[d]	MenABCWY Any Dose[a] N=1657 % (n/N1)	Bexsero Any Dose[b] N=1971 % (n/N1)	Menveo Any Dose[c] N=1031 % (n/N1)
Solicited systemic reactions[f]: Day 1-7	74.2 (1224/1650)	74.9 (1466/1958)	43.4 (447/1029)
Grade 3 or above	6.8 (112/1650)	6.6 (129/1958)	2.3 (24/1029)
Unsolicited AEs: Day 1-30	21.4 (352/1648)	23.0 (451/1961)	11.3 (117/1031)
Severe AEs	1.0 (17/1648)	1.4 (28/1961)	0.6 (6/1031)
Related AEs[g]	5.4 (89/1648)	5.7 (111/1961)	1.3 (13/1031)
Severe and related AEs[g]	0.3 (5/1648)	0.3 (6/1961)	0.1 (1/1031)
MAAEs: through 2 months after dose*	13.5 (222/1648)	14.4 (282/1961)	9.1 (94/1031)
Severe MAAEs	1.3 (21/1648)	1.3 (26/1961)	0.6 (6/1031)
Related MAAEs[g]	0.7 (11/1648)	0.6 (11/1961)	0.2 (2/1031)
Severe and related MAAEs[g]	0.1 (2/1648)	0.1 (2/1961)	0.1 (1/1031)
AESIs: through 2 months after dose*	0.1 (2/1648)	0.1 (1/1961)	0
Severe AESIs	0	0	0
Related AESIs[g]	0	0.1 (1/1961)	0
AEs leading to study discontinuation: through 2 months after dose	0.2 (3/1648)	0.3 (5/1961)	0.1 (1/1031)
SAEs: through 2 months after dose*	0.7 (11/1648)	0.9 (17/1961)	0.7 (7/1031)
Related SAEs[g]	0	0	0.1 (1/1031)
Deaths: through 2 months after study dose*	0	0	0
Related deaths[g]	0	0	0

Source: Adapted from STN 125546/1058. Additional tables – IR received March 14, 2024. Data cutoff 10OCT22.
Abbreviations: AE=adverse event; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=Exposed set; N1=number of participants with available data for the relevant safety set; n/%=number/percentage of participants who reported an event.
* Participants reporting at least 1 relevant AE through either 2 months following receipt of study dose or through date/time of receipt of the subsequent study dose, whichever is sooner
Note: Participants were allocated to the vaccine groups as received.
a. ABCWY Any Dose refers to any dose of ABCWY administered to study participants included in the solicited and/or unsolicited safety sets in any study group (i.e., study dose 1 and 3 for Group MenABCWY).
b. Bexsero Any Dose refers to any dose of Bexsero administered to study participants included in the solicited and/or unsolicited safety sets in any study group (i.e., study dose 1,2, and 3 for Group Bexsero [0, 2, 6 months]; study doses 1 and 3 for Group Bexsero [0, 6 months]; study dose 3 for Group Menveo)
c. Menveo Any Dose refers to any dose of Menveo administered to study participants included in the solicited and/or unsolicited safety sets in any study group (i.e., study dose 2 for Group Bexsero (0, 6m); study dose 1 for Group Menveo)
d. Monitoring Period: time interval of reporting for the relevant type of AE
e. Solicited local reactions included injection site pain, erythema, swelling, and induration.
f. Solicited systemic reactions included fever [body temperature ≥38.0°C], nausea, fatigue, myalgia, arthralgia, and headache.
g. Relatedness to study vaccine as determined by principal investigator.

Reviewer Comment: The safety results from Study 019 suggest similar reactogenicity for MenABCWY compared with Bexsero and greater reactogenicity compared with Menveo. There were no participant deaths assessed as related to the study vaccines. There were no substantial safety concerns identified for MenABCWY because of these data.

7.6.1.2. Deaths, Pooled Analyses, Study V72_72

There were no reported deaths in the MenABCWY study group. There were 2 deaths reported during the study period in the Bexsero groups (0, 6 months or 0, 2, 6 months) that were assessed as not related to study doses.

7.6.1.3. Serious Adverse Events, Study V72_72

Through the date of data cut-off, SAEs were reported by 1.5% of participants in the MenABCWY group, 2.2% of participants in the Bexsero (0, 2, 6 months) group, 2.4% of participants in the Bexsero (0, 6 months) group, and 2.8% of participants in the Menveo group.

> **Reviewer Comment:** The percentages and nature of reported SAEs do not suggest important safety concerns regarding MenABCWY as compared to Bexsero or Menveo.

The following SAE (also an AESI) was assessed as possibly related to the study vaccination by the study investigator:

Neuromyelitis optica: A 21-year-old female with a family history of autoimmune-related juvenile rheumatoid arthritis (mother, father and grandmother) developed vision loss in her left eye approximately 3 months (89 days) after her 2nd dose of MenABCWY. Diagnostic results, including imaging, were consistent with neuromyelitis optica. The participant required multiple hospitalizations for medical treatment after which she had improvement in her vision. At the time of data cut-off, the event was reported as resolved with sequelae. The study investigator assessed the event as related to the study vaccine. Concurrent vaccinations included COVID-19 vaccination, received 6 months prior to symptom onset.

> **Reviewer Comment:** The assessment of causality of the case of NMO is confounded by the 89-day interval between receipt of the 2nd dose of MenABCWY study vaccine and symptom onset; the participant's family history of autoimmune disease in multiple first-degree relatives increasing her risk of developing autoimmune disease, and receipt of other non-study vaccines prior to the event. Based on the clinical information provided, the episode of NMO is likely not related to the study dose of MenABCWY and does not appear to represent an important safety concern for MenABCWY.

7.6.1.4. Adverse Events of Special Interest, Study V72_72

There were eight participants who reported AESIs throughout the study period (2 in the Bexsero groups and 6 in the MenABCWY group). Of the AESIs in the MenABCWY group, one was considered related to study vaccination by the study investigator (a case of neuromyelitis optica [NMO] in the MenABCWY group, Section 7.6.1.3).

The following MenABCWY recipients reported AESIs that were not considered related to the study vaccination by the study investigators:

1. 16-year-old female with psoriasis, symptom onset 54 days after the first dose of MenABCWY, past medical history includes eczema, and family history of psoriasis.

2. 15-year-old female with psoriasis, symptom onset likely prior to vaccination and diagnosis 29 days after the first dose of MenABCWY.
3. 16-year-old female with celiac disease, symptom onset (anemia) prior to vaccination and diagnosis 28 days after the second dose of MenABCWY.
4. 12-year-old female with celiac disease, diagnosis 72 days after the second dose of MenABCWY.
5. A 15-year-old with Type 1 diabetes mellitus, diagnoses 147 days after the second dose of MenABCWY with concurrent COVID-19 infection.

Reviewer Comment: This clinical reviewer agrees with the study investigators' assessments that the above cited AESIs (#2 - #6) were likely not related to the study doses of MenABCWY based on the timing of onset relative to the study doses of MenABCWY and co-morbid conditions.

7.6.1.5. Dropouts and/or Discontinuations Due to Adverse Events, Study V72_72

A total of 15 participants withdrew from the study prematurely due to AEs (4 from the MenABCWY group, 10 from the Bexsero groups, and 1 from the Menveo group). Adverse events leading to study discontinuation by preferred term in the MenABCWY group included: chest pain, influenza, psychotic disorder, and thinking abnormal. None of the AEs leading to study discontinuation in the MenABCWY group were assessed as related to the study dose by study investigators.

Reviewer Comment: This reviewer agrees with the investigators' assessments that none of the 4 AEs leading to study discontinuation in the MenABCWY group were related to the study doses. No substantial safety concerns for MenABCWY were identified because of these results.

7.6.1.6. Unsolicited AEs Within 30 Days, Study V72_72

The unsolicited AEs most reported by MenABCWY recipients in the 30 days after vaccination and occurring in ≥1% of MenABCWY recipients included COVID-19 (3.7%), upper respiratory tract infection (2.5%), nasopharyngitis (2.4%), headache (1.5%), dysmenorrhea (1.3%), and oropharyngeal pain (1%).

The percentages of participants reporting unsolicited AEs within 30 days of vaccination were generally similar between MenABCWY recipients and Bexsero recipients.

The percentages of participants reporting unsolicited AEs within 30 days of vaccination were generally higher following MenABCWY recipients as compared to Menveo recipients. Unsolicited AEs within 30 days of vaccination assessed as causally related to vaccination by the investigator were reported by 6.3% of MenABCWY recipients, 5.2% of Bexsero recipients, and 4.5% of Menveo recipients. Unsolicited AEs assessed by study investigators as causally related to the study vaccine were generally consistent with known vaccine reactogenicity. The most reported unsolicited AEs following MenABCWY assessed as related by study investigators, by PT, were lymphadenopathy (0.4%), injection site pruritis (0.3%), and diarrhea (0.2%).

There were no substantial imbalances in the proportions of participants reporting severe and related unsolicited AEs following MenABCWY, Bexsero, or Menveo.

Reviewer Comment: Review of the reported unsolicited adverse events within 30 days of vaccination did not identify safety concerns.

7.6.1.7. Solicited Adverse Reactions (ARs) Described in Product Labeling, Study V72_72

Local and systemic ARs were solicited from study participants through 7 days following study doses.

Solicited Local ARs

Table 26 presents the frequencies and severities of solicited local ARs within 7 days of study doses. The median day of onset for solicited local ARs following MenABCWY was 1 (range 1 to 11 days) with a median duration of 3 days (range 1 to 55 days).

The most frequently reported solicited local ARs after MenABCWY were pain (91.8% after Dose 1 and 88.1% after Dose 2), followed by swelling (13.2% after Dose 1 and 12.3% after Dose 2), and erythema (13.2% after Dose 1 and 11.8% after Dose 2).

Table 26. Frequencies and Severities of Solicited Local ARs By Dose and Study Group, Study V72_72, Solicited Safety Set

Solicited Local Adverse Reaction	MenABCWY (0, 6 months) Dose 1 % N=1638	MenABCWY (0, 6 months) Dose 2 % N=1428	Bexsero (0, 6 months) Dose 1 % N=894	Bexsero (0, 6 months) Dose 2 % N=759	Menveo Dose 1 % N=178
Any local reaction	92.6	88.4	92.2	89.3	41.0
Grade 1	33.0	28.6	35.5	29.4	24.2
Grade 2	51.0	49.8	48.9	49.4	15.2
Grade 3	8.6	10.0	7.8	10.5	1.7
Pain[a]	--	--	--	--	--
Any	91.8	88.1	91.7	89.1	37.6
Grade 1	35.7	31.0	37.6	30.6	25.8
Grade 2	49.7	49.9	48.5	50.2	11.8
Grade 3	6.4	7.3	5.6	8.3	0
Erythema[b]	--	--	--	--	--
Any	13.2	11.8	9.6	11.5	6.2
Grade 1	6.2	5.0	4.6	5.5	1.7
Grade 2	5.6	4.6	4.3	4.6	3.4
Grade 3	1.4	2.1	0.8	1.3	1.1
Swelling[c]	--	--	--	--	--
Any	13.2	12.3	10.0	11.2	6.2
Grade 1	5.9	6.4	6.5	6.2	2.8
Grade 2	5.6	4.1	2.5	3.2	2.2
Grade 3	1.7	1.8	1.0	1.8	1.1
Induration[d]	--	--	--	--	--
Any	9.3	8.2	7.4	7.5	3.9
Grade 1	5.5	4.6	4.4	5.1	1.7

Solicited Local Adverse Reaction	MenABCWY (0, 6 months) Dose 1 % N=1638	MenABCWY (0, 6 months) Dose 2 % N=1428	Bexsero (0, 6 months) Dose 1 % N=894	Bexsero (0, 6 months) Dose 2 % N=759	Menveo Dose 1 % N=178
Grade 2	2.9	2.2	1.5	1.3	2.2
Grade 3	0.9	1.4	1.6	1.1	0

Source: Adapted from STN 125819/0, Study V72_72 Clinical Study Report, Tables 14.3.1.1, 14.3.1.3, and *"V72_72 Shell tables based on Bexsero IR 10Oct23 including MenABCWY,"* and IR response received February 3, 2025
Abbreviations: AR=adverse reaction, N=Number of participants with any solicited AR data for the specific solicited local/systemic AR in the group; n=Number of participants who reported the event or severity of event
Notes: Participants were allocated to the vaccine groups as received. Participants in the MenABCWY group received MenABCWY at 0 and 6 months with a placebo dose at 2 and 7 months. Participants in the Bexsero (0, 6m) group received Bexsero at 0 and 6 months with a dose of Menveo at 2 months and a placebo dose at 7 months. Participants in the Menveo group received a dose of Menveo at 0 months, a placebo dose at 2 months and a dose of Bexsero at 6 and 7 months.
a. For pain- Grade 1: Mild: Any pain neither interfering with nor preventing
normal every day activities; Grade 2: Moderate: Painful when limb is moved and interferes with every day activities; Grade 3: Severe: Significant pain at rest. Prevents normal every day activities.
b. For erythema Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm
c. For swelling Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm
d. For induration– Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm

Reviewer Comment: As shown in the table above, both MenABCWY and Bexsero are more locally reactogenic compared to Menveo. Specifically, local injection site pain was reported at high rates (approximately 90%) after each dose of MenABCWY and Bexsero compared to the rate reported after a single dose of Menveo (37%). Higher percentages of participants reported grade 3 pain after MenABCWY and Bexsero as compared with Menveo.

Solicited Systemic Reactions

Table 27 presents the frequencies and severities of solicited systemic ARs within 7 days of study doses. The median day of onset for solicited systemic ARs following MenABCWY was 2 days (range 1 to 9 days) with a median duration of 1 day (1 to 23 days).

The most frequently reported solicited systemic ARs after MenABCWY were fatigue (50.5% after Dose 1 and 42.2% after Dose 2) and headache (41.6% after Dose 1 and 35.6% after Dose 2). Fever was reported at low rates in the MenABCWY group, with more participants reporting fever after the 1st dose (3.4%) then the 2nd dose (1.9%) with the majority of events reported as Grade 1 in severity.

Table 27. Frequencies and Severities of Solicited Systemic Adverse Reactions by Dose and Study Group, Solicited Safety Set, Study V72_72

Solicited Systemic Adverse Reactions	MenABCWY (0, 6 months) Dose 1 % N=1638	MenABCWY (0, 6 months) Dose 2 % N=1428	Bexsero (0, 6 months) Dose 1 % N=894	Bexsero (0, 6 months) Dose 2 % N=759	Menveo Dose 1 % N=178
Any systemic reaction	65.0	55.5	61.5	58.1	59.6
Grade 1	36.2	31.6	38.3	31.9	36.5
Grade 2	24.0	20.0	20.0	23.2	18.0
Grade 3	4.8	3.9	3.2	3.0	5.1
Fever[a]	--	--	--	--	--
Any	3.4	2.0	2.0	3.0	1.7
Grade 1	2.9	1.5	1.8	2.4	1.1
Grade 2	0.4	0.4	0.1	0.7	0

Solicited Systemic Adverse Reactions	MenABCWY (0, 6 months) Dose 1 % N=1638	MenABCWY (0, 6 months) Dose 2 % N=1428	Bexsero (0, 6 months) Dose 1 % N=894	Bexsero (0, 6 months) Dose 2 % N=759	Menveo Dose 1 % N=178
Grade 3	0.1	0.1	0.1	0	0.6
Nausea[b]	--	--	--	--	--
Any	14.8	10.4	12.4	11.1	15.2
Grade 1	10.3	7.8	9.3	7.9	11.2
Grade 2	4.2	2.2	2.5	2.8	2.8
Grade 3	0.3	0.3	0.7	0.4	1.1
Fatigue[b]	--	--	--	--	--
Any	50.6	42.2	46.3	44.9	43.8
Grade 1	31.6	24.9	32.8	27.3	27.5
Grade 2	16.2	14.7	12.3	15.0	14.0
Grade 3	2.9	2.5	1.2	2.6	2.2
Myalgia[b]	--	--	--	--	--
Any	14.8	11.8	12.0	14.4	7.3
Grade 1	9.8	7.9	7.3	9.4	5.1
Grade 2	4.0	3.2	4.0	4.6	2.2
Grade 3	1.0	0.6	0.7	0.4	0
Arthralgia[b]	--	--	--	--	--
Any	8.1	7.3	7.8	7.0	9.6
Grade 1	5.3	5.2	5.1	4.5	8.4
Grade 2	2.1	1.8	2.3	2.5	1.1
Grade 3	0.8	0.4	0.3	0	0
Headache[b]	--	--	--	--	--
Any	41.6	35.6	36.9	37.4	38.8
Grade 1	27.2	23.2	26.1	24.4	25.8
Grade 2	12.3	11.0	9.7	12.0	10.7
Grade 3	2.1	1.4	1.1	1.1	2.2

Source: Adapted from STN 125819/0, Study V72_72 Clinical Study Report, Tables 14.3.1.1, 14.3.1.3, and *"V72_72 Shell tables based on Bexsero IR 10Oct23 including MenABCWY,"* and IR response received February 3, 2025
Abbreviations: N=Number of participants with any solicited AR data for the specific solicited local/systemic AR in the group; n=Number of participants who reported the event or severity of event
Note: Participants were allocated to the vaccine groups as received. Participants in the MenABCWY group received MenABCWY at 0 and 6 months with a placebo dose at 2 and 7 months. Participants in the Bexsero (0, 6 months) group received Bexsero at 0 and 6 months with a dose of Menveo at 2 months and a placebo dose at 7 months. Participants in the Menveo group received a dose of Menveo at 0 months, a placebo dose at 2 months and a dose of Bexsero at 6 and 7 months.
a. For fever - Grade 1: 38.0 – 38.9 C; Grade 2: 39.0 – 39.9 C; Grade 3: ≥40.0 C
b. Other than fever (nausea, fatigue, myalgia, arthralgia, headache) - Grade 1: Mild (easily tolerated); Grade 2: Moderate (interferes with normal activity); Grade 3: Severe (prevents normal activity)

Reviewer Comment: Overall, the rates of solicited systemic reactions were similar across all three study groups and doses.

7.6.2. Safety Results, Study 019

7.6.2.1. Overall Adverse Event Summary, Study 019

Study 019 safety analyses included safety data from 626 participants who received MenABCWY (0, 6 months) and 621 participants who received a single dose of Menveo. Participants in the Menveo group received a dose of Bexsero at 6 and 7 months after their Menveo dose. As of the

data cutoff date of December 28, 2023, safety data were available through 30 days after Dose 2 for 91.2% of enrolled participants the MenABCWY group and 99.5% of the Menveo group. Safety data through 6 months following the final study dose were available for 86.4% of participants in the MenABCWY group and 87.3% of participants in the Menveo group. These safety databases were considered adequate to evaluate the safety of MenABCWY (0, 6 months) in individuals 10 through 25 years of age in conjunction with the safety data from the other clinical studies provided with the BLA submission.

Overall, the proportion of participants reporting adverse events and adverse reactions following MenABCWY were similar to the proportion reported following Bexsero (Table 28). Solicited adverse reactions (ARs) and unsolicited adverse events (AEs) were more common following MenABCWY (0, 6 months) as compared with Menveo. The severities of ARs were similar following MenABCWY and Bexsero and were higher than following Menveo. The percentages of participants reporting related and severe and related unsolicited AEs were similar following all 3 vaccines. Serious adverse events (SAEs), AEs leading to study discontinuation, and adverse events of special interest (AESIs) occurred with similar frequencies following MenABCWY, Bexsero, and Menveo.

Table 28. Proportions of Participants Reporting at Least One Adverse Event Following Vaccination*, Safety Sets, All Ages, Study 019

AE Type: Monitoring Period[a]	MenABCWY Any Dose % (n) N=626	Menveo Any Dose % (n) N=621
Immediate: 30 minutes	16.9 (106)	8.4 (52)
Immediate Unsolicited AEs	0.8 (5)	0.3 (2)
Solicited local reactions[b] at the injection site: Day 1-7	83.2 (521)	31.7 (197)
Grade 3 or above solicited local	6.9 (43)	0.8 (5)
Solicited systemic reactions[c]: Day 1-7	68.4 (428)	51.7 (321)
Grade 3 or above solicited systemic	6.2 (39)	1.9 (12)
Unsolicited AEs: Day 1-30	23.5 (147)	15.0 (93)
Severe AEs	1.1 (7)	0.2 (1)
Related AEs	2.2 (14)	1.8 (11)
Severe and related AEs[d]	0.2 (1)	0.2 (1)
MAAEs: through 2 months after final series dose	16.0 (100)	8.9 (55)
Severe MAAEs	1.0 (6)	0.3 (2)
Related MAAEs	0.6 (4)	0.2 (1)
Severe and related MAAEs	0.2 (1)	0.2 (1)
AESIs: through 2 months after final series dose	0	0.2 (1)
Severe AESIs	0	0
Related AESIs	0	0
Severe and related AESIs	0	0
AEs leading to withdrawal: through 2 months after final series dose	0.3 (2)	0.5 (3)
SAEs: through 2 months after final series dose	1.1 (7)	0
Related SAEs	0	0
Deaths: through 2 months after final series dose	0	0
Related deaths	0	0
MAAEs: Entire study period	35.6 (223)	33.2 (206)
Severe MAAEs	2.9 (18)	1.6 (10)
Related MAAEs	1.6 (10)	1.8 (11)

AE Type: Monitoring Period[a]	MenABCWY Any Dose % (n) N=626	Menveo Any Dose % (n) N=621
Severe and related MAAEs[d]	0.3 (2)	0.6 (4)
AESIs: Entire study period	0	0.6 (4)
Severe AESIs	0	0
Related AESIs	0	0
Severe and related AESIs[d]	0	0
AEs leading to withdrawal: Entire study period	0.6 (4)	1.0 (6)
SAEs: Entire study period	2.9 (18)	1.1 (7)
Related SAEs: Entire study period	0	0
Deaths: Entire study period	0.2 (1)	0.2 (1)
Related deaths[d]: Entire study period	0	0

Source: Adapted from STN 125819, Study MENABCWY-019 (213171) Clinical Study Report (17Jan2024), Tables 14.3.1.1.3, 14.3.1.1.2, 14.3.2.1, 14.3.2.1.2. Additional tables – MenABCWY IR 06 May 2024 Table 7, 8, and 9 and MenABCWY 21Jan2025 Table A. Data cutoff 07NOV2024.
Abbreviations: AE=Adverse Event; MAAE=medically-attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=exposed set; N1= number of participants with available data for the relevant safety set; n=number of participants who reported an event, %=proportion of participants with available data who reported an event
Notes: MenABCWY group= Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of Placebo at Month 7. Menveo group=Participants received 1 dose of Menveo vaccine at Month 0 and two doses of Bexsero at Months 6 and 7. Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.
The Safety Set included all participants who are in the solicited safety set and/or unsolicited safety set.
The Solicited Safety Set included all randomized participants who receive at least 1 vaccine dose and have solicited safety data.
Note: Participants were allocated to the vaccine groups as received.
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local reactions included injection site pain, erythema, swelling, induration.
c. Solicited systemic reactions included fever, nausea, fatigue, myalgia, arthralgia, headache.
d. Relatedness to study vaccine as determined by principal investigator.

Reviewer Comment: The safety findings from Study 019 are comparable those reported in Study V72_72 without substantial differences observed when MenABCWY was administered to participants who were MenABCWY-experienced or MenABCWY-naïve.

7.6.2.2. Deaths, Study 019

There was 1 death in due to completed suicide 108 days after the last MenABCWY dose. This death was not considered related to the study dose by the study investigator.

Reviewer Comment: The clinical reviewer agrees with the investigators' assessments that the reported death was unrelated to the study dose.

7.6.2.3. Serious Adverse Events (SAEs), Study 019

Through the date of data cut-off, SAEs were reported by 2.9% of participants in the MenABCWY group and 1.1% of participants in the Menveo group. There were no SAEs that were considered as related to the study doses by study investigators.

Reviewer Comment: The clinical reviewer agrees with the investigator's assessment that the reported SAEs are likely not related to the study vaccines.

7.6.2.4. Adverse Events of Special Interest (AESIs), Study 019

There were no AESIs reported following MenABCWY during the study. There were 4 AESIs reported in the Menveo group. None of these were considered related to the study doses.

7.6.2.5. Dropouts and/or Discontinuations Due to Adverse Events, Study 019

A total of 4 participants in the MenABCWY group withdrew from the study prematurely due to AEs. Of these, one AE was assessed by the investigator as causally related to study vaccination:

- A 16-year-old female with a history of anxiety, depression, and attention disturbance developed worsened anxiety and trichotillomania 26 days after the second dose of MenABCWY.

  Reviewer Comment: The reported AE of trichotillomania was assessed as possibly related to MenABCWY by the study investigator and as possibly or probably related by the Applicant. The assessment of causality is confounded by the participant's co-morbid conditions including anxiety and depression, which are often associated with a diagnosis of trichotillomania. Therefore, it is plausible that the reported AE was associated with this participant's baseline conditions and not study vaccination, though causality cannot be fully excluded due to the time to onset of the event following vaccination. Similar adverse events of trichotillomania have not been reported across the Applicant's safety database; therefore, this AE does not represent an important safety concern for MenABCWY recipients.

7.6.2.6. Unsolicited AEs Within 30 Days, Study 019

Unsolicited Adverse Events Within 30 days

The unsolicited AEs most reported within 30 days of any dose of MenABCWY recipients and occurring in ≥1% of MenABCWY recipients included COVID-19 (3.5%), headache (1.6%), upper respiratory tract infection (1.3%), upper abdominal pain (1.1%), and nasopharyngitis (1%).

Unsolicited AEs within 30 days of vaccination assessed as causally related to vaccination by the study investigators were reported by 2.2% of MenABCWY recipients, 2.1% of single dose Bexsero recipients, and 1.8% of Menveo recipients. The reported causally related unsolicited AEs were similar/same clinical events that were frequently reported solicited adverse reactions, such as headache.

There were no substantial imbalances in the proportions of participants who had reported unsolicited AE related to vaccination across all three study groups (MenABCWY, Bexsero, or Menveo).

7.6.2.7. Solicited ARs, Study 019

In Study 019, local and systemic ARs were solicited from study participants through 7 days following study Doses 1 and 2.

Solicited Local Reactions

Table 29 presents the frequencies and severities of solicited local ARs within 7 days of study doses. The median day of onset for solicited local ARs following MenABCWY was 1 day (range 2 to 7 days) with a median duration of 2 days (range 1 to 20 days).

The most reported solicited local ARs after MenABCWY were pain (79.9% after Dose 1 and 74.4% after Dose 2), erythema (4.8% after Dose 1 and 6.1% after Dose 2), and Swelling (4.3% after Dose 1 and 5.9% after Dose 2).

Table 29. Frequencies and Severities of Solicited Local ARs By Dose and Study Group, Solicited Safety Set, Study 019

Solicited Local Adverse Reaction	MenABCWY Dose 1 % (n/N1) N=626	MenABCWY Dose 2 % (n/N1) N=571	Menveo % (n/N1) N=621
Any local reaction	78.0 (488/626)	66.2 (378/571)	31.7 (197/621)
Grade 1	36.7 (223/608)	37.5 (190/507)	26.0 (156/601)
Grade 2	39.0 (237/608)	33.3 (169/507)	6.0 (36/601)
Grade 3	4.6 (28/608)	3.7 (19/507)	0.8 (5/601)
Pain[a]	--	--	--
Any	79.9 (486/608)	74.4 (377/507)	31.8 (191/601)
Grade 1	38.3 (233/608)	38.5 (195/507)	25.8 (155/601)
Grade 2	38.5 (234/608)	32.9 (167/507)	5.7 (34/601)
Grade 3	3.1 (19/608)	3.0 (15/507)	0.3 (2/601)
Erythema (redness)[b]	--	--	--
Any	4.8 (29/608)	6.1 (31/505)	1.5 (9/600)
Grade 1	2.1 (13/608)	4.4 (22/505)	1.0 (6/600)
Grade 2	2.1 (13/608)	1.2 (6/505)	0.5 (3/600)
Grade 3	0.5 (3/608)	0.6 (3/505)	0
Swelling [c]	--	--	--
Any	4.3 (26/608)	5.9 (30/505)	2.2 (13/600)
Grade 1	2.6 (16/608)	4.4 (22/505)	1.3 (8/600)
Grade 2	1.3 (8/608)	1.0 (5/505)	0.5 (3/600)
Grade 3	0.3 (2/608)	0.6 (3/505)	0.3 (2/600)
Induration [d]	--	--	--
Any	3.9 (24/608)	4.6 (23/505)	2.3 (14/600)
Grade 1	1.8 (11/608)	3.6 (18/505)	2.0 (12/600)
Grade 2	0.7 (4/608)	0.4 (2/505)	0.2 (1/600)
Grade 3	1.5 (9/608)	0.6 (3/505)	0.2 (1/600)

Source: Adapted from STN 125819, Study MENABCWY-019 (213171) Clinical Study Report (17Jan2024), Table 14.3.1.2. Additional Table 19 and IR response received November 13, 2024. Data cutoff 28Dec2023.

Abbreviations: N=Number of participants with any solicited adverse reaction data for the specific solicited local/systemic AR in the group; N1=number of participants with available data for the relevant adverse reaction; n=Number of participants who reported the event or severity of event
Note: Participants were allocated to the vaccine groups as received. Solicited local adverse reactions were collected following Menveo administered as study dose 1 to participants in the Menveo group.
a. For pain- Grade 1: Mild: Any pain neither interfering with nor preventing normal every day activities.; Grade 2: Moderate: Painful when limb is moved and interferes with every day activities; Grade 3: Severe: Significant pain at rest. Prevents normal every day activities.
b. For erythema Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm
c. For swelling Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm
d. For induration– Grade 1: 25 – 50 mm; Grade 2: 51 – 100 mm; Grade 3: >100 mm

Solicited Systemic Reactions

Table 30 presents the frequencies and severities of solicited systemic ARs within 7 days of study doses. The median day of onset for solicited systemic ARs following MenABCWY was 2 days (1 to 7 days) with a median duration of 1 day (1 to 24 days).

The most frequently reported solicited systemic ARs after MenABCWY were headache (41.0% after Dose 1 and 33.1% after Dose 2), fatigue (40.3% after Dose 1 and 33.1% after Dose 2), and myalgia (14.8% after Dose 1 and 13.3% after Dose 2).

Table 30. Frequencies and Severities of Solicited Systemic ARs By Dose and Study Group, Study 019, Solicited Safety Set

Solicited Systemic Adverse Reaction	MenABCWY Dose 1 % (n/N1) N=626	MenABCWY Dose 2 % (n/N1) N=571	Menveo % (n/N1) N=621
Any systemic reaction	58.9 (369/626)	44.3 (253/571)	51.5 (320/621)
Grade 1	35.9 (218/608)	28.7 (145/505)	32.9 (198/601)
Grade 2	22.0 (134/608)	16.8 (85/505)	18.3 (110/601)
Grade 3	2.8 (17/608)	4.6 (23/505)	2.0 (12/601)
Fever[a]	--	--	--
Any	2.0 (12/608)	1.8 (9/505)	1.2 (7/600)
Grade 1	1.3 (8/608)	1.2 (6/505)	1.0 (6/600)
Grade 2	0.5 (3/608)	0.2 (1/505)	0
Grade 3	0.2 (1/608)	0.4 (2/505)	0.2 (1/600)
Nausea[b]	--	--	--
Any	14.5 (88/608)	11.5 (58/505)	12.5 (75/600)
Grade 1	9.9 (60/608)	8.3 (42/505)	8.3 (50/600)
Grade 2	4.1 (25/608)	2.2 (11/505)	3.5 (21/600)
Grade 3	0.5 (3/608)	1.0 (5/505)	0.7 (4/600)
Fatigue[b]	--	--	--
Any	40.3 (245/608)	33.1 (167/505)	37.0 (222/600)
Grade 1	25.8 (157/608)	18.4 (93/505)	24.0 (144/600)
Grade 2	13.3 (81/608)	12.3 (62/505)	12.5 (75/600)
Grade 3	1.2 (7/608)	2.4 (12/505)	0.5 (3/600)
Myalgia[b]	--	--	--
Any	14.8 (90/608)	13.3 (67/505)	11.2 (67/600)
Grade 1	10.2(62/608)	8.7 (44/505)	8.2 (49/600)
Grade 2	4.4 (27/608)	4.2 (21/505)	2.7 (16/600)
Grade 3	0.2 (1/608)	0.4 (2/505)	0.3 (2/600)
Arthralgia[b]	--	--	--
Any	7.4 (45/608)	5.9 (30/505)	8.2 (49/600)

Solicited Systemic Adverse Reaction	MenABCWY Dose 1 % (n/N1) N=626	MenABCWY Dose 2 % (n/N1) N=571	Menveo % (n/N1) N=621
Grade 1	5.9 (36/608)	4.2 (21/505)	5.3 (32/600)
Grade 2	1.5 (9/608)	1.6 (8/505)	2.8 (17/600)
Grade 3	0	0.2 (1/505)	0
Headache[b]	--	--	--
Any	41.0 (249/608)	33.1 (167/505)	34.6 (208/601)
Grade 1	29.3 (178/608)	22.2 (112/505)	25.1 (151/601)
Grade 2	10.5 (64/608)	9.5 (48/505)	8.8 (53/601)
Grade 3	1.2 (7/608)	1.4 (7/505)	0.7 (4/601)

Source: Adapted from STN 125819, Study MENABCWY-019 (213171) Clinical Study Report (17Jan2024), Tables 14.3.1.2. Additional tables – MENABCWY IR 06 May 2024 Table 19 and IR response received November 13, 2024. Data cutoff 28Dec2023.
Abbreviations: N=Number of participants with any solicited AR data for the specific solicited local/systemic AR in the group; N1=number of participants with available data for the relevant AR; n=Number of participants who reported the event or severity of event.
Notes: Participants were allocated to the vaccine groups as received. Solicited systemic adverse reactions were collected following Menveo administered as study dose 1 to participants in Group ACWY.
a. For fever- Grade 1: 38.0 - 38.9 C; Grade 2: 39.0 - 39.9 C; Grade 3: ≥40 C.
b. For nausea, fatigue, myalgia, arthralgia, and headache - Grade 1: Mild: is easily tolerated; Grade 2: Moderate: interferes with normal activity; Grade 3: Severe: prevents normal activity.

Reviewer Comment: Overall, the reported rates and severities of solicited local and systemic ARs in Study 019 were similar to the results of Study V72_72 and do not suggest substantial differences in the safety profile of MenABCWY when administered to those who received a MenACWY conjugate vaccine at least 4 years prior.

7.6.3. Safety Results, Pooled Analyses

Integrated analyses of safety across the 12 studies were performed according to 3 groups based on participants who received at least one dose of:

1. MenABCWY (final formulation): 3718 participants
2. Bexsero: 2969 participants, not included in the MenABCWY group
3. Menveo: 361 participants, not included in the other groups

Safety data following additional doses administered after the primary series were not included in these analyses.

MenABCWY recipients were a median of 16 years (range 9-42 years). Bexsero recipients were a median age of 16 years (range 9-26 years). Menveo recipients a median age of 14 years (range 10 - 42 years). Females accounted for 43%-53% of participants, 76-90% were white, 6%-15% were black, and 12%-28% were Hispanic or Latino. U.S. participants accounted for 33% of MenABCWY recipients and 34% of Bexsero recipients while 70% of Menveo recipients were from the U.S.

Reviewer Comment: The sample size for the integrated analyses of safety was sufficient to draw meaningful conclusions.

7.6.3.1. Overall Adverse Event Summary, Pooled Analyses

Table 31 shows the proportions of participants with adverse events in pooled safety analyses across the 12 studies. The results of these analyses demonstrated similar patterns of reported adverse events to those of the results of safety analyses in Studies V72_72 and 019.

Table 31. Proportions of Participants Reporting at Least One Adverse Event Following Vaccination, Pooled Analyses of Safety Data[a], 10-25 Years of Age

AE Type: Monitoring Period	MenABCWY[b] % (n/N1) N=3718	Bexsero[c] % (n/N1) N=2969	Menveo[d] % (n/N1) N=361
Unsolicited AEs through 30 days[e]	28.8 (1072)	24.8 (736)	13.0 (47)
Related AEs[f]	6.9 (256)	5.2 (155)	2.8 (10)
MAAEs through 30 days[g]	11.9 (416/3488)	10.6 (302/2861)	3.8 (8/213)
Related MAAEs	0.6 (22/3488)	0.5 (15/2861)	0
SAEs through 30 days	0.6 (22)	0.4 (11)	0.3 (1)
Related SAEs	0.1 (2)	0	0
AESIs through 30 days	0.1 (3/3718)	0.1 (3/2969)	0
Related AESIs	0	0.0 (1/2969)	0
Deaths through 30 days	0.0 (1/3718)	0.1 (2/2969)	0.3 (1/361)
Related Deaths	0	0	0
MAAEs entire study period	33.3 (1162/3488)	27.9 (798/2861)	22.1 (47/213)
Related MAAEs	0.9 (31)	0.7 (20)	0
SAEs: Entire study period	1.9 (70)	2.0 (58)	1.4 (5)
Related SAEs	0.1 (3)	0.1 (2)	0
AESIs: Entire study period	0.4 (15)	0.3 (8)	0.8 (3)
Related AESIs	0.0 (1)	0.1 (2)	0
Deaths: Entire study period	0.0 (1)	0.1 (2)	0
Related Deaths	0	0	0

Source: Adapted from STN 125819, Integrated Summary of Safety, Tables 3, 4, 15, 18, 21, 24, 35, 37
Abbreviations: AE=adverse event; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=exposed set; N1=number of participants with available data for the relevant safety set; n=number of participants who reported an event, %=proportion of participants with available data who reported an event
Notes:
a. Pooled analyses included safety data from studies V102P1, V102_02, V102_02E1, V102_02E2, V102_03, V102_03E1, V102_15, V102_15E1, V102_16, V102_16E1, V72_72 and MenABCWY-019 except as noted below
b. Participants who received at least one vaccination of MenABCWY (final formulation) at any time across studies regardless of other vaccinations received. Participants receiving booster doses were not included in these analyses.
c. Participants not included in the MenABCWY group, who received at least one vaccination of Bexsero at any time across studies regardless of other vaccinations received.
d. Participants not included in the MenABCWY or Bexsero groups, who received at least one vaccination of Menveo at any time across studies regardless of other vaccinations received.
e. In Studies V102P1, V102_02, and V102_03E2, unsolicited safety data were collected through day 7 only.
f. Relatedness to study vaccine as determined by principal investigator.
g. MAAEs were not differentiated from other AE categories in Studies V102P1, V102_02, V102_02E1 and V102_03. As such individuals from these trials were not included in these analyses

7.6.3.2. Deaths, Pooled Analyses

Across the 12 studies, there was one death reported in the MenABCWY group (see Section 7.6.2.2), two deaths in the Bexsero group, and 1 death in the Menveo group. There were no deaths considered related to study doses.

7.6.3.3. Serious Adverse Events (SAEs), Pooled Analyses

A total of 1.9% (n=70) of MenABCWY recipients, 2.0% (n=58) of Bexsero recipients, and 1.4% (n=5) of Menveo recipients reported SAEs. Of these 3 were considered possibly related to the dose of MenABCWY by study investigators. These included 1 participant in Study V72_72 who reported an event of neuromyelitis optica spectrum disorder (NMO), reviewed in Section 7.6.1.3) 1 participant in Study V102_15 who reported an event of connective tissue disorder (case #1 below), and 1 participant in Study V102_15 who reported an event of seizures (case #2 below) following MenABCWY

1. Connective tissue disorder: A 12-year-old female in the MenABCWY (0, 1 month) group in Study V102_15 developed petechiae 7 days after MenABCWY Dose 1, 18 days after MenABCWY Dose 2, and 17-days following Hepatitis A vaccine (Havrix). She was diagnosed with a connective tissue disorder 44 days after PENMENVY Dose 2. Diagnostic testing demonstrated elevated levels of anti-nuclear antibody (ANA) titers, suggestive of an autoimmune connective tissue disorder. The participant had a history of petechiae with abnormal labs prior to study participation. The participant's symptoms resolved, and the event was considered possibly related to the dose of MenABCWY by the study investigator but was considered not related by the Applicant.

   Reviewer Comment: Based on the information provided, the clinical reviewer agrees with the investigator's assessment that the episodes of petechiae were possibly related to the study vaccines associated with post-vaccination exacerbation of an underlying autoimmune condition. Information pertaining to this adverse event will be included in the prescribing information.

2. Seizures: An 18-year-old female in Study V102_15 had a seizure episode 9 hours after receiving MenABCWY, which included feeling dizzy, loss of consciousness, followed by convulsions without fever or other symptoms. Laboratory and imaging evaluations were normal in the Emergency Department and did not experience any further events. The event was considered possibly related to the dose of MenABCWY by the study investigator but was considered not related by the Applicant as they considered psychogenic nonepileptic seizure a more plausible diagnosis.

   Reviewer Comment: The clinical reviewer agrees with the investigator's assessment that the event of seizure is possibly related to the study vaccine based on temporality of the event following vaccination. Information pertaining to this adverse event will be included in the prescribing information.

7.6.3.4. Adverse Events of Special Interest (AESIs), Pooled Analyses

Overall, AESIs within 30 days of study doses were reported by 0.1% of participants included in the MenABCWY group, 0.1% of participants in the Bexsero group, and no participants in the Menveo group. AESIs through study completion were reported by 0.4% (n=15) of participants in the MenABCWY group, 0.3% (n=8) of participants in the Bexsero group, and 0.8% (n=3) of participants in the Menveo group. Among MenABCWY recipients, one AESI was assessed as related to the dose by the study investigator (neuromyelitis optica, see Section 7.6.1.4).

Five of the 14 participants reporting AESIs assessed by study investigators as unrelated to MenABCWY were in Study V72_72 (see Section 7.6.1.4). The remaining 9 participants reporting AESIs assessed as unrelated to the study dose by study investigators included:

1. A 16-year-old female with Crohn's disease 28 days after the second dose of MenABCWY. She had a past medical history of anemia and a family history of ulcerative colitis.
2. A 10-year-old female with Type 1 diabetes mellitus 116 days after the first dose of MenABCWY
3. An 11-year-old female with arthritis (also an SAE) 136 days after the second dose of MenABCWY
4. A 15-year-old male with chondromalacia of the knees 85 days after the first dose of MenABCWY
5. A 17-year-old female with suspected systemic lupus erythematosus 151 days after the second dose of MenABCWY
6. A 22-year-old male with temporomandibular joint syndrome 84 days after the second dose of MenABCWY
7. A 15-year-old female with facial paresis 99 days after the second dose of MenABCWY
8. A 10-year-old male with psoriasis 151 days after the 4th vaccine (Hep A)
9. An 11-year-old female with psoriasis 23 days after the second vaccination (Hep A) and 56 days after the first dose of MenABCWY

Reviewer Comment: The clinical reviewer agrees with the investigators' assessments that the reported AESIs are likely not related to the study doses of MenABCWY based on the interval between study dose and event onset (#1 - #9). For case #1, positive family history likely increased the participant's risk of developing autoimmune disease and the history of anemia that preceded study enrollment was also associated the subsequent diagnosis of Crohn's disease.

7.6.3.5. Dropouts and/or Discontinuations Due to AEs, Pooled Analyses

Through the end of the study periods, unsolicited AEs leading to study withdrawal were reported by 0.4% of MenABCWY recipients, 0.4% of Bexero recipients, and 0.8% of Menveo recipients.

Reviewer Comment: There were no notable imbalances in the overall percentages of participants with unsolicited AEs that led to early study withdrawal.

7.6.3.6. Medically Attended Adverse Events (MAAEs), Pooled Analyses

Across the 8 studies that collected MAAEs as a distinct AE category, MAAEs were reported by 33.3% of MenABCWY recipients, 27.9% of Bexsero recipients, and 22.1% of Menveo recipients. Of these, MAAEs considered related to the study dose were reported by 0.9% of MenABCWY recipients (n=31), 0.7% of Bexsero recipients (n=20), and 0% of Menveo recipients.

Reviewer Comment: MAAEs reported after MenABCWY that were considered related to the study doses by investigators were generally consistent with expected vaccine

reactogenicity characterized with solicited adverse reaction data in the relevant sections above.

MAAE of Interest

A 12-year-old male enrolled in Study V102_15 had a non-serious event reported as 'circulatory collapse' that occurred 1 day after dose 2 of MenABCWY. This event was medically attended but no treatment was reported. The event resolved spontaneously on the same day. The event was assessed as possibly related to study vaccination by the investigator.

Reviewer Comment: The short duration and spontaneous resolution without treatment suggest that this event is consistent with a syncopal episode. Syncope is a potential risk of MenABCWY described in prescribing information.

7.6.3.7. Unsolicited AEs Within 30 Days, Pooled Analyses

Overall, 28.8% (n=1072) of the MenABCWY group, 24.8% (n=736) of the Bexsero group, and 13.0% (n=47) of the Menveo group reported at least one unsolicited AE within 30 days of any vaccination. Unsolicited AEs assessed by study investigators as related to study doses were reported by 6.9% (n=256) of the MenABCWY group, 5.2% (n=155) of the Bexsero group, and 2.8% (n=10) of the Menveo group.

Those unsolicited AEs assessed as related to MenABCWY by study investigators most commonly belonged to the SOCs *General disorders and administration site conditions* (4.6%), *Nervous system disorders* (1.2%), and *Skin and subcutaneous tissue disorders* (0.4%). The most common PTs were *Injection site induration* (1.5%), *Injection site pain* (1.2%), and *Headache* (0.6%).

Unsolicited AEs that were assessed as causally related by the Applicant included syncope, dizziness, and presyncope (0.9%); lymphadenopathy (0.2%); and hypersensitivity (0.1%). The onset of syncope, dizziness, pre-syncope, and lymphadenopathy ranged from 1 to 30 days and the onset of hypersensitivity ranged from 9 to 27 days.

Reviewer Comment: Most unsolicited AEs were consistent with expected vaccine reactogenicity or were common medical conditions in the general population. There were no substantial imbalances in the frequencies of reported AEs following MenABCWY compared with Bexsero or Menveo.

7.7. Pharmacovigilance

7.7.1. Applicant's Pharmacovigilance Plan

In the risk management plan for MenABCWY (Version 1.0), the Applicant notes anaphylactic reactions and syncope as risks not considered important for inclusion in the safety specifications, as they are known risks of administration with vaccines like MenABCWY that require no further characterization and are to be followed via routine pharmacovigilance. Both "allergic reactions" and "syncope" are included in the Warnings and Precautions section of the draft label.

The Applicant identified no important identified risks, important potential risks, or missing information. There were no plans for safety-related postmarketing studies or Risk Evaluation and Mitigation Strategies. The Applicant is thus proposing routine pharmacovigilance for all safety specifications, which includes collection, investigation, and submission to FDA of Individual Case Safety Reports (ICSRs) from postmarketing sources (spontaneous, solicited, literature, and regulatory authorities) according to the timelines defined in 21 CFR 600.80.

7.7.2. Other Relevant Pharmacovigilance Plans

The safety specifications in the risk management plan for Menveo and Bexsero are summarized in the table below.

Table 32. Summary of Safety Concerns for Related Products

Type of Concern	Menveo Risk Management Plan 1.0 (10/10/2018)	Bexsero Risk Management Plan 3.0 (11/17/2022)
Identified	Reconstitution Errors	--
Potential	• Guillain-Barré • Acute disseminated encephalomyelitis • Thrombocytopenia • Vasculitis including Kawasaki disease • Facial paresis • Vaccination failure	• Vasculitis/Kawasaki syndrome • Febrile Seizures • Arthritis
Missing	• Safety during pregnancy and lactation • Safety in subjects with altered immunocompetence • Safety in subjects with bleeding disorder • Safety in patients with serious acute, chronic, or progressive disease • Safety in subjects with a history of GBS • Safety and immunogenicity data in elderly subjects (above 65 years of age)	• Elderly subjects (>50 years of age) • Immuno-compromised subjects • Safety during pregnancy or lactation

Source: FDA generated table

Currently, routine pharmacovigilance are the only risk mitigation activities for the safety concerns for both Menveo and Bexsero, which for Bexsero includes the use of follow-up questionnaires for events of Kawasaki disease, seizures, and arthritis.

7.7.3. FDA Analysis of Applicant's Pharmacovigilance Plan

Based on review of the clinical trial data for MenABCWY as well as the risk management plans and postmarketing experience with Bexsero and Menveo, DPV identified arthritis and seizure as AEs that may be of continued concern for MenABCWY in the indicated population and recommended that arthritis and seizure be added to the safety specifications. The Applicant responded (STN125819/0.43) that the risks did not meet the criteria for inclusion in the risk

management plans and indicated that the data from the MenABCWY pivotal trial safety analysis population, which included approximately 3,600 individuals who received at least 1 dose of the final MenABCWY formulation and were followed for 6 months, should be considered sufficient to characterize its safety profile.

Specifically with respect to the safety issue of seizure, the Applicant suggested that most of the cases associated with Bexsero have been cases of febrile seizures outside of the U.S., occurring in younger children and not within the age range for which MenABCWY is indicated. The Applicant noted that, among the 3718 clinical trial participants who received only the final formulation of MenABCWY, there were 3 non-febrile seizure cases. Two were considered by investigators as not related. The third, an 18-year-old female with a history of panic attacks who experienced generalized convulsive seizures 9 hours after receiving the first dose of MenABCWY, was considered serious and possibly related, but, in response to an IR (STN125819/0.43), the Applicant noted psychogenic nonepileptic seizure as the more plausible diagnosis.

With respect to arthritis, the Applicant noted in STN125819/0.43 that the single case that occurred among participants who received the final formulation of MenABCWY was assessed by the investigator as not related to vaccination. They also note that arthritis is a common condition, occurring in 3.6% of adults 18–34 years of age.

DPV acknowledges that the number of seizure and arthritis cases potentially related to vaccination was low, even when considering those who received the component vaccines in addition to those who received the final formulation of MenABCWY. The pharmacovigilance plans for Menveo and Bexsero did not include risk minimization beyond routine activities. Accordingly, FDA agrees that, for MenABCWY, seizure and arthritis can be monitored through routine pharmacovigilance.

Missing Information:

Pregnancy/lactation: Given that pregnant persons were excluded from the clinical trials in support of this BLA and that the proposed indication includes persons of childbearing age, DPV considers vaccine-associated risks in pregnancy and lactation to be missing information that should be included in the risk management plan. Potential risk minimization activities should include a summary and analysis of all reports of exposure during pregnancy and lactation in the postmarketing dataset in each periodic safety report for both interval and cumulative data as well as a postmarketing study.

The Applicant has proposed a study titled “Assessment of Pregnancy and Birth Outcomes after Exposure to Penmenvy Vaccine in the U.S.: A Cohort Study.” This postmarketing pregnancy safety study will use electronic health records to assess the incidence and risk of pregnancy outcomes in at least 50 individuals exposed to MenABCWY (Penmenvy). The study design is a population-based cohort of publicly and commercially insured pregnant individuals nested within U.S. electronic healthcare claims databases.

Milestone dates for the pregnancy study are listed below:

- Protocol submission date: 06/30/2025

- Study initiation date: 10/31/ 2025
- Study completion date: 08/31/2032
- Final report submission date: 02/28/2033

Pharmacovigilance Conclusion: Should Penmenvy be approved for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age, the proposed pharmacovigilance plan (PVP), version 1.0, dated Jan 10, 2024, is adequate to monitor postmarketing safety for MenABCWY with routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement (PMR) study. Safety in pregnancy and lactation will be characterized in the planned postmarketing commitment (PMC) study.

7.8. Key Review Issues Relevant to the Evaluation of Risk

There were no key review issues identified relevant to the evaluation of risk; there were no trial design concerns that impacted the reviewer's assessment of causality, or any other concerns with the design and conduct of the studies that interfered with the reviewer's evaluation of risk. Refer to Section 7.6 for the safety data applicable to this review.

8. Therapeutic Individualization

8.1. Intrinsic Factors Impacting Dosing Recommendations

Not applicable/available.

8.2. Drug Interactions

Not applicable/available.

8.3. Pediatric Labeling / Plans for Pediatric Product Development

8.4. Pregnancy and Lactation

Pregnancy was an exclusion criterion in all the clinical studies. Women of childbearing potential were evaluated for pregnancy at the screening visit and prior to each study vaccination. Women with a positive pregnancy test were not enrolled (if positive at the screening visit) or did not receive study doses. Participants were followed for outcomes for all reported pregnancies that occurred after study enrollment (Table 33).

Table 33. Outcome of Pregnancies Reported Across All Studies, Exposed Sets (Women), All Studies (BLA 125819/0)

Parameter	MenABCWY n (%) N=2072	*Bexsero* n (%) N=1159	*Menveo* n (%) N=544
Total number of participants reporting pregnancies	9 (0.4%)	10 (0.9%)	3 (0.6%)
Most recent study dose relative to LMP[a]	--	--	--
MenABCWY	2 (0.1%)	0 (0.0%)	1 (0.2%)
Bexsero	0 (0.0%)	3 (0.3%)	1 (0.2%)
Menveo	0 (0.0%)	2 (0.2%)	1 (0.2%)
Other*	6 (0.3%)	1 (0.1%)	0 (0.0%)
Timing of most recent study dose relative to LMP	--	--	--
Prior to LMP	8 (0.4%)	9 (0.8%)	2 (0.4%)
≤30 days after LMP	0 (0.0%)	0 (0.0%)	1 (0.2%)
>30 days after LMP	0 (0.0%)	0 (0.0%)	0 (0.0%)
LMP unknown	1 (0.0%)	1 (0.1%)	0 (0.0%)
Outcome n (%)	--	--	--
Live born – preterm	1 (0.0%)	3 (0.3%)	1 (0.2%)
Live born – full term	3 (0.1%)	5 (0.4%)	1 (0.2%)
Spontaneous abortion/ miscarriage	2 (0.1%)	2 (0.2%)	0 (0.0%)
Elective abortion	0 (0.0%)	0 (0.0%)	1 (0.2%)
Lost to follow-up	3 (0.1%)	0 (0.0%)	0 (0.0%)

Source: STN 125819/0 Am. 52 IR response received December 9, 2024.
Abbreviations: LMP=last known menstrual period; N=Total number of females in exposed set; n (%)=number/percentage of participants.
Note: For Bexsero only data from the final formulation is presented; 1 pregnancy reported in *Bexsero* non-final formulation is not displayed. Other refers to any vaccines used as control including Hepatitis A: HAVRIX and Tdap: ADACEL. Participants in all groups were potentially exposed to other vaccines as per the respective study designs, only the most recent study dose is shown in the table.
a. LMP is unknown for 2 cases (one each in MenABCWY final formulation and *Bexsero* groups) so the most recent dose relative to LMP could not be determined

> **Reviewer Comment:** Interpretation of the pregnancy outcome data is limited by small numbers of reported pregnancies. However, the clinical reviewer agrees with the investigators' assessments of the relatedness of the reported pregnancy outcomes with the MenABCWY doses due to participant co-morbid conditions and timing of the study doses in relation to the pregnancy. No safety concerns regarding MenABCWY were identified.

Lactation

It is not known whether MenABCWY is excreted in human milk. Data are not available to assess the effects of MenABCWY on the breastfed infant or on milk production/excretion.

9. Product Quality

MenABCWY consists of two Drug Product (DP) components that are combined prior to administration. One component is the MenB Component (liquid) supplied in a pre-filled syringe (PFS) containing three recombinant protein antigens (NHBA and fHbp) derived from the *N. meningitidis* serogroup B strains and Outer Membrane Vesicles purified from *N. meningitidis* serogroup B that have been adsorbed onto aluminum hydroxide. The other component is the Lyophilized MenACWY Component (also referred to as MenACWY Lyo) (powder) supplied in

a single-dose vial containing four *N. meningitidis* oligosaccharides generated from the capsular polysaccharides of serogroups A, C, W, and Y (MenA, MenC, MenW, and MenY) that have been conjugated individually to *Corynebacterium Diphtheriae* CRM_{197} protein. The Lyophilized MenACWY Component is reconstituted at the time of use with the serogroup B Component to form MenABCWY.

The Applicant developed and validated in-process and release tests for the manufacture of the drug substances (DS) Intermediates, DSs, DP components, and Final DP. Sufficient chemistry, manufacturing, and controls (CMC) information was provided to assure the identity, strength, purity, potency, and safety of both the liquid and lyophilized drug product components. The proposed manufacturing and testing facilities were found to be acceptable based on their current GMP compliance status and recent relevant inspectional coverage.

Data provided by the Applicant supports an expiry dating period for the Lyophilized MenACWY Component of 18 months from the date of manufacture when stored at 2°C to 8°C and an expiry dating period for the MenB Component of 48 months from the date of manufacture when stored at 2°C to 8°C. The dates of manufacture shall be defined as the date of filling into final containers for the Lyophilized MenACWY Component and the date of formulation for the MenB Component. The expiration date for the packaged product, Lyophilized MenACWY Component plus MenB Component, shall be dependent on the shorter expiration date of either component. The vaccine will be supplied in cartons containing ten single doses of MenABCWY. Each carton of MenABCWY will contain ten vials of Lyophilized MenACWY Component (powder) and ten prefilled TIP-LOK syringes (Luer Lock syringes) of MenB Component (liquid) packaged without needles.

For demonstration of immunogenicity, nonclinical studies in mice and rabbits were first conducted by the Applicant and serological readouts included total IgG antibody and functional antibody titers as measured in ELISAs and serum bactericidal activity assays, respectively. Results indicated the individual vaccine components were immunogenic, with overall enhanced seroresponses observed for animals immunized with three versus two vaccine doses.

The claim for the Categorical Exclusion for the Environmental Assessment was granted.

The Office of Compliance and Biologics Quality has made a final overall “Approval” recommendation for the facilities involved in this application.

For additional product information and specifics, please refer to Section 5.1. above and the CBER CMC BLA Review Memorandum.

9.1. Device or Combination Product Considerations

The MenB Component (liquid) of MenABCWY is supplied in a prefilled syringe (PFS). A review of the PFS description, PFS design verification (including device essential performance, e.g., deliverable volume, break loose force, glide force, withdrawal force), verification of device essential performance over the proposed shelf life and after shipping, control strategy to ensure the final combination product meets essential performance requirements, PFS biocompatibility,

and compliance with applicable device quality system regulations (design controls regulations (21 CFR 820.30), purchasing control regulations (21 CFR 820.50) provided in the application, as well as additional information submitted interactively, and of the Applicant's commitment to provide confirmatory Essential Performance Requirements (EPR) verification data for product stored for 6 and 48 months as product correspondences, were found to be acceptable.

With the BLA, the Applicant proposed a change in (b) (4) presentation from the (b) (4) used in studies conducted under IND to an (b) (4) presentation. Based on the review of the use-related risk assessment rationale submitted under BLA 125819 for PENMENVY and the review of the change to the (b) (4) design, it was determined that the Applicant did not need to submit human factors validation study results with this marketing application.

10. Human Subjects Protections / Clinical Site and Other GCP Inspections / Financial Disclosure

10.1. Submission Quality and Completeness

The submission was adequate for a sufficient assessment of the safety and effectiveness of MenABCWY for the indication of prevention of invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

> **Reviewer comment:** The dataset integrity review team did not identify any major data quality or integrity issues that precluded performing a thorough review.

10.2. Compliance With Good Clinical Practices and Submission Integrity

The studies submitted to this BLA were conducted in accordance with Good Clinical Practice guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR 50.25.

10.3. Clinical Site Inspections

BIMO inspection assignments were issued for four clinical investigator study sites that participated in the conduct of Study Protocol 213171 (MENABCWY–019). The inspections did not reveal significant issues impacting the data submitted in this original Biologics License Application (BLA).

10.4. Financial Disclosure

There were no identified issues related to financial disclosures that would substantially impact the interpretation of study safety and effectiveness results. Refer to Section 23 for Financial Disclosure information.

11. Advisory Committee Summary

An FDA advisory committee was not convened because no unexpected or controversial issues were raised that would benefit from discussion by an advisory committee.

III. Additional Analyses and Information

12. Summary of Regulatory History

The Applicant has developed Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY, proper name: Penmenvy) for active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A, B, C, W, and Y in individuals 10 through 25 years of age. This product was initially developed by Novartis Vaccines and Diagnostics, Inc. Transfer of ownership of the vaccine from Novartis Vaccines and Diagnostics, Inc. to GlaxoSmithKline Biologicals S.A. occurred on July 12, 2016.

A pre-investigational new drug (pre-IND) meeting was held with the Applicant on June 28, 2010, to discuss regulatory, nonclinical, and clinical plans to support the clinical development program in adolescents beginning with a Phase 2 clinical study. A Type B End of Phase 2 (EOP2) meeting was held on September 26, 2019, during which the Applicant discussed their plans for: 1) proposed studies to include the objective to demonstrate noninferiority for the MenB Component, based on an enc-hSBA assay using a randomly selected panel of endemic U.S. serogroup B strains; 2) study vaccination schedule; and 3) appropriate comparator group.

On February 10, 2020, a Type C meeting was held to discuss: 1) a proposal to merge the BEXSERO (Meningococcal Group B Vaccine) post-approval confirmatory study V72_72 with the MenABCWY Phase 3 study (MenABCWY-018) and 2) determination of study endpoints and statistical success criteria.

FDA agreed with the proposed trial design that merged the two Phase 3 studies V72_72 (Bexsero confirmatory trial) and MenABCWY-018 (MenABCWY Phase 3 trial) into a single study. Subsequent communications regarding the study endpoints conveyed the FDA's position that the test-based and responder-based analyses of enc-hSBA responses and analyses of hSBA responses against serogroup B indicator strains were important to demonstrate the effectiveness of the serogroup B component of MenABCWY.

FDA also conveyed that the immune responses following MenABCWY should be reasonably similar to those following Bexsero and that pre-specified statistical non-inferiority criteria should compare the responses following MenABCWY with those following the fully licensed schedule for Bexsero.

The acceptability of the Applicant's revised V72_72 protocol to assess non-inferiority of their MenABCWY vaccine compared with Bexsero in V72_72 was conditional upon the traditional approval of Bexsero. Bexsero was approved under traditional approval on August 19, 2024.

The marketing application for MenABCWY, BLA 125819, was received on February 15, 2024. The BLA was reviewed according to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) VII. The Mid-Cycle Communication meeting occurred on August 19, 2024, with minutes issued on September 18, 2024. The Late Cycle Meeting materials and agenda for the November 15, 2024, meeting was sent to the Applicant on November 5, 2024. The Applicant requested the Late Cycle Meeting be cancelled on November 14, 2024, since no significant review issues were identified by FDA. Discussion of the product labeling for MenABCWY with the Applicant began on January 15, 2025. The applicant included a proprietary name request for PENMENVY which was reviewed and found acceptable by the Advertising and Promotional Labeling Branch**.**

13. Pharmacology Toxicology Assessments and Additional Information

13.1. Summary Review of Studies Submitted Under IND

The nonclinical safety studies of MenABCWY vaccine included a good laboratory practice (GLP) 5-dose intramuscular toxicology study in rabbits with a 2-week recovery period and a pivotal GLP 5-dose intramuscular female fertility, developmental and perinatal/postnatal reproductive study in rabbits. All pertinent studies and findings are summarized below. Reviews of the studies had been completed under the IND.

No adverse, vaccine-related findings were observed in the GLP 5-dose intramuscular toxicology study in (b) (4) rabbits up to the highest doses tested (MenA:C:Y:W10:5:5:5:100 µg of the respective Men A, C, Y, W, and B antigens). No observed adverse effects were reported other than reversible local inflammatory reactions at the injection sites, expected immunogenic response in the lymph nodes and elevations of fibrinogen and c-reactive protein.

In a developmental toxicity study, female rabbits were administered 0.5 mL of MenABCWY at dose of 10:5:5:5:50 µg of the respective Men A, C, Y, W, and B antigens by intramuscular injection on 5 occasions: 35, 21 and 7 days prior to mating, and on gestation days 7 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

13.2. Individual Reviews of Studies Submitted to the BLA

Not applicable.

14. Clinical Pharmacology Assessment: Additional Information

Not applicable

15. Trial Design: Additional Information and Assessment

This section describes the study design of the two pivotal phase 3 studies (V72_72 and 019) that were submitted as evidence of effectiveness and safety. Please refer to Section 16.2 for discussion of the designs of the supportive trials evaluating the safety and effectiveness of MenABCWY.

15.1. Study V72_72

15.1.1. Overview and Objectives

Study V72_72 intends to investigate two products: a meningococcal Group B vaccine (Bexsero) and a Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY). However, this original BLA review focuses on MenABCWY-related objectives only.

The main objectives on the MenABCWY part of V72_72 include:

- to demonstrate the consistency of immune responses from 3 production lots of the MenACWY component of the MenABCWY vaccine,
- to demonstrate the non-inferiority of a 2-dose series of MenABCWY vaccine versus a single dose of Menveo in terms of immune response to meningococcal serogroups A, C, W and Y,
- to demonstrate the vaccine effectiveness using enc-hSBA against a panel of 110 randomly selected endemic U.S. *N. meningitidis* serogroup B invasive disease strains, when administered in a 2-dose (0, 6 months) schedule as a combined MenABCWY vaccine.
- to demonstrate the non-inferiority of the effectiveness of the MenABCWY vaccine versus Bexsero against a randomly selected panel of endemic U.S. *N. meningitidis* serogroup B invasive disease strains, and
- to assess the safety of all study vaccines administered as per their vaccination schedule to healthy subjects aged 10-25 years.

15.1.2. Study Design

Study V72_72 was a phase 3, randomized, controlled, observer-blind, multi-center study to evaluate effectiveness, immunogenicity, and safety of Bexsero and MenABCWY vaccines.

The study was conducted in seven countries (Australia, Canada, Czechia, Estonia, Finland, Turkey, and the United States [U.S.]) for approximately 12 months, including the extended safety follow-up (ESFU) phone call 6 months post-vaccination 3 (Day 181; Visit 5) at Day 361.

Healthy participants between 10 and 25 years of age, inclusive, were eligible for the study. Participants must not have current or previous, confirmed or suspected disease caused by *N. meningitidis.*

Data were to be collected in an observer-blind manner, i.e., the vaccine(s)/product(s) recipient and those responsible for the evaluation of any study endpoint (e.g. safety, reactogenicity, and effectiveness) were unaware of which vaccine/product was administered. Vaccine/product preparation and administration was to be performed by qualified healthcare professional who would not participate in any of the study clinical evaluation.

The laboratory in charge of the laboratory testing was to be blinded to the treatment, and codes were to be used to link the subject and study (without any link to the treatment attributed to the subject) to each sample.

The study interventions administered included injections of MenABCWY (0.5 mL), Menveo (0.5 mL), Bexsero (0.5 mL), or saline placebo (0.65 mL).

Participants were randomly assigned in a 5:5:3:3:3:1 ratio to one of the six parallel study groups:

- Bexsero (0, 2, 6 months): participants to receive 3 doses of Bexsero at Day 1, Day 61 and Day 181 (0, 2, 6-month schedule). These participants were to receive 1 dose of Menveo vaccine at Day 211*. Data from this group will be used to assess both the 0, 2-month and 0, 2, 6-month schedules; the 0, 2-month schedule will be assessed 1 month after the second dose of Bexsero administered at Day 61 (Visit 3), and the 0, 2, 6-month schedule will be assessed 1 month after the third dose of Bexsero at Day 181 (Visit 5), in the same group.
- Bexsero (0, 6 months): participants to receive 2 doses of Bexsero at Day 1 and Day 181 and 1 dose of MenACWY vaccine at Day 61 (Bexsero [0, 6-month schedule]). These participants were to receive 1 dose of placebo at Day 211*.
- MenABCWY-1**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Days 1 and 181 with Lot 1 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- MenABCWY-2**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Day 1 and 181 with Lot 2 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- MenABCWY-3**: participants to receive 2 doses of MenABCWY vaccine 6 months apart (0, 6-month schedule), at Day 1 and 181 with Lot 3 of the MenACWY lyophilized vial component of the vaccine. They were to receive 1 dose of placebo at Day 61 and at Day 211*.
- Menveo group: participants to receive 1 dose of MenACWY vaccine at Day 1, 1 dose of placebo at Day 61 and 2 doses of Bexsero at Day 181 and Day 211*.

* To allow participants in the Bexsero (0, 2, 6 months) group to receive a dose of Menveo and for participants in Menveo group to receive the second dose Bexsero in line with the vaccine as standard of care (also in line with the Advisory Committee on Immunization Practices (ACIP) recommendations in the U.S. [ACIP, 2011]), the participants in these groups received a

vaccination of Menveo and Bexsero, respectively, on Day 211 (Visit 6) after completion of the post-vaccination 3 blood sampling. To maintain the blinding of the study, participants in the rest of the groups (Bexsero [0, 6 months], MenABCWY-1, MenABCWY-2, and MenABCWY-3) received a dose of placebo. All these vaccines/products administered at Day 211 are not associated with any study objectives/ endpoints (safety assessment conducted after 1 dose of Bexsero in the Menveo group at Day 181 is to maintain the blind of the study).

** (1) A Bexsero lot will be used for the pre-filled syringe component of the MenABCWY vaccine; (2) The groups MenABCWY-1, MenABCWY-2, MenABCWY-3 will be pooled into a single group, MenABCWY (pooled lots) (except for analysis of lot-to-lot consistency), if lot-to-lot consistency criteria are met.

Blood samples were planned to be taken for all participants at Visit 1 before vaccination (Day 1), and 30 days after the first, second and third vaccinations (Day 31, Day 91 and Day 211). Solicited local and systemic adverse events (AEs) were collected during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61, and Day 181. Unsolicited AEs were collected during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61, and Day 181. SAEs, AEs leading to withdrawal, AESIs, and medically attended AEs were collected throughout the 12-month study period.

15.1.3. Inclusion and Exclusion Criteria

Inclusion Criteria

- Participants or/and participants' parent(s)/Legally Acceptable Representative(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g., completion of the eDiaries, return for follow-up visits and is available for telephone calls).
- Written or witnessed/thumb printed informed consent obtained from the subject/ parent(s)/ Legally Acceptable Representative(s) of the subject prior to performance of any study specific procedure.
- Written informed assent obtained from the subject (if applicable) prior to performing any study specific procedure.
- A male or female between, and including, 10 and 25 years of age (i.e., 25 years + 364 days) at the time of the first vaccination.
- Healthy participants as established by medical history physical examination and clinical judgment of the investigator before entering the study.
- Participants who are either unvaccinated with Menveo vaccine or have received a single previous dose of Menveo vaccine can participate in the study, if they have received it at least 4 years prior to informed consent and assent as applicable (with the exception of meningococcal C vaccination (MenC), if the last dose of MenC was received at ≤24 months of age).

    - Female participants of non-childbearing potential may be enrolled in the study.
    - Female participants of childbearing potential may be enrolled in the study if the participant

- Has practiced adequate contraception for 30 days prior to vaccination and has a negative pregnancy test on the day of vaccination and has agreed to continue adequate contraception until 30 days after completion of Visit 6.

Exclusion criteria

- Current or previous, confirmed or suspected disease caused by *N. meningitidis*.
- Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitidis* infection within 60 days of enrolment.
- Progressive, unstable or uncontrolled clinical conditions.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Any neuroinflammatory (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalised tonic-clonic seizures, partial complex seizures, partial simple seizures). History of febrile convulsions should not lead to exclusion.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product(s).
- Abnormal function or modification of the immune system
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study
- Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable.
- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s)/product(s) during the period starting 30 days before the first dose of study vaccine(s)/product(s) (Day -29 to Day 1), or planned use during the study period
- Administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 90 days before the first dose of study vaccine/ product or planned administration during the study period until the post-vaccination 3 blood sample (Visit 6).
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 90 days prior to the vaccine/product dose(s) until the post-vaccination 3 blood sample (Visit 6). For corticosteroids, this will mean prednisone ≥20 mg/day (for adult participants) or ≥0.5 mg/kg/day (for pediatric participants), or equivalent. Inhaled and topical steroids are allowed.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- History of /current chronic alcohol abuse and/or drug abuse as determined by the investigator.

15.1.4. Randomization and Subsets

Allocation of the subject to a study group/a treatment number at the investigator site was performed using a randomization system on internet (SBIR). The randomization algorithm used a minimization procedure accounting for study, region (U.S. and ex-U.S. countries)**,** previous MenACWY vaccination (experienced) (Yes and No), and age category (10 through 17 years of

age and 18 through 25 years of age). Minimization factors were planned to have equal weight in the minimization algorithm**.** To ensure adequate representation in the U.S. in line with the postmarketing commitment, a minimum of 30% of adolescents and young adults were to be enrolled in the U.S.

Strain Testing for Serogroup B-Related Primary Objectives

The evaluation of the randomly selected panel of invasive serogroup B strains for each vaccinated subject was not performed for all 110 strains. For each applicable serum sample, a target of 35 strains were chosen completely at random from the 110 strains. The serum sample collected from each subject was sent on an ongoing basis to GSK Clinical Laboratory Sciences or to laboratories delegated by GSK where the assays were available and qualified for the intended use. Aliquots for immunogenicity and enc-hSBA testing were prepared depending on the serum volume available for a visit from one subject. A minimum amount of 5 mL of serum needed to be available to confirm eligibility to perform enc-hSBA testing. In case the volume of serum shipped to the laboratory for enc-hSBA testing was <5 mL, enc-hSBA testing was still performed if the volume of serum allowed to test a minimum number of 20 strains. Otherwise, no enc-hSBA testing was performed with the specific sample.

Serogroup B Randomization Subsets

Endogenous (Enc-hSBA) for serogroup B - Primary Objectives

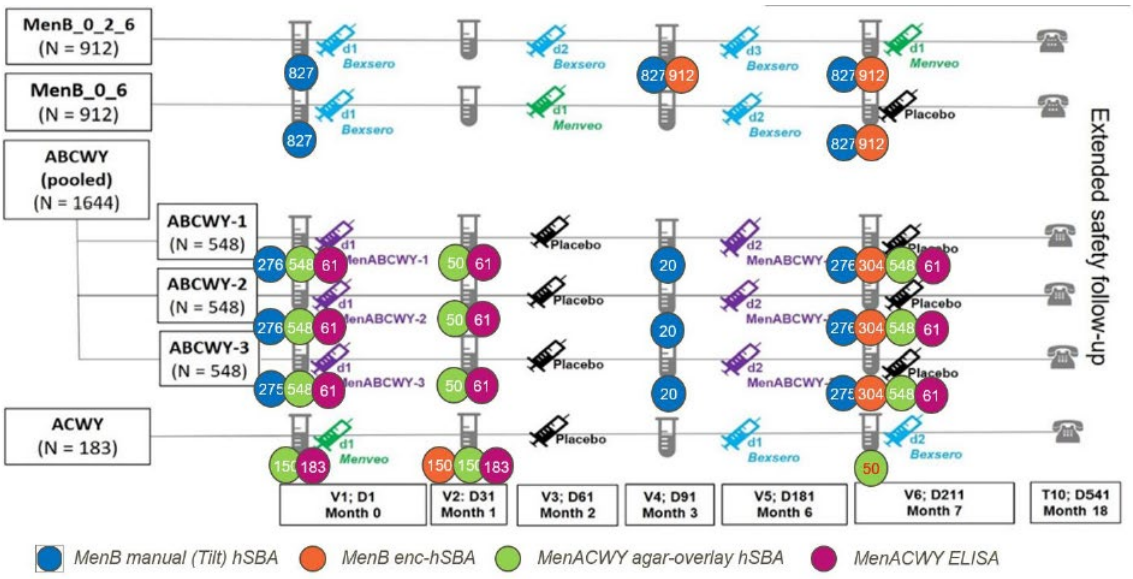
- Bexsero (0, 2, 6 months): all enrolled participants (912) were to be tested for serogroup B enc-hSBA testing, for Visits 4 and 6.
- Bexsero (0, 6 months) group: all enrolled participants (912) were to be tested, for Visit 6.
- For each of the three MenABCWY lots, a subset of 304 out of the enrolled 548 participants could be sampled, for Visit 6.
- For Menveo group, a subset of 150 out of the enrolled 183 participants could be sampled, for Visit 2.

hSBA for serogroup B - Key Secondary Objective

- Bexsero (0, 2, 6 months): a subset of 827 out of the enrolled 912 participants could be sampled, for Visits 1, 4 and 6.
- Bexsero (0, 6 months): a subset of 827 out of the enrolled 912 participants could be sampled, for Visits 1 and 6.
- For each of the three MenABCWY lots, a subset of 276 (MenABCWY-1 and MenABCWY-2) and 275 (MenABCWY-3) out of the enrolled 548 participants could be sampled, for Visits 1 and 6. A subset of 20 out of the enrolled 548 participants could be sampled, for Visit 4.

An overview of the randomization subsets for primary objectives and the key secondary objective is shown in Figure 6.

Figure 6. Study Randomization Subsets, Study V72_72



Source: Additional Analysis Request Form submitted to IND 14605/231.
Abbreviations: MenB_0_2_6=Bexsero (0, 2, 6 months) group; MenB_0_6=Bexsero (0, 6 months) group; ABCWY=MenABCWY group; ACWY=Menveo group

Reviewer Comment: Neither the submitted protocol nor SAP explicitly stated that the immunogenicity data would be based on randomized subsets, except that the sample size and power calculations were based on the sizes of the randomized subsets. The relevant information on randomized subsets was submitted to IND 14605/231 and is included here for completeness.

15.1.5. Study Endpoints

Although all endpoints of Study V72_72 are listed below for completeness, only the results for MenABCWY-related objectives (underlined) are included and reviewed in this memo while the Bexsero-related results were reviewed under BLA 125546/1058.

Note: If the co-primary effectiveness objectives for Bexsero are met, then all objectives below for MenABCWY will be evaluated at 5% type I error rate.

Primary Effectiveness Endpoints

Test-based analysis of Bexsero: The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic U.S. *N. meningitidis* serogroup B strains, at 1 month after the:

- 3-dose vaccination series in Bexsero (0, 2, 6 months) group (i.e. Day 211, Month 7)
- 2-dose vaccination series in Bexsero (0, 6 months) group (i.e. Day 211, Month 7), and
- 2-dose vaccination series in Bexsero (0, 2, 6 months) group (i.e. Day 91, Month 3)
- 1 month after the Menveo vaccination in Menveo group (i.e. Day 31, Month 1).

Responder-based analysis of Bexsero: The percentages of participants whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the:

- 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months group])
- 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months group])
- 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months group])

Lot-to-lot consistency of MenABCWY vaccine: GMTs directed against serogroups A, C, W and Y for each lot (MenABCWY-1 group, MenABCWY-2 group, MenABCWY-3 group) at 1 month after the last vaccination (i.e. Day 211, Month 7).

Immunological non-inferiority of MenABCWY vaccine versus Menveo vaccine: The percentages of participants with 4-fold rise* in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the:

- last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7), and
- 1 month after the Menveo vaccination for the Menveo group (i.e. Day 31, Month 1) relative to baseline (Day 1, Month 0). This objective is evaluated only in participants without a previous MenACWY vaccination (naive).

Table 34 contains the LODs, LLOQs, and ULOQs of each of the serogroups A, C, W, and Y used in the 4-fold rise* definition.

Table 34. LODs, LLOQs, and ULOQs of Serogroups A, C, W, and Y

Serogroup (Antigen)	LOD	LLOQ	ULOQ
A (3125)	5	12	4,295
C (C11)	4	8	61,263
W (240070)	4	8	10,057
Y (860800)	4	10	7,624

Source: Submission to BLA 125819/0, Amendment 3.

*: 4-fold rise for serogroups A, C, W, and Y was defined as:

- a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD
- a post-vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥LOD and <LLOQ, and
- a post-vaccination hSBA titer ≥4 times the pre-vaccination titer for participants with a pre-vaccination hSBA titer ≥LLOQ

Test-based analysis of MenABCWY: The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic U.S. *N. meningitidis* serogroup B strains, at 1 month after the:

- last vaccination for the MenABCWY group (pooled) (i.e. Day 211, Month 7), and
- 1 month after the Menveo vaccination in Menveo group (i.e. Day 31, Month 1).

Non-inferiority of MenABCWY versus Bexsero: The percentages of samples with bactericidal serum activity using enc-hSBA against each of the endemic U.S. *N. meningitidis* serogroup B strains at 1 month after the:

- last MenABCWY vaccination (i.e. Day 211, Month 7) for the MenABCWY group (pooled lots), and
- 3-dose vaccination series of Bexsero (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months group]) or 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months group]) or 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months group]), depending on which objectives of Bexsero are met.

Responder-based analysis of MenABCWY: The percentages of participants whose sera kill ≥70% of the strains tested using enc-hSBA, at 1 month after the last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7).

Primary Safety Endpoints

The frequencies and percentages of participants with solicited local (i.e., injection site pain, erythema, swelling, induration) and systemic (i.e., fever [body temperature ≥38.0°C], nausea, fatigue, myalgia, arthralgia, headache) adverse events (AEs) during the 7 days (including the day of vaccination) following each vaccination at Day 1, Day 61 and Day 181.

The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following each vaccination at Day 1, Day 61, and Day 181.

The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).

Secondary Effectiveness Endpoints

The percentages of subjects with 4-fold rise** in hSBA titers against *N. meningitidis* serogroup B indicator strains at 1 month after the:

- last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7), and
- 3-dose vaccination series of Bexsero (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group or 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group) or 2-dose vaccination series (Day 91, Month 3 in Bexsero [0, 2, 6 months] group), depending on which objectives of Bexsero are met relative to baseline (Day 1, Month 0).

Note: *This objective was identified in the protocol as a "key secondary objective."*

The percentages of samples without bactericidal serum activity using enc-hSBA against each of the endemic U.S. *N. meningitidis* serogroup B strains at 1 month after the:

- 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
- 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
- 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months] group)
- last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7), and
- Menveo vaccination (i.e. Day 31, Month 1 in Menveo group).

The percentages of serogroup B invasive disease strains killed using enc-hSBA in each subject at 1 month after the:

- 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
- 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
- 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months] group), and
- last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7)

The immune response to Bexsero and MenABCWY vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroup B indicator strains as following:

- The percentages of subjects with hSBA titers ≥lower limit of quantitation (LLOQ) for each (individual response) and all (composite response) serogroup B indicator strains at baseline (Day 1, Month 0) and at 1 month after the:

    - 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
    - 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
    - 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months] group), and
    - last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7)

- The percentages of subjects with 4-fold rise** in hSBA titers at 1 month after the:

    - 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
    - 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
    - 2-dose vaccination series (i.e. Day 90, Month 3 in Bexsero [0, 2, 6 months] group), and
    - last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7)

relative to baseline (Day 1, Month 0).

- hSBA GMTs at baseline (Day 1, Month 0) and at 1 month after the:

    - 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
    - 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
    - 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months] group), and
    - last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7)

- hSBA GMRs at 1 month after the:

    - 3-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 2, 6 months] group)
    - 2-dose vaccination series (i.e. Day 211, Month 7 in Bexsero [0, 6 months] group)
    - 2-dose vaccination series (i.e. Day 91, Month 3 in Bexsero [0, 2, 6 months] group), and
    - last vaccination for the MenABCWY group (pooled lots) (i.e. Day 211, Month 7)

  relative to the baseline (Day 1, Month 0).

The immune response to the MenABCWY and Menveo vaccines will be evaluated by measuring bactericidal activity against *N. meningitidis* serogroups A, C, W, and Y as following:

- The percentage of subjects with hSBA titers ≥LLOQ for serogroups A, C, W, and Y at baseline (Day 1, Month 0) and:

    - at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the MenABCWY group (pooled lots), and
    - at 1 month after the MenACWY vaccination in the Menveo group (Day 31, Month 1).

- The percentages of subjects with 4-fold rise* in hSBA titers at 1 month after the:
  - first vaccination (Day 31, Month 1) for the MenABCWY group (pooled lots) compared with the Menveo vaccination in the Menveo group (Day 31, Month 1) relative to baseline (Day 1, Month 0).
- hSBA GMTs against *N. meningitidis* serogroups A, C, W, and Y at baseline (Day 1, Month 0) and:
  - at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the MenABCWY group (pooled lots), and
  - at 1 month after the Menveo vaccination in the Menveo group (Day 31, Month 1).
- hSBA GMRs against *N. meningitidis* serogroups A, C, W, and Y at:
  - 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the MenABCWY group (pooled lots) as compared with baseline (Day 1, Month 0), and
  - 1 month after the single Menveo vaccination in the Menveo group (Day 31, Month 1) as compared with baseline (Day 1, Month 0).
- The total IgG as measured by ELISA GMCs against serogroups A, C, W, and Y at baseline (Day 1, Month 0) and:
  - at 1 month after the first (Day 31, Month 1) and the last MenABCWY vaccination (Day 211, Month 7) for the MenABCWY group (pooled lots), and
  - at 1 month after the Menveo vaccination in the Menveo group (Day 31, Month 1).

Table 35 shows the corresponding LODs and LLOQs of hSBA titers against *N. meningitidis* serogroup B indicator strains used in the definition of 4-fold rise** provided by the laboratory.

Table 35. LODs and LLOQs of hSBA Titers Against *N. meningitidis* Serogroup B Indicator Strains

Strain	Antigen	LOD	LLOQ
NZ98-254	OMV	4	6
96217	NadA	6	14
M14459	fHBP	4	5
M13520	NHBA	4	6

Source: Amendment 3 submitted to BLA 125819/0.

**4-fold rise per each serogroup B indicator strain was defined as:

- a post-vaccination‡ hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for subjects with a pre-vaccination hSBA titer <LOD
- a post-vaccination‡ hSBA titer ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titer ≥LOD and <LLOQ, and
- a post-vaccination‡ hSBA titer ≥4 times the pre-vaccination hSBA titer for subjects with a pre-vaccination hSBA titer ≥LLOQ

‡=post-2nd vaccination of Bexsero for Bexsero (0, 6 months) group and Bexsero (0, 2, 6 months); post-2nd vaccination of MenABCWY for MenABCWY group; and post-3rd vaccination of Bexsero for the Bexsero (0, 2, 6 months) group.

15.1.6. Analysis Sets

The following analysis sets were defined:

- Enrolled Set: Subjects/ Subjects for whom parents/ Legally Acceptable Representatives agreed to participate in a clinical study after completion of the informed consent process, and who met screening/eligibility criteria and were randomized and/or received study intervention or undergone an invasive procedure.
- Exposed Set: All subjects who received at least 1 dose of the study treatment. The allocation in a group is done in function of all administered treatments.
- Full Analysis Set (FAS): All subjects who received at least 1 dose of the study treatment and have post-vaccination effectiveness or immunogenicity data. The FAS is analyzed as randomized.
- Per Protocol Set (PPS): All subjects in the Full Analysis Set minus subjects with protocol deviations that lead to exclusion from the Per Protocol Set.
- Solicited Safety Set: All subjects who received at least 1 dose of the study treatment (Exposed Set) and had solicited safety data beyond 30 minutes post vaccination.
- Unsolicited Safety Set: All subjects who received at least 1 dose of the study treatment (Exposed Set) and reported unsolicited AEs/reported not having unsolicited AEs.
- Overall Safety Set: All subjects that belong to the Unsolicited safety or/and to the Solicited safety set.

15.2. Study 019

15.2.1. Overview and Objective

The co-primary objectives of the study were to demonstrate immunological non-inferiority of the MenABCWY vaccine, compared with Menveo vaccine given to healthy participants, previously vaccinated with a Menveo vaccine, as measured by the percentages of participants achieving a 4-fold rise in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y, at 1 month after the **second** MenABCWY vaccination (0, 6 months) and 1 month after the Menveo vaccination (single dose); and at 1 month after the **first** MenABCWY vaccination (0, 6 months) and 1 month after the Menveo vaccination (single dose).

15.2.2. Study Design

Study 019 was a phase 3, randomized, controlled, observer-blind, multi-center study. The main purpose of the study was to assess the immunogenicity and safety of the MenABCWY vaccine when administered as a booster in healthy adolescents and young adults (15-25 years of age), previously vaccinated with a Menveo conjugate vaccine at least 4 years prior to study enrollment. The study was conducted in four countries (Argentina, Australia, Canada, and the

United States [U.S.]) for approximately 12 months, including the 6 months of Extended Safety Follow-Up (ESFU) period after the last dose of investigational vaccine (Visit 3, Day 181).

Healthy participants between 15 and 25 years of age, inclusive, were eligible for the study. Participants must have been previously vaccinated with 1 dose of MenACWY conjugate vaccine at an age of 10 years or older, with an interval of at least 4 years between the previous MenACWY vaccine and enrollment.

Data were to be collected in an observer-blind manner, i.e., participants, investigators, and teams responsible for assessment of any study endpoints will be blinded to the administered vaccine(s)/product. Study vaccine(s)/product was to be prepared and administered by qualified study personnel would not participate in data collection, evaluation, review, or the entry of any study endpoint (i.e., reactogenicity, safety, immunogenicity).

The laboratory in charge of the laboratory testing was to be blinded to the treatment, subject and visit number, and codes were to be used to link the subject, visit and study (without any link to the treatment attributed to the subject) to each sample.

The study interventions administered included injections of MenABCWY (0.5 mL), Menveo (0.5 mL), Bexsero (0.5 mL), or saline placebo (0.65 mL).

Participants were randomly assigned in a 1:1 ratio to one of two treatment groups:

- MenABCWY group: participants to receive 2 doses of MenABCWY vaccine 6 months apart at Visit 1 (Day 1) and Visit 3 (Day 181) (0, 6-month schedule) and 1 dose of placebo at Visit 4 (Day 211).
- Menveo group: participants to receive 1 dose of Menveo at Visit 1 (Day 1) (single dose) and 2 doses of Bexsero vaccine at Visit 3 (Day 181) and Visit 4 (Day 211).

Blood samples were planned to be taken for all participants at Visit 1 before vaccination (Day 1), and 30 days after the first and second vaccinations (Day 31 and Day 211). Solicited local and systemic adverse events (AEs) were collected during the 7 days (including the day of vaccination) following each vaccination at Day 1 and Day 181. Unsolicited AEs were collected during the 30 days (including the day of vaccination) following each vaccination at Day 1 and Day 181. SAEs, AEs leading to withdrawal, AESIs, and medically attended AEs were collected throughout the 12-month study period.

15.2.3. Inclusion and Exclusion Criteria

Inclusion Criteria

- Participants or/and participants' parent(s)/Legally Acceptable Representative(s) who, in the opinion of the investigator, can and will comply, with the requirements of the protocol (e.g., completion of the eDiaries, return for follow-up visits and is available for telephone calls).
- Written or witnessed/thumb printed informed consent obtained from the subject/parent(s)/ Legally Acceptable Representative(s) of the subject prior to performance of any study specific procedure.

- Written or witnessed/thumb printed informed assent obtained from the subject (if applicable) prior to performing any study specific procedure.
- Previous vaccination with 1 dose of MenACWY conjugate vaccine at an age of 10 years or older, with an interval of at least 4 years between the previous MenACWY vaccine and enrollment into this study.
- A male or female between, and including, 15 and 25 years of age (i.e., 25 years + 364 days) at the time of the first vaccination.
- Healthy participants as established by medical history physical examination and clinical judgment of the investigator before entering into the study.
- Female participants of non-childbearing potential may be enrolled in the study.
- Female participants of childbearing potential may be enrolled in the study, if the participant Has practiced adequate contraception for 30 days prior to vaccination, and has a negative pregnancy test on the day of vaccination, and has agreed to continue adequate contraception until 30 days after completion of Visit 6.

Exclusion criteria

- Current or previous, confirmed or suspected disease caused by N. meningitidis.
- Household contact with and/or intimate exposure to an individual with laboratory confirmed N. meningitidis infection within 60 days of enrolment.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccine(s)/product(s).
- Hypersensitivity, including allergy, to any component of vaccines, including diphtheria toxoid (CRM 197) and latex medicinal products or medical equipment whose use is foreseen in this study.
- Progressive, unstable or uncontrolled clinical conditions.
- Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
- Abnormal function or modification of the immune system resulting from:
- Autoimmune disorders (including, but not limited to: blood, endocrine, hepatic, muscular, nervous system or skin autoimmune disorders; lupus erythematosus and associated conditions; rheumatoid arthritis and associated conditions; scleroderma and associated disorders) or immunodeficiency syndromes (including, but not limited to: acquired immunodeficiency syndromes and primary immunodeficiency syndromes).
- Systemic administration of corticosteroids (oral/intravenous/intramuscular) for more than 14 consecutive days within 90 days prior to study vaccination until the following post-vaccination blood sample. This will mean prednisone equivalent ≥20 mg/day for adult participants / and ≥0.5 mg/kg/day with maximum ≥20 mg/day for pediatric participants. Inhaled and topical steroids are allowed.
- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to study vaccination.
- Administration of long-acting immune-modifying drugs at any time during the study period (e.g., infliximab).

- Any neuroinflammatory (including but not limited to: demyelinating disorders, encephalitis or myelitis of any origin), congenital neurological conditions, encephalopathies, seizures (including all subtypes such as: absence seizures, generalized tonic-clonic seizures, partial complex seizures, partial simple seizures). History of febrile convulsions should not lead to exclusion.
- Any other clinical condition that, in the opinion of the investigator, might pose additional risk to the subject due to participation in the study.
- Use of any investigational or non-registered product (drug, vaccine or medical device) other than the study vaccine(s)/product(s) during the period starting 30 days before the first dose of study vaccine(s)/product(s) (Day -29 to Day 1), or planned use during the study period
- Previous vaccination against any group B meningococcal vaccine at any time prior to informed consent and assent as applicable.
- Previous vaccination with 2 or more doses of MenACWY vaccine.
- Administration/planned administration of immunoglobulins and/or any blood products or plasma derivatives during the period starting 3 months before any dose of study vaccine (s)/product until the following post-vaccination blood sample.
- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs during the period starting 3 months prior to any vaccine/product dose until the following post-vaccination blood sample. For corticosteroids, this will mean prednisone equivalent ≥20 mg/day for adult participants and ≥0.5 mg/kg/day with maximum ≥20 mg/day for pediatric participants. Inhaled and topical steroids are allowed.
- Concurrently participating in another clinical study, at any time during the study period, in which the participant has been or will be exposed to an investigational or a non-investigational vaccine/product (drug or medical device).
- Child in care.
- Pregnant or lactating female.
- Female planning to become pregnant or planning to discontinue contraceptive precautions.
- History of/current chronic alcohol and/or drug abuse.
- Involvement in the study as a study staff member or being immediate dependents, family, or household member of a study staff member.

15.2.4. Randomization and Subsets

The system's randomization algorithm used a minimization procedure accounting for country.

For immunogenicity assessments relevant to the serogroups A, C, W, and Y, samples from all study participants were tested at Day 1 and Day 31, and samples from a random subset of 250 participants in the MenABCWY group and 20 participants in the control group were tested at Day 211. For immunogenicity assessments relevant to the serogroup B test strains, samples from a random subset of 189 participants in the MenABCWY group and 20 participants in the control group were tested at all time points (including Day 1, Day 31, and Day 211).

15.2.5. Relevant Study Endpoints

15.2.5.1. Primary Effectiveness Endpoints

The percentages of participants with a 4-fold rise*** in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the second vaccination for the MenABCWY group (Day 211, Month 7), and 1 month after the single Menveo vaccination for the Menveo group (Day 31, Month 1) relative to baseline (Day 1, Month 0).

The percentages of participants with a 4-fold rise*** in hSBA titers against *N. meningitidis* serogroups A, C, W, and Y at 1 month after the first vaccination for the ABCWY group (Day 31, Month 1), and 1 month after the single dose of Menveo vaccination for the Menveo group (Day 31, Month 1), relative to baseline (Day 1, Month 0).

***: 4-fold rise for the serogroups A, C, W, and Y and for each of the serogroup B indicator strains was defined as:

- a post-vaccination hSBA titer ≥4 times the limit of detection (LOD) for participants with a pre-vaccination hSBA titer < LOD;
- a post-vaccination hSBA titer ≥4 times the LLOQ for participants with a pre-vaccination hSBA titer ≥limit of detection (LOD) but <LLOQ; and,
- a post-vaccination hSBA titer ≥4 times the pre-vaccination titer for participants with a pre-vaccination hSBA titer ≥LLOQ.

The same LODs and LLOQs in Section 15.1for Study V72_72 apply to this study (Study 019).

15.2.5.2. Primary Safety Endpoints

The frequencies and percentages of participants with solicited administration site events (i.e., injection site pain, erythema, swelling, induration) and solicited systemic events (i.e., fever [body temperature ≥38.0°C/100.4°F], nausea, fatigue, myalgia, arthralgia, headache) during the 7 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the MenABCWY and Menveo groups) and Day 181, Month 6 (for the MenABCWY group).

The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, AESIs and medically attended AEs) during the 30 days (including the day of vaccination) following vaccination at Day 1, Month 0 (for the MenABCWY and Menveo groups) and Day 181, Month 6 (for the MenABCWY group).

The percentages of participants with SAEs, AEs leading to withdrawal, AESIs and medically attended AEs throughout the study period (Month 0 to Month 12).

15.2.6. Analysis Sets

The analysis sets for Study 019 were named and defined identically to Study V72_72.

16. Effectiveness Assessment Additional Information and Assessment

The following information and assessments are provided as additional descriptive analyses of effectiveness/immunogenicity data presented in Section 6.2 for Study V72_72 and Study 019, including subpopulation analyses and reverse cumulative distribution curves. In addition, immunogenicity data from supportive trials used to inform the design of Study V72_72 and Study 019 are reviewed, including data from the following studies: V102_15, V102_02, V102_03, V102_16.

16.1. Study V72_72

16.1.1. Descriptive Analyses of Serogroups A, C, W, and Y Responses: U.S. Sites

Table 36. Proportions and Percent Difference of ACWY-Naïve Participants Achieving ≥4-Fold Rise in hSBA Titer 1 Month After Two Doses of MenABCWY or a Single Dose of Menveo for A, C, W, and Y Serogroups, Per Protocol Set, U.S. Study Sites, Study V72_72

Serogroup	MenABCWY n/N (%) (95% CI)	Menveo n/N (%) (95% CI)	MenABCWY-Menveo % Difference (95% CI)
A	220/226 (97.3) (94.3, 99.0)	21/22 (95.5) (78.1, 99.9)	1.89 (-3.00, 19.26)
C	216/225 (96.0) (92.5, 98.2)	15/24 (62.5) (40.6, 81.2)	33.50 (16.87, 53.49)
W	219/225 (97.3) (94.3, 99.0)	20/26 (76.9) (56.4, 91.0)	20.41 (8.08, 39.53)
Y	225/229 (98.3) (95.6, 99.5)	23/26 (88.5) (69.8, 97.6)	9.79 (1.91, 27.33)

Source: Adapted from Table 14.2.2.8 Submitted to Amendment 3 of BLA 125819/0.
Notes: MenABCWY: participants received 2 doses of MenABCWY vaccine at Months 0 and 6, and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY.
Menveo: participants received 1 dose of Menveo at Month 0, 1 dose of placebo at Month 2, and 1 dose of Bexsero at Month 6 with serum taken 1 month after the single dose of Menveo
4-fold rise definition: The 4-fold rise definition differs by pre-vaccination hSBA titer. 4-fold rise is: a post-vaccination hSBA titer ≥4 times the LOD or ≥LLOQ, whichever is greater, for participants with a pre-vaccination hSBA titer <LOD; a post vaccination hSBA titer ≥4 times the LLOQ for participants with a prevaccination hSBA titer ≥LOD and <LLOQ; and a post-vaccination hSBA titer ≥4 times the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥LLOQ. Overall 4-fold rise results include participants meeting any 1 of the 3 definitions.
n: number of participants meeting 4-fold rise definition N: number of U.S. participants with immunogenicity data at baseline and post-vaccination in the per-protocol set.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LOD=5 for MenA (3125), 4 for MenC (C11), MenW (240070), and MenY (860800). LLOQ=12 for MenA (3125); 8 for MenC (C11); 8 for MenW (240070); 10 for MenY (860800).

Reviewer Comment: The proportions of U.S. MenABCWY recipients (N: 225-229) who achieved ≥4-fold rise were comparable to the overall MenABCWY study population (N: 1170-1196). The proportions of U.S. Menveo recipients who achieved ≥4-fold rise were higher than the overall Menveo study population. However, interpretation of these findings are limited due to small sample size of U.S. Menveo participants.

16.1.2. Descriptive Analyses of Serogroup B enc-hSBA Responses: U.S. Sites

Table 37 displays the results of descriptive analyses of the endpoints evaluating enc-hSBA activity against serogroup B strains for participants enrolled at U.S. study sites.

Table 37. Descriptive Analyses: enc-hSBA Activity Against Serogroup B Strains Using Responder-based Analysis and Test-based Analysis, MenABCWY and Bexsero (0, 6 months), 10-25 Years of Age, U.S. Study Sites, Study V72_72

Analysis	MenABCWY (0, 6 months) % (CI)	Bexsero (0, 6 months) % (CI)
Responder-based Analysis[a] enc-hSBA MenABCWY (0, 6 months) N_f =207 Bexsero (0, 6 months) N_f =214	82.1[c] (76.2, 87.1)[e]	88.8[c] (83.0, 93.1)[f]
Test-based Analysis[b] enc-hSBA MenABCWY (0, 6 months) N_p = 192 Bexsero (0, 6 months) N_p = 196	78.1[d] (75.5, 80.4)[g]	82.0[d] (79.5, 84.2)[h]

Source: Adapted from STN 125819/0, Study V72_72 Clinical Study Report, Tables 14.2.2.3.4, 14.2.2.4.4, 14.2.2.9.4, 14.2.2.11.4
Abbreviations: %=percent; CI=confidence interval; Nf=number of participants contributing immunogenicity data to the Full Analysis Set; N_p=number of participants contributing immunogenicity data to the Per Protocol Set.
a. Analysis based on Full Analysis Set.
b. Analysis based on Per Protocol Set.
c. Responder-based point estimate (as a percent): Percent of participants whose sera kill ≥70% of the strains tested using enc-hSBA.
d. Test-based point estimate (as reduction in risk relative to Menveo): 1 - risk ratio=(1- percentage of samples without bactericidal serum activity measured by enc-hSBA in the MenACBWY group / percentage of samples without bactericidal serum activity in the Menveo group) x 100%. The risk ratio and corresponding confidence intervals are estimated using a generalized linear model where treatment group, randomization factors (region (U.S. or ex-U.S.), age category (10-17 years of age or 18-25 years of age), and previous ACWY vaccination (experienced or naive)) were modeled as fixed effects. A repeated statement was used to estimate the variance of the RR including correlation within subject's responses to different strains (approximately 35 strain results/subject).
e. 95% CI for responder-based analysis: 95% two-sided exact CI based on Clopper-Pearson method.
f. 97.5% CI for responder-based analysis: 97.5% two-sided exact CI based on Clopper-Pearson method.
g. 95% CI for test-based analysis: 95% two-sided confidence interval.
h. 97.5% CI for test-based analysis: 97.5% two-sided confidence interval.

Reviewer Comment: Results of descriptive analyses of the enc-hSBA endpoints for U.S. participants were similar to the per protocol test-based and responder-based analyses in Section 6.

16.1.3. Descriptive Analyses of enc-hSBA Responses Against Serogroup B Across Individual Strains

For each individual strain in the 110-strain panel, the percentage of tests with bactericidal activity were as follows by vaccine and dosing regimen:

- MenABCWY (0, 6 months): range 2% to 100%
  - median 97% (25th percentile, 70%; 75th percentile, 99%)
- Bexsero: range 4% to 100%

- Bexsero (0, 6 months): median 97% (25th percentile, 80%; 75th percentile, 99%)
- Bexsero (0, 2, 6 months): median 98% (25th percentile, 85%; 75th percentile, 99%)

- Menveo (single dose): range 0% to 100%,

- median 12% (25th percentile, 3%; 75th percentile, 28%)

Of the approximately 35 serogroup B strains tested per participant in the enc-hSBA assay at 1 month following vaccination, the median percentage killed by each participant's serum was as follows by vaccine and dosing regimen (after last dose):

- MenABCWY (0, 6 months): median 85.3% (25th percentile, 74.3%; 75th percentile, 91.4%)
- Bexsero (0, 6 months): median 88.2% (25th percentile, 80.0%; 75th percentile, 94.3%)
- Bexsero (0, 2, 6 months): median 88.6% (25th percentile, 80.0%; 75th percentile, 94.3%)
- Menveo (single dose): median 17.1% (25th percentile, 11.1%; 75th percentile, 26.7%)

Individual isolates of the 110-strain enc-hSBA panel and their molecular characterization are shown in Table 38 with Study V72_72 results for percent of sera that were positive for bactericidal killing.

Table 38. Molecular Characterization of 110 Endemic U.S. *N. meningitidis* Serogroup B Invasive Disease Isolates and Percent of Sera with enc-hSBA Killing by Vaccine Group, Study V72_72.

Strain	Clonal Complex[b]	VR-2=4[c]	fHbp[d]	NHBA[e]	nadA[f]	MenABCWY[g] (% Sera with enc-hSBA[a] Killing)	Bexsero[h] (% Sera with enc-hSBA[a] Killing)	Menveo[i] (% Sera with enc-hSBA[a] Killing)
(b) (4)		no	2.p0019	29	no	67.6	81.2	9.4
		no	1.p0001	5	yes	99.3	98.8	9.1
		no	1.p0170	10	no	99.1	100.0	76.7
		no	2.p0019	2	no	49.0	65.3	7.5
		no	1.p0001	5	yes	98.9	100.0	58.6
		no	2.p0024	11	no	82.9	91.9	14.9
		no	2.p0024	10	no	96.5	98.2	51.0
		no	1.p0013	24	no	19.9	24.3	0.0
		no	2.p0048	21	no	2.3	4.1	0.0
		no	1.p0001	5	yes	98.9	98.8	22.5
		no	3.p0061	3	yes	99.6	99.6	25.7
		no	1.p0001	5	yes	98.7	99.2	9.3
		no	1.p0001	5	yes	98.0	97.5	2.9
		no	1.p0001	5	yes	97.9	95.9	5.1
		no	1.p0013	122	no	99.6	100.0	100.0
		no	1.p0014	2	no	45.5	56.7	8.9
		no	3.p0061	3	yes	99.3	99.6	15.7
		no	2.p0019	144	no	91.8	95.3	28.6
		no	2.p0078	356	no	65.5	75.3	37.1
		no	3.p0030	12	no	54.5	58.4	8.9
		no	1.p0180	20	no	95.2	98.5	2.3
		no	2.p0021	20	no	88.4	93.1	13.3
		no	1.p0001	5	yes	98.4	99.6	5.0
		no	1.p0001	5	yes	99.6	99.2	61.8
		no	1.p0180	44	no	92.0	93.8	3.4

Strain	Clonal Complex[b]	VR-2=4[c]	fHbp[d]	NHBA[e]	nadA[f]	MenABCWY[g] (% Sera with enc-hSBA[a] Killing)	Bexsero[h] (% Sera with enc-hSBA[a] Killing)	Menveo[i] (% Sera with enc-hSBA[a] Killing)
(b) (4)		no	1.p0001	5	yes	98.5	99.2	7.5
		no	2.p0024	43	no	21.8	25.6	0.0
		yes	1.p0014	2	no	99.6	99.6	46.2
		no	1.p0068	10	no	100.0	100.0	100.0
		no	1.p0001	5	yes	98.1	99.6	14.9
		no	2.p0019	29	no	92.7	92.1	35.5
		yes	2.p0021	20	no	87.9	91.9	33.3
		no	1.p0001	5	yes	98.7	98.0	2.2
		no	1.p0001	5	yes	99.2	99.6	4.8
		no	1.p0001	5	yes	99.6	99.6	27.9
		no	2.p0019	29	no	66.7	79.8	12.5
		no	1.p0001	5	yes	100.0	98.8	20.0
		no	1.p0013	10	no	98.5	98.4	53.1
		no	1.p0001	5	yes	99.6	98.2	2.6
		no	1.p0014	331	no	43.1	53.5	2.0
		no	1.p0013	191	no	33.7	49.2	4.2
		no	1.p0012	18	yes	13.8	16.6	0.0
		no	1.p0001	5	yes	98.8	98.8	7.0
		no	3.p0211	2	no	11.6	13.2	2.0
		no	2.p0019	29	no	99.6	100.0	97.0
		no	1.p0212	10	no	96.4	98.9	16.7
		no	2.p0019	2	no	36.4	47.7	2.4
		no	2.p0016	21	no	100.0	100.0	100.0
		no	2.p0024	10	no	82.4	91.6	17.9
		no	1.p0013	24	no	31.1	52.1	0.0
		no	2.p0021	335	no	85.4	85.7	8.3
		no	1.p0161	20	no	87.0	88.1	25.9
		no	1.p0001	3	yes	97.1	97.1	3.0
		no	1.p0001	5	yes	98.5	98.0	7.5
		no	2.p0024	10	no	98.8	99.6	84.4
		no	2.p0019	29	no	60.7	72.2	8.8
		no	1.p0001	3	yes	99.2	99.2	0.0
		no	2.p0024	10	no	69.5	82.2	14.9
		no	2.p0021	20	no	66.1	73.9	14.0
		no	2.p0019	6	no	33.2	35.8	2.2
		no	2.p0021	20	no	46.1	56.5	19.6
		no	2.p0019	29	no	32.6	38.3	0.0
		no	1.p0001	5	yes	98.0	98.7	16.7
		no	1.p0083	29	no	59.2	69.0	7.7
		no	1.p0001	5	yes	98.8	99.3	32.6
		no	1.p0001	5	yes	97.5	97.6	4.7
		no	2.p0016	143	no	88.0	89.4	34.1
		no	1.p0012	20	no	71.0	70.4	31.8
		yes	1.p0004	2	no	99.6	98.8	2.0
		no	1.p0164	5	yes	99.6	99.6	14.7
		no	1.p0001	5	yes	99.6	99.6	18.4
		no	2.p0024	5	no	99.6	99.2	84.0
		no	2.p0019	2	no	97.1	99.1	33.3
		no	2.p0024	11	no	95.0	93.0	52.3
		yes	1.p0004	2	no	94.9	96.2	5.0

Strain	Clonal Complex[b]	VR-2=4[c]	fHbp[d]	NHBA[e]	nadA[f]	MenABCWY[g] (% Sera with enc-hSBA[a] Killing)	Bexsero[h] (% Sera with enc-hSBA[a] Killing)	Menveo[i] (% Sera with enc-hSBA[a] Killing)
(b) (4)		no	1.p0001	5	yes	98.8	97.1	3.2
		no	1.p0001	5	yes	95.1	94.3	0.0
		no	1.p0189	20	no	78.0	78.8	0.0
		no	1.p0001	5	yes	100.0	99.6	17.5
		no	3.p0317	335	no	54.5	74.9	4.3
		no	1.p0001	5	yes	100.0	98.6	7.3
		no	2.p0021	20	no	100.0	99.2	83.7
		yes	1.p0004	2	no	98.8	99.6	16.3
		yes	1.p0192	26	no	96.8	98.4	0.0
		no	1.p0001	5	yes	96.7	96.6	5.3
		no	1.p0015	21	no	58.8	72.6	2.3
		no	1.p0013	114	FS	93.5	97.9	78.7
		no	1.p0004	2	no	89.5	94.2	5.0
		no	2.p0024	10	no	86.7	91.2	31.4
		no	1.p0195	2	no	98.8	100.0	40.0
		no	2.p0024	10	no	68.2	79.5	13.5
		no	2.p0078	19	no	36.9	40.8	10.0
		no	1.p0001	5	yes	97.9	98.8	7.1
		no	1.p0001	5	yes	98.5	100.0	12.2
		no	2.p0016	21	no	81.6	91.6	3.0
		no	1.p0001	5	yes	99.2	99.3	22.5
		no	1.p0001	5	yes	99.2	97.8	12.2
		no	1.p0001	5	yes	99.2	98.3	4.9
		no	1.p0004	3	yes	100.0	100.0	100.0
		no	1.p0015	21	no	17.8	23.6	0.0
		no	1.p0001	5	yes	97.7	94.6	0.0
		no	1.p0001	5	yes	98.5	100.0	3.2
		no	1.p0001	120	yes	100.0	99.6	7.3
		no	1.p0001	18	yes	81.8	82.6	59.6
		no	1.p0001	5	yes	90.5	96.0	0.0
		no	3.p0031	16	yes	45.6	47.3	13.6
		no	1.p0001	3	yes	99.2	99.6	21.3
		yes	1.p0012	222	no	95.5	94.0	16.2
		no	2.p0016	339	no	90.1	95.8	24.2
		no	1.p0013	114	FS	90.2	96.9	20.6

Source: FDA generated table adapted from STN 125819/0 Study V72_72 Clinical Study Report Tables 14.2.2.13 and (b) (4) *MenB SER enc hSBA 110 strains MQR01*' Appendix 3

[a] enc-hSBA: endogenous complement human serum bactericidal assay. enc-hSBA responses were measured one month after Dose 2 of MenABCWY, one month after Dose 2 of Bexsero (0, 6 months), or one month after a single dose of Menveo. Each participant's serum was tested using the enc-hSBA assay for bactericidal activity (yes/no) against a maximum of 35 strains randomly selected from the 110-strain panel.

[b] Clonal Complex: Multi-Locus Sequence Type (MLST) clonal complex

[c] VR2=4: PorA variable region 2 sequence type 4

[d] fHbp: factor H binding protein variant

[e] NHBA: neisserial Heparin Binding Antigen variant

[f] nadA: neisserial adhesin A gene

[g] MenABCWY Group: participants received 1 dose of MenABCWY vaccine at Day 1, 1 dose of placebo at Day 61, 1 dose of MenABCWY vaccine at Day 181, and 1 dose of placebo at Day 211.

[h] Bexsero Group: participants received 2 doses of Bexsero at Day 1 and Day 181 and 1 dose of Menveo at Day 61 (Bexsero, 0, 6-months schedule). These participants received 1 dose of placebo at Day 211.

[i] Menveo group: participants received 1 dose of Menveo at Day 1, 1 dose of placebo at Day 61 and 2 doses of Bexsero at Day 181 and Day 211.

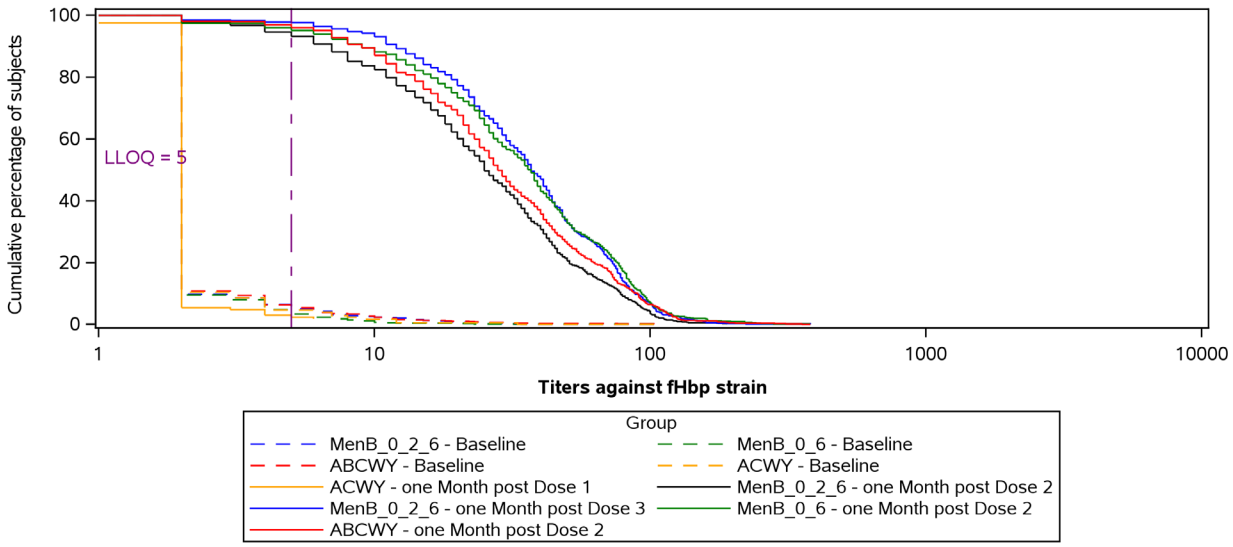
16.1.4. Subpopulation Analyses of Primary Endpoints

The findings of subpopulation analyses of the primary endpoints evaluating responses against serogroup A, B, C, W, and Y strains based on sex, age (10 through 17 years versus 18 through 25 years) were similar to those of the primary analyses. Subgroup analyses by White race showed results that were similar to those of the primary analyses. Meaningful conclusions for subgroup analyses by race were limited by the numbers of participants who reported their race as American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, or Other.

16.1.5. Reverse Cumulative Distribution Curves for Serogroup B hSBA Responses

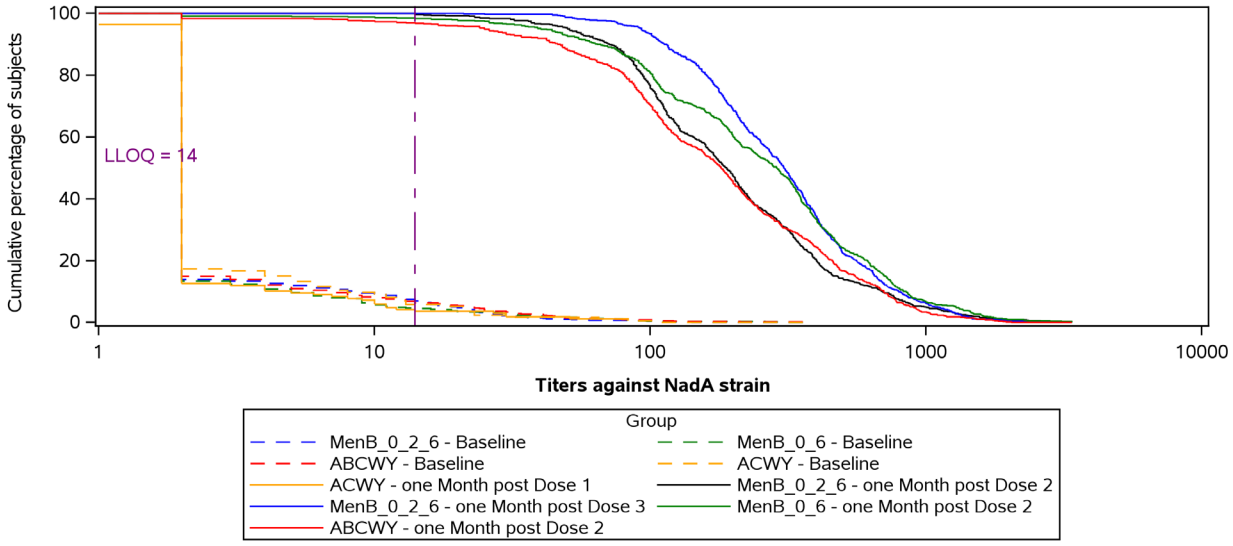
Figure 7, Figure 8, Figure 9 and Figure 10 display the RCD curves of the hSBA titers against each of the four serogroup B indicator strains (fHbp, NadA, NHBA and OMV (PorA) at baseline and following doses 1 and 2 of MenABCWY (0, 6 months), Bexsero (0, 6 months), or Bexsero (0, 2, 6 months).

Figure 7. Reverse Cumulative Distribution of the hSBA Titers Against fHbp Indicator Strain, Study V72_72, Per Protocol Set



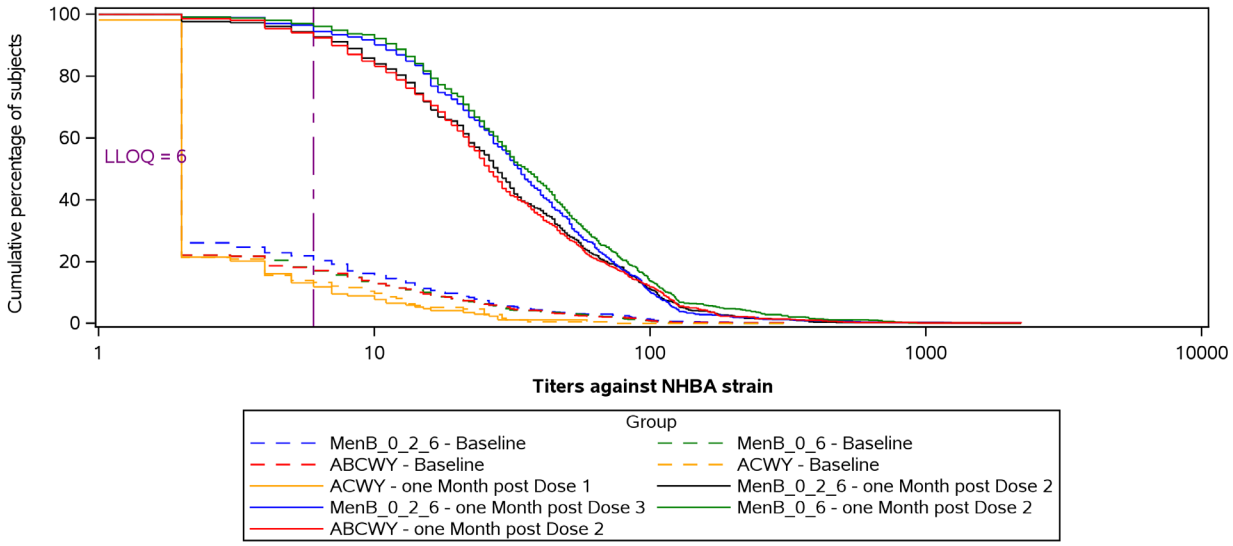
Source: Adapted from STN 125819/0 IR response received October 4, 2024. Figure 1
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY group=Participants received 1 dose of Menveo vaccine, MenB 0_2_6 group received 3 doses of Bexsero at 0, 2, and 6 months, MenB_0_6 group received 2 doses of Bexsero at 0 and 6 months

Figure 8. Reverse Cumulative Distribution Curve of the hSBA Titers Against NadA Indicator Strain, Study V72_72, Per Protocol Set



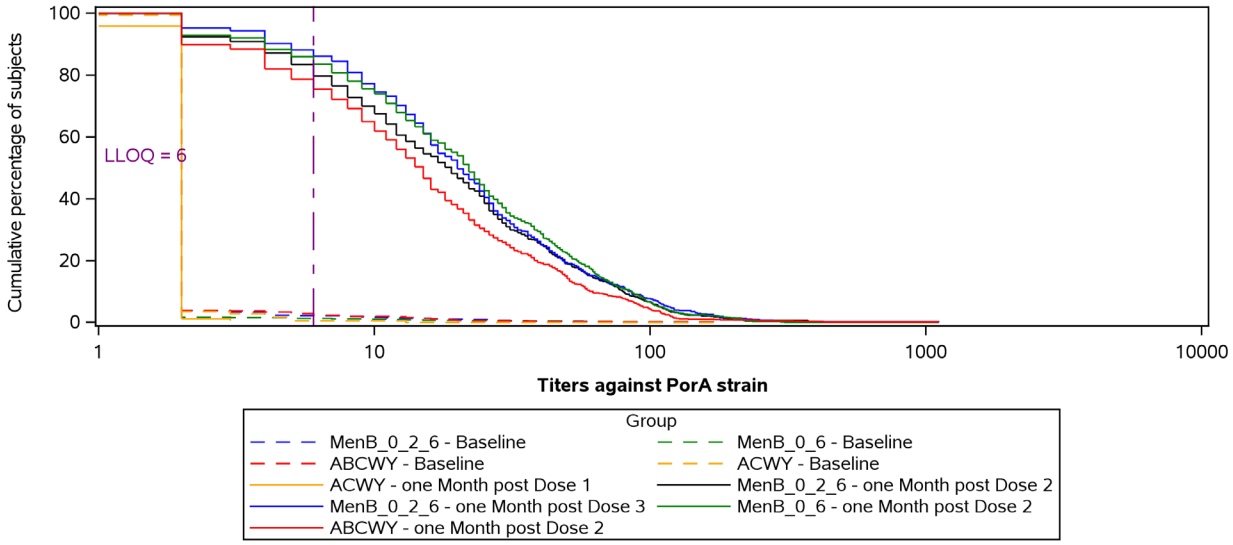
Source: Adapted from STN 125819/0 IR response received October 4, 2024. Figure 1
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY group=Participants received 1 dose of Menveo vaccine, MenB 0_2_6 group received 3 doses of Bexsero at 0, 2, and 6 months, MenB_0_6 group received 2 doses of Bexsero at 0 and 6 months

Figure 9. Reverse Cumulative Distribution Curve of the hSBA Titers Against NHBA Indicator Strain, Study V72_72, Per Protocol Set



Source: Adapted from STN 125819/0 IR response received October 4, 2024. Figure 1
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY group=Participants received 1 dose of Menveo vaccine, MenB 0_2_6 group received 3 doses of Bexsero at 0, 2, and 6 months, MenB_0_6 group received 2 doses of Bexsero at 0 and 6 months

Figure 10. Reverse Cumulative Distribution Curve of the hSBA Titers Against the OMV Indicator Strain, Study V72_72, Per Protocol Set



Source: Adapted from 125819/0 IR response received October 4, 2024. Figure 1
Abbreviations: LLOQ=lower limit of quantification
Notes: ABCWY=Participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2; ACWY group=Participants received 1 dose of Menveo vaccine, MenB 0_2_6 group received 3 doses of Bexsero at 0, 2, and 6 months, MenB_0_6 group received 2 doses of Bexsero at 0 and 6 months

Reviewer Comment: The RCD curves of the hSBA titers against the serogroup B indicator strains demonstrated similar patterns of responses as the key secondary endpoints (section 6.2.1.4) with similar responses against the fHbp and NadA indicator strains and lower responses against the NHBA and OMV indicator strains following MenABCWY (0, 6 months) as compared with (Bexsero 0, 6 months).

16.1.6. Composite hSBA Responses Against Serogroup B Indicator Strains

Table 39 summarizes, for each antigen individually and for all four antigens as a composite, the proportions and corresponding 95% CIs of participants with seroresponses (defined as titers ≥LLOQ) before vaccination 1 and 1 month after Bexsero (0, 6 months) and 1 month after 2 doses of MenABCWY (0, 6 months).

Table 39. Proportions and Percent Difference of Participants Achieving hSBA Titers Greater or Equal to LLOQ for Each (Individual Response) and All (Composite Response) Serogroup B Indicator Strains 1 Month After Two Doses of MenABCWY or Two Doses of Bexsero for Serogroup B Indicator Strains, Full Analysis Set, Study V72_72

Antigen	Rise Definition	MenABCWY n/N (%) (95% CI)	Bexsero n/N (%) (95% CI)	MenABCWY-Bexsero % Difference (95% CI)
fHbp	≥LLOQ before Vaccination 1	41/762 (5.4) (3.9, 7.2)	25/730 (3.4) (2.2, 5.0)	--
--	≥LLOQ 1 month after final	708/738 (95.9) (94.2, 97.2)	669/707 (94.6) (92.7, 96.2)	1.31 (-0.89, 3.58)

Antigen	Rise Definition	MenABCWY n/N (%) (95% CI)	Bexsero n/N (%) (95% CI)	MenABCWY-Bexsero % Difference (95% CI)
	vaccination of schedule			
NadA	≥LLOQ before Vaccination 1	49/780 (6.3) (4.7, 8.2)	32/731 (4.4) (3.0, 6.1)	--
--	≥LLOQ 1 month after final vaccination of schedule	707/734 (96.3) (94.7, 97.6)	693/707 (98.0) (96.7, 98.9)	-1.7 (-3.52, 0.02)
OMV	≥LLOQ before Vaccination 1	16/751 (2.1) (1.2, 3.4)	10/716 (1.4) (0.7, 2.6)	--
--	≥LLOQ 1 month after final vaccination of schedule	534/709 (75.3) (72.0, 78.5)	565/684 (82.6) (79.5, 85.4)	-7.28 (-11.55, -3.01)
NHBA	≥LLOQ before Vaccination 1	129/764 (16.9) (14.3, 19.7)	128/731 (17.5) (14.8, 20.5)	--
--	--			--
--	≥LLOQ 1 month after final vaccination of schedule	679/738 (92.0) (89.8, 93.9)	678/711 (95.4) (93.5, 96.8)	-3.35 (-5.92, -0.86)
Composite --	≥LLOQ before Vaccination 1	8/747 (1.1) (0.5, 2.1)	4/708 (0.6) (0.2, 1.4)	--
--	≥LLOQ 1 month after final vaccination of schedule	495/707 (70.0) (66.5, 73.4)	547/683 (80.1) (76.9, 83.0)	-10.07 (-14.58, -5.54)

Source: Adapted from Table 14.2.2.19IR21 submitted as Amendment 3 to BLA 125819/0.
Abbreviations: CI=confidence interval, hSBA=human serum bactericidal activity, fHbp=factor H binding protein, LLOQ=lower limit of quantitation, NadA= neisserial adhesion protein A, NHBA=neisserial heparin-binding antigen, n= number of participants with response ≥ LLOQ, N= number of participants with available immunogenicity data from the full analysis set
Notes: MenABCWY: participants received 2 doses of MenABCWY vaccine at Months 0 and 6 and 1 dose of placebo at Month 2 with serum taken 1 month after the second dose of MenABCWY as post-vaccination.
Bexsero: participants received 2 doses of Bexsero at Months 0 and 6 and 1 dose of Menveo at Month 2 with serum taken 1 month after the second dose of Bexsero as post-vaccination.
Composite: defined as hSBA titer ≥ LLOQ for all 4 serogroup B antigens.
95% CI*: 95% exact 2-sided confidence interval based upon the observed proportion of participants achieving 4-fold rise, using the Clopper-Pearson method.
95% CI**: 95% confidence interval for the difference in proportions based on the method of Miettinen and Nurminen.
LLOQ=5 for fHbp (M14459); 14 for NadA (96217); 6 for OMV (NZ98/254); 6 for NHBA (M13520).

Both treatment groups showed an increase in proportions of participants with hSBA titers ≥LLOQ compared to baseline. The composite endpoint results were higher for the Bexsero treatment group at 80.1% (95% CI: 76.9%, 83.0%) compared to the MenABCWY group at 70.0% (95% CI: 66.5%, 73.4%), with a difference of -11.48% (95% CI: -15.97%, -6.96%).

Reviewer Comment: The results in Table 39 based on SDTM files submitted to Amendment 3 of BLA 125819/0. Amendment 3 provided updated seroresponse results based on the FDA agreed upon LODs and LLOQs for Serogroup B antigen assays.

16.2. Study 019

16.2.1. Subpopulation Analyses of Primary Endpoints

The findings of subpopulation analyses of the primary endpoints evaluating hSBA responses against serogroup A, C, W, and Y strains based on sex, age (15 – 17 years vs. 18 – 25 years) were similar to those of the primary analyses. Subgroup analyses by White race showed results that were similar to those of the primary analyses. Meaningful conclusions for subgroup analyses by race were limited by the numbers of participants who reported their race as American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, or Other.

16.3. Other Supportive Studies Relevant to the Demonstration of Benefit

16.3.1. Study V102_15 and Study V102_15E1

Study V102_15 was a randomized, controlled, observer-blind, Phase 2b, multicenter study in adolescents 10 through 18 years of age. Participants in the MenABCWY groups received different dosing schedules of MenABCWY (0, 1 month; 0, 2 months; 0, 6 months; 0, 11 months; and 0, 2, 6 months). Participants in the comparator group received the unlicensed Bexsero (0, 2 months) schedule. Hepatitis A vaccine and saline placebo doses were administered to maintain study blinding. The study started August 21, 2014, and completed March 03, 2016.

A total of 1063 participants ages 10 through 18 years old were enrolled in the study from 3 countries (Finland, Poland, and the U.S.) with 228 participants enrolled in the Bexsero group and 134 participants enrolled in the MenABCWY (0, 6 months) group. U.S. participants accounted for 13% of study participants. Participant demographics were generally similar across study groups. Overall, the median age of study participants was 14 years (10 years to 18 years), 57% were female, 95% were White, 4% were Black and 1% were Hispanic or Latino. Study participants were generally healthy and meningococcal vaccine and Hepatitis A vaccine naïve.

Descriptive immunogenicity analyses evaluated hSBA vaccine responses against serogroup A, B, C, W, and Y test strains at 1 month following the last dose of MenABCWY and included hSBA GMTs, and percentages of participants with hSBA titers ≥LLOQ, and with a four-fold rise in hSBA titers. Immunogenicity results from Study V102_15 evaluating different dosing regimens contributed to the selection of the final dosing schedule of MenABCWY administered as 2 doses with a 6-month interval between doses.

> **Reviewer Comment:** Based on the review of immunogenicity data from this study, the Applicant's selection of MenABCWY (0, 6 months) is appropriate.

Study V102_15E1 was an open-label extension study following Study V102_15. In this study, participants in the parent study who received the MenABCWY (0, 2 months), MenABCWY (0, 6 months), or MenABCWY (0, 2, 6 months) schedules received an additional dose of MenABCWY approximately 2 years after the last meningococcal vaccine.

Reviewer Comment: The analyses from V102_15E1 are not presented because the Applicant is not seeking an indication for additional doses of MenABCWY following the completion of the 2-dose regimen administered at 0 and 6 months.

16.3.2. Study V102_16 and Study V102_16E1

Study V102_16 was a randomized, controlled, observer-blind, Phase 2b, multicenter study in adolescents 10 to 18 years of age. Study objectives evaluated the enc-hSBA responses against the 110-strain panel of invasive *N. meningitidis* serogroup B strains prior to and at 1 month after receipt of MenABCWY administered as a 2-dose series, 2 months apart compared with a single dose of Menveo. The study started May 29, 2014, and completed February 15, 2015.

Study V102_16E1 was an extension study in adolescents and young adults that evaluated the hSBA immune response of a third dose of MenABCWY in participants who had previously received two doses of MenABCWY administered two months apart in the parent study, compared with a dose of placebo in participants who had received a single dose of Menveo in the parent study.

Reviewer Comment: Studies V102_16 and V102_16E1 did not evaluate the MenABCWY (0, 6 months) dosing schedule that the Applicant is seeking with this BLA. However, results from these studies were used to evaluate to assess the performance of the enc-hSBA assay for evaluating the breadth of coverage against diverse *Neisseria meningitidis* serogroup B strains and to select the primary immunogenicity endpoints used in Study V72_72.

16.3.3. Study V102_03 and Study V102_03E1

Study V102_03 was an observer-blinded, randomized controlled, Phase 2, multicenter study in adolescents and young adults 10 through 25 years of age to evaluate two different formulations of MenABCWY, one with a full dose OMV and one with a quarter dose OMV (qOMV). Immunogenicity objectives pertinent to selection of the final formulation of MenABCWY evaluated the hSBA responses against serogroup B test strains following a 2-dose, 2-month interval of either of the 2 formulations of MenABCWY compared to Bexsero (0, 2 months). The study started on August 8, 2011, and completed on September 11, 2012.

A total of 484 participants were enrolled in the study from 2 countries (United States and Poland). The median age of participants was 13.0 years; 52% were female; 61% were Caucasian and 32% Hispanic. Participants in the United States were younger (age range 11.0 – 14.0 years), compared with participants in Poland (age range 17.5 – 21.0 years).

The primary immunogenicity population (PPSi) included 343 participants (90 participants in the MenABCWY+OMV group and 85 participants in the MenABCWY+qOMV group). Demographic characteristics were similar to those the overall study population.

Pertinent immunogenicity results from Study V102_03 are summarized in Table 40.

Table 40. Percentage of Participants With a 4-Fold Increase in hSBA Titer at 30 Days After Second Vaccination Against Serogroup B Test Strains: PPS Immunogenicity

Indicator Strain[a]	MenABCWY (0, 2 months) % (95% CI)	MenABCWY-1/4 OMV (0, 2 months) % (95% CI)
fHbp	56 (45, 67)	62 (51, 73)
NHBA	28 (19, 38)	25 (16, 36)
NadA	79 (69, 87)	70 (59, 79)
OMV	47 (36, 58)	48 (37, 59)

Source: Adapted from STN125819/0 Table 11.4.1.4-3, Study V102_03 study report
Abbreviations: CI=confidence interval, hSBA=human serum bactericidal activity, fHbp=factor H binding protein, NadA=neisserial adhesion protein A, NHBA=neisserial heparin-binding antigen, PPS=per-protocol set
a. Serogroup B indicator strains used in exogenous human serum bactericidal activity assay; fHbp=M14459, NHBA=M07-0241084, NadA=M01-0240364, OMV=NZ98/254
Note: Two vaccine groups will be considered significantly different if the two-sided 95% CI for the difference in the percentages between the two vaccine groups will not contain the value '0'.

Reviewer Comment: The immunogenicity results from Study V102_03 supported selection of the final formulation of MenABCWY with the full dose OMV component.

Study V102_03E1 was an extension studies following Study V102_03. In this study, participants in the parent study who received the MenABCWY or MenABCWY (qOMV) received either a 3rd dose of the vaccine or placebo, participants who received Bexsero or Menveo in the parent study received a dose of either MenABCWY, MenABCWY (qOMV), or placebo.

Reviewer Comment: Study V102_03E1 evaluated MenABCWY dosing schedules that the Applicant is not seeking an indication for; therefore, data from this extension study are not considered relevant to assessment of MenABCWY benefit for this BLA.

16.3.4. Study V102_02, V102_02E1, and V102_02E2

Study V102_02 was a phase 2, observer blind, controlled, randomized multi-center study in adolescents, 11 to 18 years of age that evaluated different formulations the MenB component of MenABCWY (full dose fHbp and OMV, full dose fHbp without OMV, double dose fHbp without OMV, full dose fHbp and quarter dose OMV) administered as 2-dose, 2-month interval schedule. The study started on 20 December 2010 and completed on 27 July 2011.

A total of 495 participants were enrolled in the study from 3 countries (Chile, Columbia, and Panama). The median age of participants was 14.0 years (median range in all groups 13.0 – 15.0); 53% were female; 73% were Hispanic (ethnic origin) and 23% were "Other" (ethnic origin). The immunogenicity analysis population (per-protocol set) included 478 participants 1 month after the first vaccination and 478 participants 1 months after the second vaccination. The demographics were similar across all study groups. The relevant immunogenicity results from Study V102_02 are summarized in Table 41.

Table 41. Percentages of Participants With 4-Fold Increase in hSBA Titers Against Serogroup B Indicator Strains at 30 Days After Second Vaccination with MenABCWY, by Vaccine Formulation, Per Protocol Set for Immunogenicity, Study V102_02

Antigen (Indicator Strain)	MenABCWY No OMV % (95% CI)	MenABCWY 2x B and No OMV % (95% CI)	MenABCWY* % (95% CI)	MenABCWY 1/4 OMV % (95% CI)
fHbp	95 (87-99)	96 (89-99)	99 (93-100)	97 (91-100)

Antigen (Indicator Strain)	MenABCWY No OMV % (95% CI)	MenABCWY 2x B and No OMV % (95% CI)	MenABCWY* % (95% CI)	MenABCWY 1/4 OMV % (95% CI)
(H44/76)				
OMV (NZ98/254)	10 (5-19)	14 (7-24)	46 (35-58)	46 (35-58)
NadA (5/99)	95 (87-99)	100 (95-100)	99 (93-100)	100 (95-100)

Source: Adapted from Table 14.2.1.3, Study V102_02 Study Report. *Final formulation.
Abbreviations: CI=confidence interval, hSBA=human bactericidal activity, PP=per-protocol, P=placebo

Reviewer Comment: The immunogenicity results from Study V102_02 contributed to the selection of the final formulation of MenABCWY with full dose fHbp and OMV components.

Study V102_02E1 and Study V102_02E2 were extension studies following Study V102_02. In Study V102_02E1, participants in the parent study received either additional study doses or Tdap, for those vaccinated with one of the formulations of MenABCWY or Bexsero, or Tdap only for those who received Menveo in the parent study. In Study V102_02E2, participants who received MenABCWY (V102_02) + Tdap (V102_02E1) received a dose of MenABCWY and participants who received Menveo (V102_02) + Tdap (V102_02E1) received MenABCWY (0, 2 months).

Reviewer Comment: Studies V102_02E1 and V102_02E2 evaluated MenABCWY dosing schedules that the Applicant is not seeking an indication for; therefore, data from these extension studies are not considered relevant to assessment of MenABCWY benefit for this BLA.

17. Clinical Safety Assessment Additional Information and Assessment

Refer to Section 7.6 for analyses of safety data.

17.1. Subpopulation Analyses of Solicited Adverse Reactions

For the two key studies, Study V72_72 and Study 019, subgroup analyses by age group and sex found similar rates and severities of solicited local ARs as the overall study population. Subgroup analyses for those racial groups that contained sufficient numbers of participants to draw meaningful conclusions demonstrated similar results to those of the overall study population. Subgroup analyses by some races (American Indian/Alaskan Native, Asian, Black/African American [Study V72_72, only], Native Hawaiian/Other Pacific Islander, or Other) were limited by small sample size.

18. Mechanism of Action / Drug Resistance Additional Information and Assessment

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing of *N. meningitidis* strains. (Goldschneider 1969) Immunization with MenABCWY is intended to stimulate the production of antibodies with bactericidal activity specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y and to the protein antigens NHBA, NadA, fHbp and OMV expressed by serogroup B meningococcal strains.

NHBA, NadA, and fHbp are proteins found on the surface of meningococci and contribute to the ability of the bacterium to cause disease. OMV derived from the bacterial outer membrane contains PorA and other surface proteins. The susceptibility of serogroup B meningococci to complement-mediated antibody-dependent killing following vaccination with MenABCWY is dependent on both the antigenic similarity of the bacterial and vaccine antigens, as well as the amount of antigen expressed on the surface of the invading meningococci.

19. Other Drug Development Considerations Additional Information/Reviews

Not applicable.

20. Data Integrity-Related Review (BIMO)

BIMO inspection assignments were issued for four clinical investigator (CI) study sites that participated in the conduct of Study Protocol 213171 (MENABCWY–019) in support of this original BLA. Additionally, BIMO inspections were previously issued for four CI study sites to review the study conduct of Protocol 205416 (V72_72) under a different sBLA submission: BLA STN 125546/1058. The inspections did not reveal significant problems impacting the data submitted in the BLA.

21. Labeling Summary of Considerations and Key Additional Information

The Prescribing Information was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 42. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	N/A
1 INDICATIONS AND USAGE	No major changes made
2 DOSAGE AND ADMINISTRATION	Removed (b) (4) indication and reference to any dosing schedule other than MenABCWY two doses 6 months apart. The data originally submitted for the (b) (4) indication and alternative schedules were from small and/or open-label studies and are not sufficient support for alternative dosing regimens.
3 DOSAGE FORMS AND STRENGTHS	Clarified that the dose is approximately 0.5mL
4 CONTRAINDICATIONS	No major changes made
5 WARNINGS AND PRECAUTIONS	Changed to align with Bexsero and Menveo USPIs, including adding the phrase "PENMENVY may not provide protection against all meningococcal serogroup B strains" under 5.3 "Limitation of Vaccine Effectiveness" and adding a section 5.5 "Guillain-Barré Syndrome."
6 ADVERSE REACTIONS	Added solicited adverse reactions for Study 019 as this was one of the two primary studies contributing safety and immunogenicity data to this review. Added two related serious adverse events. Updated 6.2 "Postmarketing Experience" to include all events in the Bexsero and Menveo USPIs.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Clarified the description of the nonclinical developmental toxicity study, no other significant changes made.
9 DRUG ABUSE AND DEPENDENCE	N/A
10 OVERDOSAGE	N/A
11 DESCRIPTION	Added phrasing to align with Bexsero and Menveo USPIs
12 CLINICAL PHARMACOLOGY	Changed to align with Bexsero USPI, clarified that the protein antigens NHBA, NadA, fHbp and OMV are not unique to meningococcal serogroup B but are expressed by serogroup B meningococcal strains.
13 NONCLINICAL TOXICOLOGY	No major changes
14 CLINICAL STUDIES	Updated to align with Bexsero USPI. Included Bexsero (0, 6 months) and Bexsero (0, 2, 6 months) as comparators for enc-hSBA and exogeneous hSBA responses to better present reduced meningococcal B responses compared with Bexsero (see section 6.3.1). Removed test-based enc-hSBA table and instead consolidated responses in Table 4 "Percentages of Tests With Bactericidal Activity Against Meningococcal Serogroup B Strains Following PENMENVY, Bexsero, and Menveo, Study V72_72" to improve readability and reduce redundancy. Removed references to MenABCWY (b) (4) months dosing regimen and a (b) (4) dose, as these data were from small and/or open-label studies and are not sufficient support for alternative dosing regimens.
16 HOW SUPPLIED/STORAGE AND HANDLING	Edited for clarity
17 PATIENT COUNSELING INFORMATION	No major changes

Source: PENMENVY (Meningococcal Groups A, B, C, W and Y Vaccine) package insert. GlaxoSmithKline Biologics SA.
[1] Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): PI, Prescribing Information

The Advertising and Promotional Labeling Branch reviewed the proposed proprietary name, PENMENVY**,** draft PI, and container from a promotional and comprehension perspective and has found it acceptable. Additionally, the assigned DRMRR labeling reviewers reviewed the carton and container labeling for compliance with the regulations (i.e., Drug Supply Chain Security Act, National Drug Code, Bar Code and Product Identifier) and found the labeling acceptable.

22. Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMRs) and Postmarketing Commitment (PMC) were agreed upon with the Applicant and will be included in the Approval Letter.

PMRs - REQUIRED PEDIATRIC ASSESSMENTS:

1. Deferred pediatric study under PREA (Study MENACWY-MEN7B-003) to evaluate the safety and immunogenicity of MenABCWY in infants and toddlers approximately 2 months through 12 months of age (3-dose series administered at 2, 4, and 12 months of age)

   Final Protocol Submission: June 27, 2024 (Submitted)
   Study Completion Date: March 31, 2025
   Final Report Submission: May 31, 2026

2. Deferred pediatric study under PREA (Study MENABCWY-022) to evaluate the safety and immunogenicity of MenABCWY in children 12 months through 9 years of age

   Final Protocol Submission: June 30, 2025
   Study Completion Date: April 30, 2027
   Final Report Submission: July 31, 2027

3. Deferred pediatric study under PREA (Study MENABCWY-027) to evaluate the safety and effectiveness of MenABCWY in children 2 years through 9 years of age

   Final Protocol Submission: October 31, 2027
   Study Completion Date: March 31, 2031
   Final Report Submission: September 30, 2031

4. Deferred pediatric study under PREA (Study MENABCWY-026) to evaluate the safety and effectiveness of MenABCWY in infants and toddlers 6 weeks through 23 months of age

   Final Protocol Submission: January 31, 2027
   Study Completion Date: May 31, 2032
   Final Report Submission: November 30, 2032

PMC

5. Study titled "Assessment of Pregnancy and Birth Outcomes after Exposure to PENMENVY Vaccine in the U.S: A Cohort Study." This postmarketing pregnancy safety study will use electronic health records to assess the incidence and risk of pregnancy outcomes in at least 50 women exposed to MenABCWY (PENMENVY). The study design is a population-based cohort of publicly and commercially insured pregnant women nested within U.S. electronic healthcare claims databases.

   Final Protocol Submission date: June 30, 2025
   Study Completion Date: August 31, 2032
   Final Report Submission: February 28, 2033

23. Financial Disclosure

Table 43. Covered Clinical Studies: Studies V102P1, V102_02, V102_02E1, V102_02E2, V102_03, V102_03E1, V102_15, V102_15E1, V102_16, V102_16E1, V72_72, and 019

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Sponsor)
Total number of investigators identified: 1449		
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): 1		
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)): Significant payments of other sorts: 1 1. Study 019: One investigator in Study 019 reported payments totaling (b) (4), comprising honoraria as well as speaker fees related to the Sponsor's other meningococcal vaccine (Bexsero). The study site enrolled 1.76% of the overall study participants (n=22).		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Sponsor)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Sponsor)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Sponsor)

24. References

Centers for Disease Control and Prevention (2021) Q&As About Vaccination Options for Preventing Measles, Mumps, Rubella, and Varicella | CDC https://www.cdc.gov/vaccines/vpd/mmr/hcp/vacopt-faqs-hcp.html#:~:text=About%202%2D5%25%20of%20young,and%20varicella%20vaccines%20are%20recommended.

Centers for Disease Control and Prevention (2024) Fainting and Vaccines | Vaccine Safety | CDC https://www.cdc.gov/vaccine-safety/about/fainting.html

Centers for Disease Control and Prevention (2024) Manual for the Surveillance of Vaccine-Preventable Diseases | Chapter 8: Meningococcal Disease | CDC https://www.cdc.gov/surv-manual/php/table-of-contents/chapter-8-meningococcal-disease.html

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Marshall, G. S., Abbing-Karahagopian, V., Marshall, H. S., Cenci, S., Conway, J. H., Occhipinti, E., Bekkat-Berkani, R., Banzhoff, A., & Sohn, W. Y. (2023). A comprehensive review of clinical and real-world safety data for the four-component serogroup B meningococcal vaccine (4CMenB). Expert review of vaccines, 22(1), 530–544. https://doi.org/10.1080/14760584.2023.2222015

25. Review Team Acknowledgments

Table 44. Review Team

Discipline Reviews	Reviewer / Consultant - Office/Division
Clinical • Clinical (Product Office) • Postmarketing safety pharmacovigilance (OBPV/DE) • BIMO	Alaina Halbach, MD, OVRR/DCTR Matthew Swierzbinski, MD, OVRR/DCTR Maria Said, MD, OBPV/DPV Haecin Chun, MS, OCBQ/DIS
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Marcos Battistel, PhD, OVRR/DBPAP Maria Haurat, PhD, OVRR/DBPAP Lunhua Liu, PhD, OVRR/DBPAP Margaret Bash, MD, OVRR/DBPAP Kathryn Matthias, PhD, OVRR/DBPAP Rebecca Brady, PhD, OVRR/DBPAP Jared Greenleaf, PhD, OCBQ/DMPQ Debbie Vause, RN, OCBQ/DMPQ Anil Choudhary, PhD, MBA OCBQ/DBSQC Simleen Kaur, PhD, OCBQ/DBSQC Brianna Davis, PhD, OCBQ/DBSQC Kouassi Ayikoe, PhD, OCBQ/DBSQC Tao Pan, PhD, OCBQ/DBSQC George Kastanis, MS, OCBQ/DBSQC
Statistical • Clinical data (OBPV/DB) • Nonclinical data	Nancy Murray, PhD, OBPV, DB Fang Chen, PhD, OBPV, DB
Nonclinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Ching-Long Sun, PhD, OVRR/DCTR
Labeling Promotional (OCBQ/APLB) Carton and Container (OVRR/RMSB)	Michael Brony, PharmD, OCBQ/DCM CAPT Oluchi Elekwachi, PharmD, OCBQ/DCM Daphne Stewart, OVRR/DRMMR Ching Yim-Banzuelo, OVRR/DRMMR
Other Review(s) not captured above categories, for example: • Medical Device	Andrea Gray, PhD, ORO/DROP

Discipline Reviews	Reviewer / Consultant - Office/Division
• Data Integrity	Brenda Baldwin, PhD, OVRR/DRMMR
• Clinical Data Analyst	Henry (Harry) Houghton, PhD, OBPV/DB
• eDiary/Digital Health	Jessica Zhou, MD, OBPV/DABRA Sylvia Cho, PhD, OBPV/DABRA
• Benefit Risk	Hong Yang, PhD, OBPV/DABRA
• Human Factors Consult	Avani Bhalodia, PharmD, OSE/OMEPRM/DMEPAI
Regulatory	CAPT Edward Wolfgang, PhD, OVRR/DRMRR Maria Bagh, PhD, OVRR/DRMRR Lynsay Ehui, PA-C, MPH, OVRR/DRMRR

Director, Office of Vaccines Research and Review

25.1. Reviewer Signatures

Table 45. Signature of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Alaina Halbach, MD	OVRR/DCTR	2,3,4, 6, 7, 8,10,15,16,17,18, 21, 23 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Matthew Swierzbinski, MD	OVRR/DCTR	2,3,4, 6, 7, 8,10,15,16,17,18, 21, 23 ☒ Authored ☐ Approved
Secondary Reviewer	**Signature:**		
Clinical	Mark Connelly, MD	OVRR/DCTR	2,3,4, 6, 7, 8,10,15,16,17,18, 21, 23 ☐ Authored ☒ Approved
Team Leader	**Signature:**		
Clinical	Anuja Rastogi, MD	OVRR/DCTR	2,3,4, 6, 7, 8,10,15,16,17,18, 21, 23 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Epidemiology/Pharmacovigilance	Maria Said, MD	OBPV/DPV	7 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Epidemiology/Pharmacovigilance	Meghna Alimchandani, MD	OBPV/DPV	7 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Bioresearch Monitoring	Haecin Chun, MS	OCBQ/DIS	10, 20 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Bioresearch Monitoring	Kanaeko Ravenell, MS, SBB (ASCP)	OCBQ/DIS	10, 20 ☐ Authored ☒ Approved
Supervisor	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical dataset integrity	Brenda Baldwin, PhD	OVRR/DCTR	7 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Pharmacology/Toxicology	Ching-Long (Joe) Sun, PhD	OVRR/DCTR	7, 13 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Pharmacology/Toxicology	Dave Green, PhD	OVRR/DCTR	7, 13 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Statistical	Nancy Murray, PhD	OBPV/DB	6, 7.6 (contributed), 15, 16 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Statistical	Lei Huang, PhD	OBPV/DB	6, 7.6, 15, 16 ☐ Authored ☒ Approved
Team Leader	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Tsai-Lien Lin, PhD	OBPV/DB	6, 7.6, 15, 16 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Clinical Data Analyst	Harry Houghton, MS	OBPV/DB	7 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Statistical/Clinical Data Analyst	John Scott, PhD	OBPV/DB	7 ☐ Authored ☒ Approved
Division Director	**Signature:**		
Labeling	Michael Brony, PharmD	OCBQ/DCM	21 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Labeling	Lisa Stockbridge, PhD	OCBQ/DCM	21 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Labeling	Daphne Stewart	OVRR/DRMMR	21 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Labeling	Ching Yim-Banzuelo	OVRR/DRMMR	21 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Labeling	Cassandra Overking, MPH	OVRR/DRMMR	21 ☐ Authored ☒ Approved
Supervisor	**Signature:**		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
eDiary/Digital Health Technologies	Jessica Zhou, MD	OBPV/DABRA	7 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Benefit/Risk	Hong Yang, PhD	OBPV/DABRA	2 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
Benefit/Risk	Barbee Whitaker, PhD	OBPV/DABRA	2 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
eDiary/Digital Health Technologies	Sylvia Cho, PhD	OBPV/DABRA	7 ☒ Authored ☐ Approved
Reviewer	**Signature:**		
eDiary/Digital Health Technologies	Richard Forshee, PhD	CBER/OBPV	7 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Regulatory	CAPT Edward Wolfgang, PhD	OVRR/DRMMR	1, 3, 9, 11, 12, 22, 25 ☒ Authored ☐ Approved
Chair	**Signature:**		
Regulatory	Julianne Clifford, PhD	OVRR/DRMMR	1, 3, 9, 11, 12, 22, 25 ☒ Authored ☐ Approved
Team Leader	**Signature:**		

Regulatory/Clinical Dataset Integrity	Elizabeth Sutkowski, PhD	OVRR/DRMMR	1, 3, 7, 9, 11, 12, 22, 25 ☐ Authored ☒ Approved
Supervisor	**Signature:**		
Regulatory	Loris McVittie, PhD	OVRR/DRMMR	1, 3, 9, 11, 12, 22, 25 ☐ Authored ☒ Approved
Division Director	**Signature:**		
Clinical	Douglas Pratt, MD	OVRR/DRMMR	2,3,4, 6, 7, 8,10,15,16,17,18, 21, 23 ☐ Authored ☒ Approved
Deputy Division Director	**Signature:**		