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<b>Committee Chair</b>	Mike Smith
<b>Clinical Reviewers</b>	Margaret Bash and Lucia Lee
<b>Project Manager</b>	Brynn Hollingsworth and Moonsuk Choi
<b>Priority Review</b>	No
<b>Reviewer Name</b>	Xinyu Tang
<b>Review Completion Date / Stamped Date</b>	
<b>Concurrence</b>	Lei Huang, Concurring Reviewer, VEB, DB, OBPV
	Tsai-Lien Lin, Branch Chief, VEB, DB, OBPV
	John A. Scott, Director, DB, OBPV
<b>Applicant</b>	Pfizer Ireland Pharmaceuticals
<b>Established Name</b>	Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY)
<b>Trade Name</b>	PENBRAYA®
<b>Pharmacologic Class</b>	Vaccine
<b>Formulation, including Adjuvants, etc</b>	After reconstitution, a single dose of 0.5 mL contains 5ug each of meningococcal serogroup A, C, W, and Y polysaccharides individually conjugated to tetanus toxoid [TT] (total 44 ug TT), 60 ug meningococcal B fHbp subfamily A, 60 ug meningococcal B fHbp subfamily B, and 0.25 mg aluminum as AlPO4
<b>Dosage Form and Route of Administration</b>	Suspension, intramuscular
<b>Dosing Regimen</b>	Administer 2 doses (approximately 0.5 mL each) 6 months apart
<b>Indication and Intended Population</b>	Active immunization of individuals 10 through 25 years of age to prevent invasive disease caused by <i>Neisseria meningitidis</i> groups A, B, C, W, and Y

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## GLOSSARY

ACWY	meningococcal groups A, C, W, and Y vaccine
AE	adverse event
AlPO <sub>4</sub>	Al <sub>3</sub> <sup>+</sup> as aluminum phosphate
BLA	biologics license application
CI	confidence interval
CSR	clinical study report
e-diary	electronic diary
E-DMC	external data monitoring committee
FDA	Food and Drug Administration
fHBP	factor H binding protein
GCP	Good Clinical Practice
GMT	geometric mean titer
hSBA	serum bactericidal assay using human complement
ICD	informed consent document
ICH	International Council for Harmonisation
IM	intramuscular
IND	investigational new drug application
IRT	interactive response technology
LLOQ	lower limit of quantitation
LOD	limit of detection
MAE	medically attended adverse event
MenA	<i>Neisseria meningitidis</i> serogroup A
MenABCWY	meningococcal groups A, B, C, W, and Y vaccine
MenACWY	<i>Neisseria meningitidis</i> serogroups A, C, W, and Y
MenACWY-CRM	meningococcal groups A, C, Y, and W-135 oligosaccharide diphtheria conjugate vaccine (Menveo)
MenACWY-TT	meningococcal polysaccharide groups A, C, W-135, and Y tetanus toxoid conjugate vaccine (Nimenrix)
MenB	<i>Neisseria meningitidis</i> serogroup B
MenC	<i>Neisseria meningitidis</i> serogroup C
MenCYW-135	meningococcal groups C, Y, and W-135
MenW	<i>Neisseria meningitidis</i> serogroup W
MenY	<i>Neisseria meningitidis</i> serogroup Y
mITT	modified intent-to-treat
NDCMC	newly diagnosed chronic medical condition
NI	noninferiority
PFS	prefilled syringe
Pfizer	Pfizer Ireland Pharmaceuticals
PRP-OMP	polyribosylribitol phosphate oligosaccharide of <i>Hemophilus influenzae</i> type b conjugated to outer membrane protein
SAE	serious adverse event
TT	tetanus toxoid
U.S.	United States

## 1. Executive Summary

Pfizer Ireland Pharmaceuticals (Pfizer) submitted an original Biologics License Application (BLA) on October 21, 2022 for a Meningococcal Groups A, B, C, W, and Y Vaccine (MenABCWY). The proposed indication is active immunization to prevent invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age. The proposed dosage and administration route are 2 doses (approximately 0.5 mL each) via intramuscular (IM) injection 6 months apart.

This memo focuses on the statistical review of safety and immunogenicity data from the pivotal study C3511001, a Phase 3, randomized, active-controlled, observer-blinded, multicenter trial to assess the safety, tolerability, and immunogenicity of MenABCWY in healthy participants 10 through 25 years of age. A total of 2,431 participants, who were naïve to any meningococcal group B vaccine prior to enrollment, were randomly assigned to receive either

- MenABCWY + saline at Month 0 (Vaccination 1) and MenABCWY at Month 6 (Vaccination 2) (n=1,778), or
- Trumenba + MenACWY-CRM (Menveo) at Month 0 (Vaccination 1) and Trumenba at Month 6 (Vaccination 2) (n=653),

stratified by ACWY vaccination history (i.e., ACWY-naïve and ACWY-experienced defined as receiving a United States (U.S.)-licensed MenACWY vaccine at least 4 years prior to enrollment), and geographic region (80% U.S. sites and 20% non-U.S.).

The primary immunogenicity objectives of study C3511001 were

- to demonstrate that the immune response against *Neisseria meningitidis* serogroup A (MenA), *Neisseria meningitidis* serogroup C (MenC), *Neisseria meningitidis* serogroup W (MenW), and *Neisseria meningitidis* serogroup Y (MenY) induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately, and
- to demonstrate that the immune response against *Neisseria meningitidis* serogroup B (MenB) induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.

The MenA, MenC, MenW, MenY, and MenB immune responses were measured by serum bactericidal assays using human complement (hSBAs) against MenA strain F8238, MenC strain C-11, MenW strain MP01240070, MenY strain S-1975 and MenB strains PMB2001 (A56), PMB2707 (B44), PMB80 (A22) and PMB2948 (B24), respectively.

The primary immunogenicity endpoints included

- seroresponse in hSBA titer for each of the ACWY test strains, defined as achieving at least a 4-fold rise in hSBA titer 1 month after 2 doses of MenABCWY or 1 month after 1 dose of MenACWY-CRM from baseline,
- seroresponse in hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44), defined as achieving at least a 4-fold rise in hSBA titer 1 month after 2 doses of MenABCWY or Trumenba from baseline, and

- composite response in MenB test strains, defined as achieving an hSBA titer  $\geq$  lower limit of quantitation (LLOQ) at 1 month after 2 doses of MenABCWY or Trumenba for all 4 primary MenB test strains (i.e.,  $\geq 1:16$  for A22, and  $\geq 1:8$  for A56, B24, and B44).

Only a subset of the study population contributed to immunogenicity evaluations. The immunogenicity subset included 1,080 and 537 participants randomized to MenABCWY and Trumenba + MenACWY-CRM groups, respectively. The post-Vaccination 1 evaluable immunogenicity population included 961 (89.0%) MenABCWY recipients (512 ACWY-naïve and 449 ACWY-experienced) and 485 (90.3%) Trumenba + MenACWY-CRM recipients (258 ACWY-naïve and 227 ACWY-experienced). The post-Vaccination 2 evaluable immunogenicity population included 851 (78.8%) MenABCWY recipients (456 ACWY-naïve and 395 ACWY-experienced) and 423 (78.8%) Trumenba recipients (239 ACWY-naïve and 184 ACWY-experienced). Key immunogenicity results are summarized as follows:

- For the MenACWY noninferiority (NI) evaluation in ACWY-naïve participants, proportions of subjects achieving seroresponse ranged from 93.3% to 97.8% after 2 doses of MenABCWY and ranged from 52.4% to 95.3% after 1 dose of MenACWY-CRM for the ACWY test strains. The differences in proportions (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from 2.5% to 41.0% across ACWY strains. The lower limits (LLs) of the 2-sided 95% confidence intervals (CIs) for the differences in proportions are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-naïve participants.
- For the MenACWY NI evaluation in ACWY-experienced participants, proportions of subjects achieving seroresponse ranged from 93.0% to 97.1% after 2 doses of MenABCWY and ranged from 93.7% to 96.9% after 1 dose of MenACWY-CRM. The differences in proportions (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from -3.2% to 0.7% across ACWY strains. The LLs of the 2-sided 95% CIs for the differences in proportions are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-experienced participants.
- For the MenB NI evaluation, proportions of subjects achieving seroresponse ranged from 68.1% to 95.9% after 2 doses of MenABCWY and ranged from 57.2% to 94.5% after 2 doses of Trumenba for the four primary MenB strains. The differences in proportions (2 doses of MenABCWY versus 2 doses of Trumenba) ranged from 1.4% to 10.9% across primary MenB strains. Additionally, proportions of subjects achieving composite response were 78.3% and 68.7% after 2 doses of MenABCWY and Trumenba, respectively, resulting in a difference of 9.6%. The LLs of the 2-sided 95% CIs for the differences in proportions (2 doses of MenABCWY versus 2 doses of Trumenba) are greater than -10% for all 4 primary MenB strains and the composite endpoint, meeting the NI criteria for 2 doses of MenABCWY compared with 2 doses of Trumenba.

The primary safety objective of study C3511001 was to describe the safety profile of MenABCWY as measured by local reactions, systemic events, adverse events (AEs),

serious adverse events (SAEs), newly diagnosed chronic medical conditions (NDCMCs), medically attended adverse events (MAEs), and immediate AEs.

Among the 2,431 randomized, 2,413 (99.3%) received Vaccination 1 and 2,120 (87.2%) received Vaccination 2. After excluding one participant who received Trumenba + saline as Vaccination 1, the Vaccination 1 safety population included 1,763 MenABCWY recipients and 649 Trumenba + MenACWY-CRM recipients. The Vaccination 2 safety population included 1,558 (88.4%) MenABCWY recipients and 562 (86.6%) Trumenba recipients. The main safety results are summarized as follows:

- Following 2 doses of MenABCWY, the most common local reaction within 7 days was pain at the injection site (89.3% post-Vaccination 1 and 84.4% post-Vaccination 2) and the most common systemic events were fatigue (52.1% post-Vaccination 1 and 47.6% post-Vaccination 2) and headache (46.8% post-Vaccination 1 and 39.8% post-Vaccination 2). Most local reactions and systemic events were mild to moderate in severity.
- During the vaccination phase (from the first study vaccination through 1 months after the second study vaccination), similar percentages of participants in the MenABCWY and Trumenba + MenACWY-CRM groups reported at least 1 AE (20.8% and 20.0%, respectively), related AEs (0.5% and 0.3%, respectively), and severe AEs (0.6% and 0.5%, respectively).
- During the vaccination phase and throughout the study period, similar proportions of participants in the MenABCWY and Trumenba + MenACWY-CRM groups reported SAEs (0.4% and 0%, respectively, during the vaccination phase; 0.6% and 0.6%, respectively, throughout the study period) and MAEs (14.9% and 14.2%, respectively, during the vaccination phase; 19.3% and 18.2%, respectively, throughout the study period). None of the SAEs were considered related to vaccine and a low proportion of participants experienced related MAEs ( $\leq 0.1\%$ ).
- A higher proportion of participants in the MenABCWY group than in the Trumenba + MenACWY-CRM group reported NDCMCs (1.1% and 0.3%, respectively, during the vaccination phase; 1.4% and 0.3%, respectively, throughout the study period).
- There were no immediate AEs reported during the study.
- There were no deaths reported during the study.

In conclusion, there were no statistical issues related to this BLA. Primary immunogenicity and safety results were confirmed by my independent analyses. The primary immunogenicity objectives pre-specified in this pivotal study (i.e., 2 doses of MenABCWY, administered on a 0- and 6-month schedule, induce noninferior immune responses for MenA, MenC, MenW, MenY compared to 1 dose of MenACWY-CRM, and induce noninferior immune response for MenB compared to 2 doses of Trumenba) were achieved and supported approval of the vaccine. The safety profile was generally similar between participants in the MenABCWY and Trumenba + MenACWY-CRM groups except for NDCMCs. I defer to the clinical reviewer on whether the safety profile of MenABCWY supports approval of the vaccine.

## 2. Clinical and Regulatory Background

The MenABCWY vaccine is comprised of meningococcal group B vaccine (Trumenba) and MenACWY-TT (Nimenrix) combined. The proposed regimen of MenABCWY primary series is 2 doses administered at 0 and 6 months. Trumenba is licensed in the U.S. for use in individuals 10 through 25 years of age and can be administered on a 2-dose schedule at 0 and 6 months. Nimenrix is composed of capsular polysaccharides from each of the A, C, W, and Y groups of *Neisseria meningitidis* conjugated to tetanus toxoid (TT). Nimenrix is approved in Europe as a single dose (primary vaccination), but not actively being developed as a separate MenACWY vaccine in the U.S. at this time. The original Investigational New Drug Application (IND17319) for MenABCWY was submitted on February 3, 2017. Pfizer submitted this original BLA on October 21, 2022 for MenABCWY for the prevention of invasive disease caused by *Neisseria meningitidis* groups A, B, C, W, and Y in individuals 10 through 25 years of age.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

This BLA was adequately organized for conducting a complete statistical review without unreasonable difficulty.

## 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

I defer to the corresponding discipline reviewers for this section.

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

The following documents submitted to the BLA are reviewed and/or referenced:

- Protocol C3511001 (Amendment 2 dated June 13, 2022) (BLA125770/0.0, received October 21, 2022),
- Statistical Analysis Plan (SAP) for Protocol C3511001 (Version 3.0 dated July 13, 2022) (BLA125770/0.0, received October 21, 2022),
- Final Clinical Study Report (CSR) for Protocol C3511001 (Version 1.0 dated September 29, 2022) (BLA125770/0.0, received October 21, 2022),
- CBER Request Reactogenicity Tables for Protocol C3511001 (BLA125770/0.8, received February 28, 2023),
- CBER Request AE Tables for Protocol C3511001 (BLA125770/0.8, received February 28, 2023),
- Protocol B1971057 (Amendment 1 dated August 23, 2017) (BLA125770/0.0, received October 21, 2022),
- Protocol B1971057 (Amendment 2 dated July 9, 2019) (BLA125770/0.0, received October 21, 2022),
- SAP for Protocol B1971057 (Version 3.0 dated October 29, 2018) (BLA125770/0.0, received October 21, 2022),
- SAP for Protocol B1971057 (Version 5.0 dated February 28, 2022) (BLA125770/0.0, received October 21, 2022),

- Stage 1 Interim CSR for Protocol B1971057 (Version 1.0 dated February 11, 2020) (BLA125770/0.0, received October 21, 2022),
- CBER Request Stage 1 Reactogenicity and AE Tables for Protocol B1971057 (BLA125770/0.8, received February 28, 2023),
- Stage 2 Interim CSR for Protocol B1971057 (Version 1.0 dated September 23, 2022) (BLA125770/0.0, received October 21, 2022),
- CBER Request Stage 2 Reactogenicity and AE Tables for Protocol B1971057 (BLA125770/0.8, received February 28, 2023),
- Protocol C3511004 (Amendment 1 dated January 7, 2021) (BLA125770/0.0, received October 21, 2022),
- SAP for Protocol C3511004 (Version 3.0 dated November 17, 2021) (BLA125770/0.0, received October 21, 2022), and
- Interim CSR for Protocol C3511004 (Version 1.0 dated August 24, 2022) (BLA125770/0.0, received October 21, 2022).

There were three clinical studies (C3511001, B1971057 Stages 1 and 2, and C3511004) included in this BLA (Table 1). Since this BLA is primarily based on the safety and immunogenicity data from pivotal study C3511001, this statistical review focuses on safety and immunogenicity data from study C3511001. Immunogenicity data from other studies (B1971057 Stage 2 and C3511004) are considered supportive only and are briefly described in Section 9.2.

Table 1: Clinical Trials Supporting the BLA

Study Number (Country/Region)	Description	Study Population	Investigational Product (Schedule): Number of Subjects Randomized	Study Status
C3511001 (U.S., Europe)	Phase 3, noninferiority, tolerability, safety, and immunogenicity of MenABCWY	Adults and Adolescents 10 through 25 years of age	MenABCWY (0- and 6- month schedule): N=1778;  Trumenba+MenACWY- CRM (0- and 6-month schedule): N=653	Completed
B1971057 Stage 1 (U.S., Europe)	Phase 1, first-in- human, safety, immunogenicity, and tolerability of MenABCWY	Adults and Adolescents 10 through 25 years of age	MenABCWY (0- and 6- month schedule): N=544;  Trumenba+MenACWY- CRM (0- and 6-month schedule): N=1066	Completed
B1971057 Stage 2 (U.S., Europe)	Phase 2, immunopersistence of MenABCWY after completion of 2-dose primary vaccination series and immunogenicity of booster	Adults and Adolescents 10 through 25 years of age	Booster dose of MenABCWY (~4 years following completion of 2-dose primary series): N=144;  Booster dose of Trumenba+MenACWY- CRM (~4.5 years after a	Completed



Study Number (Country/Region)	Description	Study Population	Investigational Product (Schedule): Number of Subjects Randomized	Study Status
	vaccination approximately 48 months after completion of primary vaccination series		single dose of MenACWY-CRM coadministered with Trumenba): N=98	
C3511004 (U.S.)	Phase 2b, safety, tolerability, and immunogenicity of MenABCWY of extended interval schedule	Adolescents 11 through 14 years of age	MenABCWY (0- and 12-month schedule): N=155;  MenABCWY (0- and 36-month schedule): N=154	Ongoing

*Source: Summarized by the reviewer based on information presented in BLA125770, Module 5.*

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study C3511001

Study C3511001 was a Phase 3, randomized, active-controlled, observer-blinded, multicenter study to determine the immunologic NI of MenABCWY to licensed vaccines Trumenba and MenACWY-CRM (Menveo) by assessing the safety and immunogenicity of MenABCWY and the comparators in both ACWY-naïve and ACWY-experienced healthy participants 10 through 25 years of age.

#### 6.1.1 Objectives

The study objectives are described below.

The primary immunogenicity objectives were

- to demonstrate that the immune response against MenA, MenC, MenW, and MenY induced by 2 doses of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants, separately, and
- to demonstrate that the immune response against MenB induced by 2 doses of MenABCWY is noninferior to the immune response induced by 2 doses of Trumenba.

The primary safety objective was to describe the safety profile of MenABCWY, as measured by local reactions, systemic events, AEs, SAEs, NDCMCs, MAEs, and immediate AEs.

One secondary immunogenicity objective was to demonstrate that the immune response against MenA, MenC, MenW, and MenY induced by 1 dose of MenABCWY is noninferior to the immune response induced by 1 dose of MenACWY-CRM, in both ACWY-naïve and ACWY-experienced participants, separately.

### 6.1.2 Design Overview

This was a Phase 3, randomized, active-controlled, observer-blinded, multicenter study in which approximately 2,413 participants 10 through 25 years of age were planned to be randomly assigned to receive either

- MenABCWY + saline at Month 0 (Vaccination 1) and MenABCWY at Month 6 (Vaccination 2), or
- Trumenba + MenACWY-CRM (Menveo) at Month 0 (Vaccination 1) and Trumenba at Month 6 (Vaccination 2).

Randomization was stratified by ACWY vaccination history (i.e., ACWY-naïve and ACWY-experienced), and geographic region (80% U.S. sites, 20% non-U.S.). All participants were naïve to any meningococcal group B vaccine prior to enrollment. ACWY-experienced was defined as receiving a U.S.-licensed MenACWY vaccine at least 4 years prior to enrollment. The study design is shown in Table 2. Participants in Groups 1 to 4 were considered an immunogenicity subset and contributed to both the safety and immunogenicity analyses; these participants had blood drawn prior to Vaccination 1 (Month 0) and 1 month after Vaccinations 1 (Month 1) and 2 (Month 7). Participants in Groups 5 to 8 were considered a safety subset and contributed to the safety analysis only and did not have blood drawn for immunogenicity evaluations. Enrollment targets were adjusted to achieve appropriate representation by age group (10-17 years, 18-25 years) within each subset, and ACWY strata within each subset. Each participant participated in the study for approximately 12 months.

Table 2: Study Design for Trial C3511001

ACWY Vaccine History	Group	N	Vaccination 1 at Month 0	Vaccination 2 at Month 6
ACWY-naïve	1	450	MenABCWY + saline	MenABCWY
ACWY-naïve	2	225	Trumenba + MenACWY-CRM	Trumenba
ACWY-experienced	3	675	MenABCWY + saline	MenABCWY
ACWY-experienced	4	338	Trumenba + MenACWY-CRM	Trumenba
ACWY-naïve	5	500	MenABCWY + saline	MenABCWY
ACWY-naïve	6	50	Trumenba + MenACWY-CRM	Trumenba
ACWY-experienced	7	125	MenABCWY + saline	MenABCWY
ACWY-experienced	8	50	Trumenba + MenACWY-CRM	Trumenba

Abbreviations: ACWY=meningococcal groups A, C, W, and Y vaccine; N=sample size  
Source: Adapted from Table 2 in the CSR for Protocol C3511001 submitted to STN 125770/0.

### 6.1.3 Population

The study population was both ACWY-naïve and ACWY-experienced healthy participants 10 through 25 years of age.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Trumenba is a 0.5-mL dose supplied as a prefilled syringe (PFS) and formulated to contain 60 µg each of a purified subfamily A and a purified subfamily B (b) (4) protein, (b) (4) sodium chloride, (b) (4) polysorbate 80, and 0.25 mg of Al<sup>3+</sup> as aluminum phosphate (AlPO<sub>4</sub>) in 10 mM histidine-buffered saline at pH 6.0.

MenACWY-TT is supplied as (b) (4)

(b) (4)

MenACWY-TT is (b) (4)

(b) (4) of the resultant MenABCWY is administered via intramuscular injection. The final MenABCWY vaccine composition includes (b) (4) (b) (4) of *Neisseria meningitidis* serogroups A, C, W, and Y (b) (4) type conjugated to tetanus toxoid (b) (4) respectively, in (b) (4) and (b) (4) containing (b) (4) (b) (4)

MenACWY-CRM (Menveo) is supplied in 2 vials that must be combined prior to administration: the MenA lyophilized conjugate vaccine component is reconstituted with the meningococcal group C, Y, and W-135 (MenCYW-135) liquid conjugate vaccine component immediately before administration as a 0.5-mL intramuscular injection.

The placebo is sterile normal saline solution for injection and is administered as a 0.5-mL intramuscular injection.

#### 6.1.6 Sites and Centers

This study was conducted at 75 sites in the following 5 countries: U.S., Czech Republic, Denmark, Hungary, and Poland.

#### 6.1.7 Surveillance/Monitoring

I defer to the clinical reviewer regarding the surveillance/monitoring plan for safety and immunogenicity.

#### 6.1.8 Endpoints and Criteria for Study Success

Throughout this memo, a 4-fold rise in hSBA titer is defined as an hSBA titer of  $\geq 1:16$  for participants with a baseline titer <limit of detection (LOD),  $\geq 4$  times LLOQ for participants with a baseline titer  $\geq$  LOD and <LLOQ, and  $\geq 4$  times the baseline titer for participants with a baseline titer  $\geq$  LLOQ, respectively.

The primary immunogenicity endpoints included

- seroresponse in hSBA titer for each of the ACWY test strains, defined as achieving at least a 4-fold rise in hSBA titer 1 month after Vaccination 2 (Groups 1 and 3) or 1 month after Vaccination 1 (Groups 2 and 4) from baseline,
- seroresponse in hSBA titer for each of the primary MenB test strains (A22, A56, B24, and B44), defined as achieving at least a 4-fold rise in hSBA titer 1 month after Vaccination 2 from baseline,
- composite response in MenB test strains, defined as achieving an hSBA titer  $\geq$ LLOQ at 1 month after Vaccination 2 for all 4 primary MenB test strains (i.e.,  $\geq$ 1:16 for strain A22,  $\geq$ 1:8 for strains A56, B24, and B44).

For each of the ACWY test strains and primary MenB test strains, the difference in the percentages of participants achieving seroresponse was calculated between Groups 1 and 2 among ACWY-naïve participants, and between Groups 3 and 4 among ACWY-experienced participants. The difference in the percentages of participants achieving composite response in MenB test strains was calculated between Groups 1 and 3 combined, and Groups 2 and 4 combined.

The primary safety endpoints included

- local reactions (pain, redness, and swelling), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than muscle pain at any injection site, and joint pain), and use of antipyretic medication within 7 days after each vaccination,
- AEs within 30 days after each or any vaccination, and during the vaccination phase (from the first study vaccination through 1 month after the second study vaccination),
- SAEs, MAEs, and NDCMCs within 30 days after each or any vaccination, during the vaccination phase, during the follow-up phase (from 1 month after the second study vaccination through 6 months after the second study vaccination), and throughout the study (from the first study vaccination through 6 months after the second study vaccination),
- immediate AEs (AEs that occur within 30 minutes after vaccination), and
- days missing from school or work because of AEs.

One secondary immunogenicity endpoint was seroresponse in hSBA titer for each of the ACWY test strains, defined as achieving at least a 4-fold rise in hSBA titer 1 month after Vaccination 1 from baseline. For each of the ACWY test strains, the difference in the percentages of participants achieving seroresponse (with respect to this secondary immunogenicity endpoint) was calculated between Groups 1 and 2 among ACWY-naïve participants, and between Groups 3 and 4 among ACWY-experienced participants.

For the MenACWY NI evaluation in ACWY-naïve participants, the null hypothesis was  $H_0: \pi_{G1} - \pi_{G2} \leq -10\%$ , where  $\pi_{G1}$  and  $\pi_{G2}$  were the percentages of participants achieving seroresponse for each of ACWY test strains in Group 1 and Group 2, respectively. If the LL of the 2-sided 95% CI for the difference in percentages of participants achieving seroresponse (1 month after Vaccination 2 in Group 1 versus 1 month after Vaccination 1

in Group 2) was  $> -10\%$  for all four ACWY test strains, NI of MenABCWY compared with MenACWY-CRM would be declared for the ACWY-naïve participants.

For the MenACWY NI evaluation in ACWY-experienced participants, the approach was identical to that in ACWY-naïve participants, except that Group 3 was compared to Group 4, instead of Group 1 compared to Group 2. The NI evaluations for both the ACWY-naïve and the ACWY-experienced participants were required to be successful to achieve the first primary immunogenicity objective.

For the MenB NI evaluation, the null hypothesis was  $H_0: \pi_{G1+G3} - \pi_{G2+G4} \leq -10\%$ , where  $\pi_{G1+G3}$  and  $\pi_{G2+G4}$  were the percentages of participants achieving seroresponse or composite response for Groups 1 and 3 combined and for Groups 2 and 4 combined, respectively. If the LL of the 2-sided 95% CI for the differences in percentages of participants achieving seroresponse and composite response (1 month after Vaccination 2 in Group 1+3 versus 1 month after Vaccination 2 in Group 2+4) were  $> -10\%$  for all primary MenB test strains, NI of MenABCWY compared with Trumenba would be declared.

If both primary immunogenicity objectives were met, a secondary NI evaluation of the ACWY response would be performed as for the primary ACWY NI assessment to demonstrate NI in terms of the percentage of participants achieving seroresponse 1 month following Vaccination 1 for both groups evaluated (i.e., Group 1 versus Group 2 for ACWY-naïve and Group 3 versus Group 4 for ACWY-experienced).

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Treatment assignment

Study participants were randomly assigned to receive either

- MenABCWY + saline at Month 0 (Vaccination 1) and MenABCWY at Month 6 (Vaccination 2), or
- Trumenba + MenACWY-CRM (Menveo) at Month 0 (Vaccination 1) and Trumenba at Month 6 (Vaccination 2),

as shown in Table 1. Randomization was stratified by ACWY vaccination history and geographic region.

##### Blinding techniques

In this observer-blinded study, the study staff dispensing, preparing, and administering the vaccine were unblinded. All other study and site personnel, including the investigator, investigator staff, participants, and participants' parent(s)/legal guardian, were blinded to investigational product assignments. In particular, the individuals who evaluated participant safety were blinded. Because the investigational products were different in physical appearance, the investigational product syringes were administered in a manner that prevented the study participants from identifying the vaccine type based on its appearance.

Those study team members who were involved in ensuring that protocol requirements for

investigational product preparation, handling, allocation, and administration were fulfilled at the site were unblinded for the duration of the study (e.g., unblinded study manager, unblinded clinical research associate). An unblinded clinician who was not a direct member of the study team reviewed unblinded protocol deviations. All other study team members and all laboratory testing personnel performing serology assays remained blinded to vaccine assigned/received throughout the study. All laboratory testing personnel performing serology assays also remained blinded to visit number throughout the study.

#### Sample size determination

Table 3 presents the power to demonstrate NI of the immune response against MenA, MenC, MenW and MenY strains induced by 2 doses of MenABCWY to the immune response induced by 1 dose of MenACWY-CRM in ACWY-naïve and ACWY-experienced participants, and the power to demonstrate NI of immune response against 4 primary MenB strains induced by 2 doses of MenABCWY to the immune response induced by 2 doses of Trumenba. With 360, 180, 540, and 270 evaluable participants in Groups 1, 2, 3, and 4, respectively, the power was >99.9% to demonstrate NI for all ACWY test strains in ACWY-naïve participants, >99.4% to demonstrate NI for all ACWY test strains in ACWY-experienced participants, and >91.6% to demonstrate NI for all primary MenB strains and the composite endpoint, resulting in an overall power of >91.0% across both primary immunogenicity objectives. Assuming a non-evaluable rate of 20%, 450, 225, 675, and 338 participants were to be enrolled to Groups 1, 2, 3, and 4, respectively, to ensure sufficient evaluable participants.

Table 3: Power Analyses for Primary Immunogenicity Objective

Participants	Test Strain	Rate in Reference Group <sup>a</sup> (%)	Assumed Difference (Non-reference Group <sup>b</sup> versus Reference Group (%))	Number of Evaluable Participants (Non-reference Group/Reference Group)	Power <sup>c</sup> (%)
ACWY-naïve	MenA	95.8	0	360/180	99.96
ACWY-naïve	MenC	70.0	15	360/180	>99.99
ACWY-naïve	MenW	75.9	15	360/180	>99.99
ACWY-naïve	MenY	71.9	15	360/180	>99.99
ACWY-experienced	MenA	97.0	1	270/540	>99.99
ACWY-experienced	MenC	95.8	1	270/540	>99.99
ACWY-experienced	MenW	97.0	2	270/540	99.98
ACWY-experienced	MenY	94.0	2	270/540	99.49
All	A22	73.8	0	900/450	98.03
All	A56	95.0	0	900/450	>99.99
All	B24	64.5	0	900/450	95.64
All	B44	86.4	0	900/450	99.94
All	MenB Composite	72.9	0	900/450	97.80

Abbreviations: ACWY=meningococcal groups A, C, W, and Y vaccine; MenA=*Neisseria meningitidis* group A; MenC= *Neisseria meningitidis* group C; MenW= *Neisseria meningitidis* group W; MenY= *Neisseria meningitidis* group Y; MenB= *Neisseria meningitidis* group B;

<sup>a</sup> For ACWY test strains, reference group refers to Group 2 in ACWY-naïve participants, and Group 4 in ACWY-experienced participants. For primary MenB test strains and MenB composite, reference group refers to Groups 2 and 4 combined.

<sup>b</sup> For ACWY test strains, non-reference group refers to Group 1 in ACWY-naïve participants, and Group 3 in ACWY-experienced participants. For primary MenB test strains and MenB composite, non-reference group refers to Groups 1 and 3 combined.

<sup>c</sup> Power was assessed at a 2-sided alpha of 0.05.

*Source: Adapted from Tables 7, 8, and 9 in the Protocol C3511001 submitted to STN 125770/0.*

The sample sizes in Groups 5, 6, 7, and 8 were not based on power calculation but rather on having a sufficient number of participants enrolled to adequately characterize the safety profile of MenABCWY. Overall, 1,750 participants were to be randomized to receive MenABCWY and 663 were to be randomized to receive Trumenba + MenACWY-CRM. With 1,750 participants receiving MenABCWY, the probability to detect at least 1 AE was 1.7%, 16.1%, and 82.6% for a true incidence rate of 0.001%, 0.01%, and 0.1%, respectively.

Definition of analysis population

Enrolled Set included all participants who signed the informed consent document (ICD).

Randomized Set included all participants who were assigned a randomization number in the interactive response technology (IRT) system.

Modified Intent-to-Treat (mITT) Set included all participants who received at least 1 study vaccination and had at least 1 valid and determinate MenB or MenA/C/W/Y assay result available at any time point from Month 0 to Month 7.

Safety Set included all randomized participants who received at least 1 dose of the investigational product and had safety data reported after vaccination. Participants were analyzed according to the vaccine they actually received. All safety analyses were performed on the Safety Set.

Post-Vaccination 1 Evaluable Set included all randomized participants who were eligible throughout Month 1, received the investigational products at Month 0 as randomized, had blood drawn for assay testing within the required time frames at Months 0 and 1 (1 month after the first vaccination: window 28-42 days), had at least 1 valid and determinate MenA/C/W/Y assay result at Month 1, had received no prohibited vaccines or treatment through Month 1, and had no important protocol deviations through Month 1.

Post-Vaccination 2 Evaluable Set included all randomized participants who were eligible throughout Month 7, received the investigational products at Months 0 and 6 as randomized, had blood drawn for assay testing within the required time frames at Months 0 and 7 (1 month after the second vaccination: window 28-42 days), had at least 1 valid and determinate MenA/C/W/Y or MenB assay result at Month 7, had received no prohibited vaccines or treatment through Month 7, and had no important protocol deviations through Month 7.

For Post-Vaccination 1 Evaluable Set and Post-Vaccination 2 Evaluable Set, protocol deviations that, in the opinion of the sponsor's global medical monitor, would materially affect assessment of immunogenicity, e.g., participant receipt of a prohibited vaccine or medication that might affect immune response or a medication error with suspected

decrease in potency of the vaccine, were considered important and would result in exclusion from these two analysis sets.

The analysis for the ACWY test strains was based on the post-Vaccination 1 evaluable population for Groups 2 and 4 and on the post-Vaccination 2 evaluable population for Groups 1 and 3. The analysis for the primary MenB strains was based on the post-Vaccination 2 evaluable population.

#### Analysis methods

Exact 2-sided 95% CIs for the percentages of participants achieving seroresponse and composite response were calculated using the Clopper-Pearson method. The Miettinen and Nurminen method was used to derive the CI for the difference in percentages between vaccine groups.

Safety endpoints were analyzed descriptively.

#### Missing data

Missing serology and e-diary data were not imputed.

#### Subgroup analysis planned

Subgroup analyses were performed for immunogenicity and safety endpoints. No subgroup analysis was planned for rare events. Subgroups included age strata (10-17 years, 18-25 years), sex, race, and ethnicity.

#### Study/data monitoring planned by independent personnel

This study used an external data monitoring committee (E-DMC). An independent statistician provided unblinded safety reports to the E-DMC for review. Safety data were reviewed by the E-DMC throughout the study, and no adjustments to the type I error for the NI assessments were made for these periodic safety reviews.

### 6.1.10 Study Population and Disposition

#### 6.1.10.1 Populations Enrolled/Analyzed

A total of 2,431 participants were randomized in this study (552, 276, 528, 261, 544, 57, 154, and 59 participants were randomized to Groups 1 through 8, respectively). Among them, 2,413 (99.3%) received Vaccination 1; 2,120 (87.2%) received Vaccination 2; 2,074 (85.3%) completed the vaccination phase; 2,061 (84.4%) completed the follow-up phase and completed the study.

Among the 2,413 participants who received Vaccination 1, one participant received Trumenba + saline as Vaccination 1, and thus, was excluded from the overall safety population. The overall safety population included a total of 1,763 MenABCWY recipients (i.e., participants from Groups 1, 3, 5, and 7 combined) and 649 Trumenba + MenACWY-CRM recipients (i.e., participants from Groups 2, 4, 6, and 8 combined) and all were included in the Vaccination 1 safety population. The Vaccination 2 safety



population included 1,558 (88.4%) MenABCWY recipients and 562 (86.6%) Trumenba recipients.

Only participants in Groups 1 through 4 contributed to the immunogenicity analyses. The immunogenicity subset included 1,080 and 537 participants randomized to MenABCWY and Trumenba + MenACWY-CRM groups, respectively. The post-Vaccination 1 evaluable immunogenicity population included 961 (89.0%) MenABCWY recipients (512 ACWY-naïve and 449 ACWY-experienced) and 485 (90.3%) Trumenba + MenACWY-CRM recipients (258 ACWY-naïve and 227 ACWY-experienced). The post-Vaccination 2 evaluable immunogenicity population included 851 (78.8%) MenABCWY recipients (456 ACWY-naïve and 395 ACWY-experienced) and 423 (78.8%) Trumenba recipients (239 ACWY-naïve and 184 ACWY-experienced).

#### 6.1.10.1.1 Demographics

A summary of demographic characteristics for the safety population is presented in Table 4. In the safety population, overall, 51.2% of subjects were female, and most of the subjects were White (78.0%) and non-Hispanic/non-Latino (73.6%). The mean age (standard deviation) at first vaccination was 16.1 (4.55) years. Demographic characteristics were generally similar between vaccine groups among ACWY-experienced and ACWY-naïve subjects. The demographic characteristics of the evaluable immunogenicity populations were generally similar to those of the safety population.

Table 4: Demographic Characteristics – Safety Population (As Administered [Actual ACWY History and Subset])

--	Group 1 ACWY- naïve MenABC WY + saline	Group 2 ACWY-naïve Trumenba + MenACWY- CRM	Group 3 ACWY- experience d MenABC WY + saline	Group 4 ACWY- experienced Trumenba + MenACWY- CRM	Group 5 ACWY- naïve MenABC WY + saline	Group 6 ACWY-naïve Trumenba + MenACWY- CRM	Group 7 ACWY- experience d MenABC WY + saline	Group 8 ACWY- experienced Trumenba + MenACWY- CRM	Groups 1+3+5+7 MenABC WY + saline	Groups 2+4+6+8 Trumenba + MenACWY- CRM	Total
N	547	274	526	260	537	56	153	59	1763	649	2412
Sex, n (%)	--	--	--	--	--	--	--	--	--	--	--
Male	258 (47.2)	134 (48.9)	247 (47.0)	129 (49.6)	284 (52.9)	36 (64.3)	57 (37.3)	31 (52.5)	846 (48.0)	330 (50.8)	1176 (48.8)
Female	289 (52.8)	140 (51.1)	279 (53.0)	131 (50.4)	253 (47.1)	20 (35.7)	96 (62.7)	28 (47.5)	917 (52.0)	319 (49.2)	1236 (51.2)
Race, n (%)	--	--	--	--	--	--	--	--	--	--	--
White	467 (85.4)	239 (87.2)	370 (70.3)	195 (75.0)	419 (78.0)	46 (82.1)	103 (67.3)	42 (71.2)	1359 (77.1)	522 (80.4)	1881 (78.0)
Black or African American	26 (4.8)	19 (6.9)	74 (14.1)	32 (12.3)	57 (10.6)	5 (8.9)	27 (17.6)	5 (8.5)	184 (10.4)	61 (9.4)	245 (10.2)
Asian	19 (3.5)	4 (1.5)	18 (3.4)	6 (2.3)	7 (1.3)	1 (1.8)	1 (0.7)	1 (1.7)	45 (2.6)	12 (1.8)	57 (2.4)
American Indian or Alaska Native	2 (0.4)	2 (0.7)	2 (0.4)	2 (0.8)	4 (0.7)	1 (1.8)	2 (1.3)	1 (1.7)	10 (0.6)	6 (0.9)	16 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	2 (0.4)	0	1 (0.2)	0	0	0	4 (0.2)	0	4 (0.2)
Multiracial	9 (1.6)	3 (1.1)	12 (2.3)	3 (1.2)	7 (1.3)	2 (3.6)	2 (1.3)	0	30 (1.7)	8 (1.2)	38 (1.6)
Not reported	23 (4.2)	7 (2.6)	48 (9.1)	22 (8.5)	42 (7.8)	1 (1.8)	18 (11.8)	10 (16.9)	131 (7.4)	40 (6.2)	171 (7.1)
Ethnicity, n (%)	--	--	--	--	--	--	--	--	--	--	--
Hispanic/ Latin	93 (17.0)	53 (19.3)	156 (29.7)	86 (33.1)	131 (24.4)	15 (26.8)	58 (37.9)	29 (49.2)	438 (24.8)	183 (28.2)	621 (25.7)
Non-Hispanic/ non-Latino	450 (82.3)	217 (79.2)	366 (69.6)	173 (66.5)	405 (75.4)	41 (73.2)	93 (60.8)	30 (50.8)	1314 (74.5)	461 (71.0)	1775 (73.6)
Not reported	4 (0.7)	4 (1.5)	4 (0.8)	1 (0.4)	1 (0.2)	0	2 (1.3)	0	11 (0.6)	5 (0.8)	16 (0.7)
Age group, n (%)	--	--	--	--	--	--	--	--	--	--	--

--	Group 1 ACWY- naïve MenABC WY + saline	Group 2 ACWY-naïve Trumenba + MenACWY- CRM	Group 3 ACWY- experience d MenABC WY + saline	Group 4 ACWY- experienced Trumenba + MenACWY- CRM	Group 5 ACWY- naïve MenABC WY + saline	Group 6 ACWY-naïve Trumenba + MenACWY- CRM	Group 7 ACWY- experience d MenABC WY + saline	Group 8 ACWY- experienced Trumenba + MenACWY- CRM	Groups 1+3+5+7 MenABC WY + saline	Groups 2+4+6+8 Trumenba + MenACWY- CRM	Total
≥10 Years to <18 years	259 (47.3)	132 (48.2)	370 (70.3)	182 (70.0)	450 (83.8)	44 (78.6)	109 (71.2)	51 (86.4)	1188 (67.4)	409 (63.0)	1597 (66.2)
≥18 Years to <26 years	288 (52.7)	142 (51.8)	156 (29.7)	78 (30.0)	87 (16.2)	12 (21.4)	44 (28.8)	8 (13.6)	575 (32.6)	240 (37.0)	815 (33.8)
Age at first vaccination (years)	--	--	--	--	--	--	--	--	--	--	--
n	547	274	526	260	537	56	153	59	1763	649	2412
Mean (SD)	16.7 (5.49)	16.7 (5.39)	17.3 (3.17)	17.4 (3.28)	13.5 (4.05)	13.5 (4.50)	17.1 (3.04)	16.0 (2.75)	15.9 (4.57)	16.6 (4.48)	16.1 (4.55)
Median	18	18	16	16	12	11	16	16	16	16	16
Min, max	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)	(10.0, 25.0)
Geographic location, n (%)	--	--	--	--	--	--	--	--	--	--	--
U.S.	281 (51.4)	141 (51.5)	517 (98.3)	255 (98.1)	315 (58.7)	33 (58.9)	148 (96.7)	58 (98.3)	1261 (71.5)	487 (75.0)	1748 (72.5)
Non-U.S.	266 (48.6)	133 (48.5)	9 (1.7)	5 (1.9)	222 (41.3)	23 (41.1)	5 (3.3)	1 (1.7)	502 (28.5)	162 (25.0)	664 (27.5)

Abbreviations: N=sample size, the values in this row are used as the denominators for percentage calculations; n=number of participants with the specified characteristic; SD=standard deviation; U.S.=United States

Note: “Actual ACWY history” is based on prior receipt of a meningococcal groups A, C, W, and Y vaccine. “Actual subset” refers to the safety subset.

Source: Adapted from Table 10 in the CSR for Protocol C3511001 submitted to STN 125770/0.

*Reviewer comment:*

*Among the 2,431 participants, 19 were randomized into the wrong MenACWY stratum. These participants were included in the safety population and reported according to their true MenACWY history. These participants were excluded from the evaluable immunogenicity population(s) for the MenACWY endpoints but included in the evaluable immunogenicity population(s) for the MenB endpoints.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study population was generally healthy with a medical history profile consistent with that of the general population of this age.

6.1.10.1.3 Subject Disposition

Table 5 shows the disposition for the post-Vaccination 1 and post-Vaccination 2 evaluable populations. The proportions of participants excluded from the evaluable immunogenicity populations were similar among MenABCWY (11.0% post-Vaccination 1; 21.2% post-Vaccination 2) and Trumenba + MenACWY-CRM (9.7% post-Vaccination 1; 21.2% post-Vaccination 2) recipients.

Table 5: Disposition for the Post-Vaccination 1 and Post-Vaccination 2 Evaluable Populations By Group (As Randomized [Actual ACWY History and Subset])

--	Group 1 ACWY-naïve MenABCWY+Saline	Group 2 ACWY-naïve Trumenba + MenACWY-CRM	Group 3 ACWY-experienced MenABCWY+Saline	Group 4 ACWY- experienced Trumenba + MenACWY-CRM	Groups 1 + 3 MenABCWY+Saline	Groups 2 + 4 Trumenba + MenACWY-CRM
Randomized, N	552	276	528	261	1080	537
mITT, n (%)	547 (99.1)	274 (99.3)	525 (99.4)	261 (100.0)	1072 (99.3)	535 (99.6)
Post-Vaccination 1 Evaluable	512 (92.8)	258 (93.5)	449 (85.0)	227 (87.0)	961 (89.0)	485 (90.3)
Excluded from post-Vaccination 1 evaluable	40 (7.2)	18 (6.5)	79 (15.0)	34 (13.0)	119 (11.0)	52 (9.7)
Reason for exclusion	--	--	--	--	--	--
Did not maintain eligibility based on criteria up until and including Month 1	5 (0.9)	2 (0.7)	17 (3.2)	11 (4.2)	22 (2.0)	13 (2.4)
Did not receive study intervention at Month 0 as randomized	5 (0.9)	2 (0.7)	3 (0.6)	1 (0.4)	8 (0.7)	3 (0.6)
Did not have blood drawn or was out of window at Month 0 or 1	35 (6.3)	17 (6.2)	66 (12.5)	26 (10.0)	101 (9.4)	43 (8.0)
Did not have valid and determinate MenACWY assay at Month 1	17 (3.1)	9 (3.3)	36 (6.8)	13 (5.0)	53 (4.9)	22 (4.1)
Received prohibited vaccines or treatment through Month 1	1 (0.2)	0	3 (0.6)	0	4 (0.4)	0
Post-Vaccination 2 Evaluable	456 (82.6)	239 (86.6)	395 (74.8)	184 (70.5)	851 (78.8)	423 (78.8)
Excluded from post-Vaccination 2 evaluable	96 (17.4)	37 (13.4)	133 (25.2)	77 (29.5)	229 (21.2)	114 (21.2)
Reason for exclusion	--	--	--	--	--	--
Did not maintain eligibility based on criteria up until and including Month 7	8 (1.4)	3 (1.1)	20 (3.8)	14 (5.4)	28 (2.6)	17 (3.2)
Did not receive study intervention at Month 0 and 6 as randomized	52 (9.4)	22 (8.0)	75 (14.2)	44 (16.9)	127 (11.8)	66 (12.3)
Did not have blood drawn or was out of window at Month 0 or 7	94 (17.0)	35 (12.7)	118 (22.3)	69 (26.4)	212 (19.6)	104 (19.4)

--	Group 1 ACWY-naïve MenABCWY+Saline	Group 2 ACWY-naïve Trumenba + MenACWY-CRM	Group 3 ACWY-experienced MenABCWY+Saline	Group 4 ACWY- experienced Trumenba + MenACWY-CRM	Groups 1 + 3 MenABCWY+Saline	Groups 2 + 4 Trumenba + MenACWY-CRM
Did not have valid and determinate MenACWY or MenB assay at Month 7	65 (11.8)	29 (10.5)	99 (18.8)	55 (21.1)	164 (15.2)	84 (15.6)
Received prohibited vaccines or treatment through Month 7	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0

Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Abbreviations: N=sample size, the values in this row are used as the denominators for percentage calculations; n=number of participants with the specified characteristic

Note: “Actual ACWY history” is based on prior receipt of a meningococcal groups A, C, W, and Y vaccine. “Actual subset” refers to the immunogenicity subset.

Source: *Adpated from Table 9 in the CSR for Protocol C3511001 submitted to STN 125770/0.*

### 6.1.11 Immunogenicity Analyses

Immunogenicity analyses were performed on post-Vaccination 1 and post-Vaccination 2 evaluable populations. The results from analyses of primary and secondary immunogenicity endpoints are described in this section.

#### 6.1.11.1 Analyses of Primary MenACWY Endpoints

Table 6 summarizes the proportions of participants achieving an hSBA titer  $\geq 4$ -fold 1 month after 2 doses of MenABCWY for Groups 1 and 3 and 1 months after 1 dose of MenACWY-CRM for Groups 2 and 4, by ACWY-serostatus. The LLs of the 2-sided 95% CIs for the differences in percentages of participants achieving a  $\geq 4$ -fold rise from baseline for each serogroup were greater than -10%, demonstrating NI of 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in both ACWY-naïve and ACWY-experienced participants.

Table 6: Number (%) of Participants Achieving  $\geq 4$ -Fold Rise in hSBA Titer From Baseline for MenACWY Strains – 1 Month After Vaccination 2 in the MenABCWY Groups Compared to 1 Month After Vaccination 1 in the Trumenba + MenACWY-CRM Groups – Evaluable Immunogenicity Populations

Serogroup	Group 1 ACWY-naïve MenABCWY n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>c</sup> )	Group 2 ACWY-naïve Trumenba + MenACWY- CRM n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>c</sup> )	Group 3 ACWY- experienced MenABCWY n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>c</sup> )	Group 4 ACWY- experienced Trumenba + MenACWY- CRM n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>c</sup> )	Difference <sup>d</sup> (Group 1 minus Group 2) (95% CI <sup>c</sup> )	Difference <sup>d</sup> (Group 3 minus Group 4) (%) (95% CI <sup>c</sup> )
MenA	437/447 (97.8)	242/254 (95.3)	361/385 (93.8)	220/227 (96.9)	2.5	-3.2
--	(95.9, 98.9)	(91.9, 97.5)	(90.9, 96.0)	(93.7, 98.8)	(-0.2, 6.0)	(-6.5, 0.5)
MenC	421/451 (93.3)	132/252 (52.4)	362/386 (93.8)	214/226 (94.7)	41.0	-0.9
--	(90.6, 95.5)	(46.0, 58.7)	(90.9, 96.0)	(90.9, 97.2)	(34.4, 47.5)	(-4.6, 3.3)
MenW	427/439 (97.3)	178/244 (73.0)	365/376 (97.1)	214/222 (96.4)	24.3	0.7
--	(95.3, 98.6)	(66.9, 78.4)	(94.8, 98.5)	(93.0, 98.4)	(18.8, 30.4)	(-2.2, 4.3)
MenY	421/446 (94.4)	175/248 (70.6)	360/387 (93.0)	209/223 (93.7)	23.8	-0.7
--	(91.8, 96.3)	(64.5, 76.2)	(90.0, 95.4)	(89.7, 96.5)	(18.0, 30.1)	(-4.6, 3.8)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD=limit of detection; MenA=*Neisseria meningitidis* group A; MenC= *Neisseria meningitidis* group C; MenW= *Neisseria meningitidis* group W; MenY= *Neisseria meningitidis* Y  
Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: For Group 1 and Group 3, the post-Vaccination 2 evaluable immunogenicity population is used; for the Group 2 and Group 4, post-Vaccination 1 evaluable immunogenicity population is used.

Note: LOD = 1:4 for all MenA, MenC, MenW, and MenY serogroups.

Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.

Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer  $< 1:4$ ), a response is defined as an hSBA titer  $\geq 1:16$ . (2) For participants with a baseline hSBA titer  $\geq$  LOD and  $<$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the LLOQ. (3) For participants with a baseline hSBA titer  $\geq$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the baseline titer.

<sup>a</sup> n = Number of participants who achieved hSBA titer fold rise  $\geq 4$  from baseline for the given strain.

<sup>b</sup> N = number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.

<sup>c</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

<sup>d</sup> Difference in proportions (Group 1 minus Group 2) or (Group 3 minus Group 4), expressed as a percentage.

<sup>e</sup> 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Source: Table 13 in the CSR for Protocol C3511001 submitted to STN 125770/0.

*Reviewer comments:*

1) The immunogenicity and safety analyses were verified based on data submitted in the Standard Data Tabulation Model (SDTM) format, and results were consistent with those reported by the applicant.

2) During my review of the validation of anti-MenA hSBA, it was noted that the estimated (b) (4)

(b) (4) suggesting that the 4-fold rise endpoint used in clinical trials as determined by this assay may be achieved when the actual fold-rise is less than 4-fold (details of this evaluation are included in my clinical immunogenicity assay review memo). To assess the impact of this finding on the interpretation of the MenA immunogenicity results, I performed sensitivity analyses, in which an 8-fold rise endpoint (noting that this is the fold-rise endpoint immediately higher than a 4-fold rise endpoint, given the discrete nature of the hSBA titers) was used instead of the 4-fold rise endpoint to account for potentially inflated fold-rises due to the (b) (4) noted above.

The difference in proportions of participants achieving  $\geq 8$ -fold rise in anti-MenA hSBA titers (1 month after Vaccination 2 in Group 1 versus 1 month after Vaccination 1 in Group 2) was estimated to be 6.1% (95% CI: 2.1%, 10.9%). The difference in proportions of participants achieving  $\geq 8$ -fold rise in anti-MenA hSBA titers (1 month after Vaccination 2 in Group 3 versus 1 month after Vaccination 1 Group 4) was estimated to be -7.1% (95% CI: -11.9%, -1.9%). Of note, I further compared the proportions of participants achieving  $\geq 8$ -fold rise in anti-MenA hSBA titers 1 month after vaccination 1 between Groups 3 and 4. The estimated difference (1 month after Vaccination 1 in Group 3 versus 1 month after Vaccination 1 in Group 4) was -5.2% (95% CI: -9.6%, -0.4%). These results suggest that the 8-fold rise endpoint results are largely consistent with the 4-fold rise endpoint, except that the LL of confidence interval for difference in proportions of participants achieving  $\geq 8$ -fold rise in anti-MenA hSBA titers (1 month after Vaccination 2 in Group 3 versus 1 month after Vaccination 1 Group 4) was slightly lower than -10% in ACWY-experienced participants, which might be in part because of the loss of precision due to relatively high attrition of post-Vaccination 2 evaluable population in the MenABCWY group. Overall, it appears that the NI conclusion of 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in terms of immune response for MenA is robust.



#### 6.1.11.2 Analyses of Primary MenB Endpoints

Table 7 summarizes the proportions of participants achieving an hSBA titer  $\geq 4$ -fold 1 month after 2 doses of MenABCWY for Groups 1 and 3 combined and 1 months after 2 dose of Trumenba for Groups 2 and 4 combined. The LL of the 2-sided 95% CI for the difference in percentages of participants achieving a  $\geq 4$ -fold rise from baseline was greater than -10% for each primary MenB test strain and the composite response, demonstrating NI of 2 doses of MenABCWY compared with 2 doses of Trumenba.

Table 7: Number (%) of Participants Achieving  $\geq 4$ -Fold Rise in hSBA Titer and Composite Response 1 Month After Vaccination 2 for Primary MenB Strains (MenABCWY combined versus Trumenba + MenACWY-CRM Combined) – Post-Vaccination 2 Evaluable Immunogenicity Population

Endpoint MenB Strain	Groups 1+3 MenABCWY n <sup>c</sup> /N <sup>d</sup> (%) (95% CI <sup>e</sup> )	Groups 2+4 Trumenba + MenACWY-CRM n <sup>c</sup> /N <sup>d</sup> (%) (95% CI <sup>e</sup> )	Difference <sup>f</sup> (Groups 1+3 minus Groups 2+4) (95% CI <sup>g</sup> )
Seroresponse <sup>a</sup>	--	--	--
PMB80 (A22)	646/778 (83.0)	313/396 (79.0)	4.0
--	(80.2,85.6)	(74.7,82.9)	(-0.7,8.9)
PMB2001 (A56)	774/807 (95.9)	378/400 (94.5)	1.4
--	(94.3,97.2)	(91.8,96.5)	(-1.4,3)
PMB2948 (B24)	567/833 (68.1)	239/418 (57.2)	10.9
--	(64.8,71.2)	(52.3,62.0)	(5.2,16.6)
PMB2707 (B44)	731/845 (86.5)	332/419 (79.2)	7.3
--	(84.0,88.7)	(75.0,83.0)	(2.9,11.9)
Composite response <sup>b</sup>	--	--	--
Before Vaccination 1	10/812 (1.2)	8/403 (2.0)	-0.8
--	(0.6,2.3)	(0.9,3.9)	(-2.7,0.7)
1 Month after Vaccination 2	591/755 (78.3)	263/383 (68.7)	9.6
--	(75.2,81.2)	(63.8,73.3)	(4.2,15.2)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD=limit of detection; MenB= *Neisseria meningitidis* group B

Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: Participants from Groups 1 and 2 are ACWY-naïve; participants from Groups 3 and 4 are ACWY-experienced.

Note: LOD = 1:4 for all MenB strains.

Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

<sup>a</sup> Seroresponse is defined as hSBA titer fold rise  $\geq 4$  from baseline (blood draw prior to Vaccination 1). The 4-fold rise is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer  $< 1:4$ ), a response is defined as an hSBA titer  $\geq 1:16$ . (2) For participants with a baseline hSBA titer  $\geq$  LOD and  $<$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the LLOQ. (3) For participants with a baseline hSBA titer  $\geq$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the baseline titer.

<sup>b</sup> Composite response is defined as hSBA titer  $\geq$  LLOQ for all 4 primary MenB strains.

<sup>c</sup> For hSBA titer fold rise  $\geq 4$  from baseline, n = number of participants who achieved hSBA titer fold rise  $\geq 4$  from baseline for the given strain. For composite hSBA response (hSBA  $\geq$  LLOQ for all 4 primary strains), n = number of participants with observed hSBA titer  $\geq$  LLOQ for all 4 primary strains.

<sup>d</sup> For hSBA titer fold rise  $\geq 4$  from baseline, N = number of participants with valid and determinate hSBA titers for the specified strain at both the specified time point and baseline. For composite hSBA response (hSBA  $\geq$  LLOQ for all 4 primary strains), N = number of participants with valid and determinate hSBA results for all 4 strains.

<sup>e</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

<sup>f</sup> Difference in proportions (Groups 1+3 combined MenABCWY + saline minus Groups 2+4 combined Trumenba + MenACWY-CRM), expressed as a percentage.

<sup>g</sup> 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Source: Table 14 in the CSR for Protocol C3511001 submitted to STN 125770/0.

### 6.1.11.3 Analyses of Secondary Endpoints

Table 8 summarizes the proportions of participants achieving an hSBA titer  $\geq 4$ -fold rise 1 month after 1 dose of MenABCWY for Groups 1 and 3 and 1 months after 1 dose of MenACWY-CRM for Groups 2 and 4, by ACWY-serostatus. The LLs of the 2-sided 95% CIs for the differences in percentages of participants achieving a  $\geq 4$ -fold rise from baseline were greater than -10% for each serogroup.

Table 8: Number (%) of Participants Achieving  $\geq 4$ -Fold Rise in hSBA Titer From Baseline for MenACWY Strains – 1 Month After Vaccination 1 in the MenABCWY Groups Compared to the Trumenba + MenACWY-CRM Groups – Post-Vaccination 1 Evaluable Immunogenicity Population

Serogroup	Group 1 ACWY-naïve MenABCWY n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>e</sup> )	Group 2 ACWY-naïve Trumenba + MenACWY- CRM n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>e</sup> )	Group 3 ACWY- experienced MenABCWY n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>e</sup> )	Group 4 ACWY- experienced Trumenba + MenACWY- CRM n <sup>a</sup> /N <sup>b</sup> (%) (95% CI <sup>e</sup> )	Difference <sup>d</sup> (Group 1 minus Group 2) (95% CI <sup>e</sup> )	Difference <sup>d</sup> (Group 1 minus Group 2) (95% CI <sup>e</sup> )
MenA	484/499 (97.0)	242/254 (95.3)	416/439 (94.8)	220/227 (96.9)	1.7	-2.2
--	(95.1, 98.3)	(91.9, 97.5)	(92.2, 96.7)	(93.7, 98.8)	(-1.0, 5.3)	(-5.2, 1.4)
MenC	315/501 (62.9)	132/252 (52.4)	410/439 (93.4)	214/226 (94.7)	10.5	-1.3
--	(58.5, 67.1)	(46.0, 58.7)	(90.7, 95.5)	(90.9, 97.2)	(3.0, 17.9)	(-4.9, 2.9)
MenW	390/492 (79.3)	178/244 (73.0)	417/428 (97.4)	214/222 (96.4)	6.3	1.0
--	(75.4, 82.8)	(66.9, 78.4)	(95.4, 98.7)	(93.0, 98.4)	(-0.1, 13.1)	(-1.6, 4.6)
MenY	405/494 (82.0)	175/248 (70.6)	417/442 (94.3)	209/223 (93.7)	11.4	0.6
--	(78.3, 85.3)	(64.5, 76.2)	(91.8, 96.3)	(89.7, 96.5)	(5.0, 18.2)	(-3.0, 5.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD=limit of detection; MenA= *Neisseria meningitidis* group A; MenC= *Neisseria meningitidis* group C; MenW= *Neisseria meningitidis* group W; MenY= *Neisseria meningitidis* Y  
Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: LOD = 1:4 for all MenA, MenC, MenW, and MenY serogroups.

Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups.

Note: The 4-fold increase is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer <1:4), a response is defined as an hSBA titer  $\geq$ 1:16. (2) For participants with a baseline hSBA titer  $\geq$  LOD and < LLOQ, a response is defined as an hSBA titer  $\geq$ 4 times the LLOQ. (3) For participants with a baseline hSBA titer  $\geq$  LLOQ, a response is defined as an hSBA titer  $\geq$ 4 times the baseline titer.

<sup>a</sup> n = Number of participants who achieved hSBA titer fold rise  $\geq$ 4 from baseline for the given strain.

<sup>b</sup> N = number of participants with valid and determinate hSBA titers for the specified strain at both the given sampling time point and baseline. These values are used as the denominators for the percentage calculations.

<sup>c</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

<sup>d</sup> Difference in proportions (Group 1 MenABCWY + saline minus Group 2 Trumenba + MenACWY-CRM) or (Group 3 MenABCWY + saline minus Group 4 Trumenba + MenACWY-CRM), expressed as a percentage.

<sup>e</sup> 2-Sided CI (based on Miettinen and Nurminen) for the difference in proportions, expressed as a percentage.

Source: Table 15 in the CSR for Protocol C3511001 submitted to STN 125770/0.

#### 6.1.11.4 Subpopulation Analyses

There were no obvious patterns in the subgroup analyses by sex, geographic location, race, ethnicity, or age group. The percentages of participants with hSBA  $\geq$ 4-fold rise in titer from baseline for MenACWY serogroups, 1 month after Vaccination 2 with MenABCWY compared to 1 month after Vaccination 1 with Trumenba + MenACWY-CRM, and the percentages of participants achieving a  $\geq$ 4-fold rise for each of the 4 primary MenB test strains and composite response, 1 month after Vaccination 2 with MenABCWY compared to Trumenba, are generally similar across subgroups.

#### 6.1.11.5 Dropouts and/or Discontinuations

The proportions of participant withdrawals during the vaccination phase and follow-up phase were generally similar among MenABCWY (13.2% and 0.3%, respectively) and Trumenba + MenACWY-CRM (15.9% and 1.1%, respectively) recipients. Withdrawals due to AEs were reported in 3 (0.2%) MenABCWY recipients and in 2 (0.3%) Trumenba + MenACWY-CRM recipients during the vaccination phase; no withdrawals due to AEs were reported during the follow-up phase. The most common reason for withdrawal overall was that the participant was lost to follow-up. ACWY-naïve participants, who were predominantly of younger adolescent age, tended to have lower withdrawal rates than ACWY-experienced participants who were predominantly of older adolescent/young adult age.

There were no substantial differences in the percentages of missing hSBA results for MenA, MenC, MenW, and MenY at each blood sampling visit for MenABCWY recipients and Trumenba + MenACWY-CRM recipients. Most of the missing results were because of participant withdrawals from the study. Similarly, there were no substantial differences in percentages of missing hSBA results for the 4 primary MenB strains before Vaccination 1 and 1 month after Vaccination 2 for MenABCWY recipients and Trumenba + MenACWY-CRM recipients. Most of the missing results were because of participant withdrawals from the study or an assay endpoint being not reached by the end of the testing period.

### 6.1.12 Safety Analyses

Safety analyses were performed on safety populations. The results from analyses of primary safety endpoints are described in this section.

#### 6.1.12.1 Solicited and Unsolicited AEs

Reactogenicity was collected by participants' e-diary including solicited local reactions, systemic events, and use of antipyretic medication for 7 days after Vaccination 1 and Vaccination 2. Tables 9 and 10 present solicited local and systemic adverse reactions and use of antipyretic medication reported within 7 days following each dose, respectively.

Local reactions were reported in slightly higher percentages of MenABCWY recipients than Trumenba + MenACWY-CRM recipients. Systemic reactions were reported in similar percentages of MenABCWY and Trumenba + MenACWY-CRM recipients. Generally, both local and systemic reactions were reported in lower percentages of participants following Vaccination 2 relative to Vaccination 1. The most common local and systemic reactions were pain at the injection site and fatigue and headache, respectively. Most local and systemic reactions were mild or moderate in severity. There were no substantial differences with regard to the severity or percentages of participants who reported local and systemic reactions by maximum severity within 7 days after vaccination in subgroup analyses by ACWY vaccine history, sex, age group, race, or ethnicity (data not shown). After Vaccinations 1 and 2, use of antipyretic/pain medication was reported by 29.5% and 25.1% of participants (respectively) in the MenABCWY group compared to 28.1% and 20.5% of participants (respectively) in the Trumenba + MenACWY-CRM group.

Table 9: Percentage of Participants Reporting Solicited Local Adverse Reactions Within 7 Days after Each Vaccination – Safety Population

Local Reactions	Groups 1+3+5+7 MenABCWY Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 1+3+5+7 MenABCWY Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba + MenACWY-CRM Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)
Redness <sup>c</sup>	--	--	--	--
Any	446/1724 (25.9)	338/1456 (23.2)	123/630 (19.5)	78/529 (14.7)
Mild	153/1724 (8.9)	112/1456 (7.7)	46/630 (7.3)	35/529 (6.6)
Moderate	249/1724 (14.4)	183/1456 (12.6)	63/630 (10)	38/529 (7.2)
Severe	44/1724 (2.6)	43/1456 (3)	14/630 (2.2)	5/529 (0.9)
Swelling <sup>c</sup>	--	--	--	--
Any	431/1724 (25)	352/1456 (24.2)	135/630 (21.4)	78/529 (14.7)
Mild	182/1724 (10.6)	152/1456 (10.4)	52/630 (8.3)	34/529 (6.4)
Moderate	229/1724 (13.3)	186/1456 (12.8)	78/630 (12.4)	43/529 (8.1)
Severe	20/1724 (1.2)	14/1456 (1)	5/630 (0.8)	1/529 (0.2)
Pain at the injection site <sup>d</sup>	--	--	--	--
Any	1541/1725 (89.3)	1229/1456 (84.4)	537/631 (85.1)	416/529 (78.6)
Mild	558/1725 (32.3)	423/1456 (29.1)	196/631 (31.1)	175/529 (33.1)
Moderate	853/1725 (49.4)	711/1456 (48.8)	301/631 (47.7)	213/529 (40.3)
Severe	130/1725 (7.5)	95/1456 (6.5)	40/631 (6.3)	28/529 (5.3)

Local Reactions	Groups 1+3+5+7 MenABCWY Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 1+3+5+7 MenABCWY Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba + MenACWY-CRM Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)
Any local reaction <sup>c</sup>	1553/1725 (90)	1247/1456 (85.6)	546/631 (86.5)	426/529 (80.5)

Note: Local reactions are summarized for the MenABCWY or Trumenba injection site for the left arm only. At Vaccination 1, 26 participants received MenABCWY or Trumenba in the right arm and were excluded from this summary of Vaccination 1 and from summaries across Vaccinations 1 and 2. The 6 participants who received Vaccination 2 in the right arm were excluded from this summary of Vaccination 2 and from summaries across Vaccinations 1 and 2.

Note: Groups 1, 3, 5, and 7 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2, 4, 6, and 8 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.

Note: One (1) participant who received MenABCWY + MenACWY-CRM at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.

<sup>a</sup> n = Number of participants reporting maximum severity of mild, moderate, or severe based on the severity scales.

<sup>b</sup> N = number of participants reporting at least 1 yes or no response for the specified reaction. These values are used as the denominators for the percentage calculations.

<sup>c</sup> Mild is >2.0 to 5.0 cm, moderate is >5.0 to 10.0 cm, severe is >10.0 cm.

<sup>d</sup> Mild = does not interfere with activity, moderate = interferes with activity, severe = prevents daily activity.

<sup>e</sup> Any local reaction = any redness, any swelling, or any pain at the injection site.

Source: Adapted from CBER Request Reactogenicity Tables for Protocol C3511001 submitted to BLA125770/0.8 on February 28, 2023.

Table 10: Percentage of Participants Reporting Solicited Systemic Adverse Reactions and Use of Antipyretic Medications Within 7 Days After Each Vaccination – Safety Population

Systemic Reactions	Groups 1+3+5+7 MenABCWY Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 1+3+5+7 MenABCWY Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba + MenACWY-CRM Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)
Fever	--	--	--	--
≥38.0	102/1739 (5.9)	35/1459 (2.4)	37/638 (5.8)	8/532 (1.5)
38.0 to 38.4	64/1739 (3.7)	27/1459 (1.9)	13/638 (2)	2/532 (0.4)
>38.4 to 38.9	27/1739 (1.6)	5/1459 (0.3)	18/638 (2.8)	5/532 (0.9)
>38.9 to 40.0	11/1739 (0.6)	3/1459 (0.2)	6/638 (0.9)	1/532 (0.2)
>40.0	0/1739 (0)	0/1459 (0)	0/638 (0)	0/532 (0)
Fatigue <sup>c</sup>	--	--	--	--
Any	907/1740 (52.1)	694/1459 (47.6)	349/638 (54.7)	232/532 (43.6)
Mild	409/1740 (23.5)	333/1459 (22.8)	164/638 (25.7)	117/532 (22)
Moderate	443/1740 (25.5)	318/1459 (21.8)	164/638 (25.7)	106/532 (19.9)
Severe	55/1740 (3.2)	43/1459 (2.9)	21/638 (3.3)	9/532 (1.7)
Headache <sup>c</sup>	--	--	--	--

Systemic Reactions	Groups 1+3+5+7 MenABCWY Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 1+3+5+7 MenABCWY Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba + MenACWY-CRM Vaccination 1 n <sup>a</sup> /N <sup>b</sup> (%)	Groups 2+4+6+8 Trumenba Vaccination 2 n <sup>a</sup> /N <sup>b</sup> (%)
Any	814/1740 (46.8)	581/1459 (39.8)	299/638 (46.9)	201/532 (37.8)
Mild	447/1740 (25.7)	311/1459 (21.3)	156/638 (24.5)	112/532 (21.1)
Moderate	334/1740 (19.2)	245/1459 (16.8)	130/638 (20.4)	86/532 (16.2)
Severe	33/1740 (1.9)	25/1459 (1.7)	13/638 (2)	3/532 (0.6)
Chills <sup>c</sup>	--	--	--	--
Any	349/1739 (20.1)	239/1459 (16.4)	125/638 (19.6)	86/532 (16.2)
Mild	219/1739 (12.6)	145/1459 (9.9)	65/638 (10.2)	47/532 (8.8)
Moderate	116/1739 (6.7)	88/1459 (6)	50/638 (7.8)	31/532 (5.8)
Severe	14/1739 (0.8)	6/1459 (0.4)	10/638 (1.6)	8/532 (1.5)
Vomiting <sup>d</sup>	--	--	--	--
Any	55/1739 (3.2)	22/1459 (1.5)	19/638 (3)	5/532 (0.9)
Mild	44/1739 (2.5)	20/1459 (1.4)	13/638 (2)	4/532 (0.8)
Moderate	11/1739 (0.6)	2/1459 (0.1)	6/638 (0.9)	1/532 (0.2)
Severe	0/1739 (0)	0/1459 (0)	0/638 (0)	0/532 (0)
Diarrhea <sup>c</sup>	--	--	--	--
Any	192/1739 (11)	120/1459 (8.2)	86/638 (13.5)	45/532 (8.5)
Mild	152/1739 (8.7)	100/1459 (6.9)	76/638 (11.9)	32/532 (6)
Moderate	34/1739 (2)	20/1459 (1.4)	10/638 (1.6)	13/532 (2.4)
Severe	6/1739 (0.3)	0/1459 (0)	0/638 (0)	0/532 (0)
Muscle pain <sup>c</sup>	--	--	--	--
Any	447/1739 (25.7)	332/1459 (22.8)	175/638 (27.4)	118/532 (22.2)
Mild	236/1739 (13.6)	146/1459 (10)	86/638 (13.5)	53/532 (10)
Moderate	183/1739 (10.5)	174/1459 (11.9)	76/638 (11.9)	61/532 (11.5)
Severe	28/1739 (1.6)	12/1459 (0.8)	13/638 (2)	4/532 (0.8)
Joint pain <sup>c</sup>	--	--	--	--
Any	352/1739 (20.2)	267/1459 (18.3)	144/638 (22.6)	83/532 (15.6)
Mild	186/1739 (10.7)	140/1459 (9.6)	82/638 (12.9)	42/532 (7.9)
Moderate	149/1739 (8.6)	121/1459 (8.3)	55/638 (8.6)	36/532 (6.8)
Severe	17/1739 (1)	6/1459 (0.4)	7/638 (1.1)	5/532 (0.9)
Any systemic event <sup>f</sup>	1269/1741 (72.9)	961/1459 (65.9)	477/638 (74.8)	329/532 (61.8)
Use of antipyretic Medication <sup>g</sup>	513/1739 (29.5)	366/1459 (25.1)	179/638 (28.1)	109/532 (20.5)

Abbreviation: IV = intravenous.

Note: Groups 1, 3, 5, and 7 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2, 4, 6, and 8 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.

Note: One (1) participant who received MenABCWY + MenACWY-CRM at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.

<sup>a</sup> n = Number of participants with the specified characteristic.

<sup>b</sup> N = number of participants reporting at least 1 yes or no response for the specified event. These values are used as the denominators for the percentage calculations.

<sup>c</sup> Mild = does not interfere with activity; moderate = some interference with activity; severe = prevents daily routine activity.

<sup>d</sup> Mild = 1 to 2 times in 24 hours; moderate = >2 times in 24 hours; severe = requires IV hydration.

<sup>e</sup> Mild = 2 to 3 loose stools in 24 hours, moderate = 4 to 5 loose stools in 24 hours; severe = 6 or more loose stools in 24 hours.

<sup>f</sup> Any systemic event = any fever  $\geq 38.0^{\circ}\text{C}$ , any fatigue, any headache, any chills, any vomiting, any diarrhea, any muscle pain, or any joint pain.

<sup>g</sup> Severity is not collected for use of antipyretic medication.

*Source: Adapted from CBER Request Reactogenicity Tables for Protocol C3511001 submitted to BLA125770/0.8 on February 28, 2023.*

Table 11 presents a summary of participants who reported at least 1 AE during the vaccination phase and throughout study in the safety population. During the vaccination phase, similar percentages of participants reported at least 1 AE, related AEs, and severe AEs in the MenABCWY and the Trumenba + MenACWY-CRM groups. During the vaccination phase and throughout the study period, similar proportions of participants in the MenABCWY and Trumenba + MenACWY-CRM groups reported SAEs and MAEs. None of the SAEs were considered to be related to vaccine and a low proportion of participants experienced related MAEs ( $\leq 0.1\%$ ). During the vaccination phase and throughout the study period, a higher proportion of participants in the MenABCWY group (1.1% and 1.4%, respectively) than in the Trumenba + MenACWY-CRM group (0.3% and 0.3%, respectively) reported NDCMCs.

There were no immediate AEs reported during the study.

During the vaccination phase, 88 (5.0%) participants in the MenABCWY group and 29 (4.5%) participants in the Trumenba + MenACWY-CRM group missed school or work because of AEs, none of which were considered to related to vaccine by the applicant.

Table 11: Number (%) of Participants Reporting at Least 1 Adverse Event During the Vaccination Phase and Throughout Study – Safety Population

--	Groups 1+3+5+7 MenABCWY During Vaccination Phase <sup>a</sup>	Groups 1+3+5+7 MenABCWY Throughout Study <sup>b</sup>	Groups 2+4+6+8 Trumenba + MenACWY-CRM During Vaccination Phase <sup>a</sup>	Groups 2+4+6+8 Trumenba + MenACWY-CRM Throughout Study <sup>b</sup>
N	--	--	--	--
All AEs, n (%)	367 (20.8)	458 (26.0) <sup>c</sup>	130 (20.0)	163 (25.1) <sup>c</sup>
Related	9 (0.5)	9 (0.5)	2 (0.3)	2 (0.3)
Severe	11 (0.6)	18 (1.0)	3 (0.5)	6 (0.9)
All SAEs, n (%)	7 (0.4)	11 (0.6)	0	4 (0.6)
Related	0	0	0	0
All MAEs, n (%)	263 (14.9)	340 (19.3)	92 (14.2)	118 (18.2)
Related	2 (0.1)	2 (0.1)	0	0

--	Groups 1+3+5+7 MenABCWY During Vaccination Phase <sup>a</sup>	Groups 1+3+5+7 MenABCWY Throughout Study <sup>b</sup>	Groups 2+4+6+8 Trumenba + MenACWY-CRM During Vaccination Phase <sup>a</sup>	Groups 2+4+6+8 Trumenba + MenACWY-CRM Throughout Study <sup>b</sup>
Severe	8 (0.5)	13 (0.7)	2 (0.3)	2 (0.3)
All NDCMCs, n (%)	20 (1.1)	25 (1.4)	2 (0.3)	2 (0.3)
Related	0	0	0	0
Severe	1 (<0.1)	1 (<0.1)	0	0

Abbreviations: MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; N= number of participants in the specified group. These values are used as the denominator for percentage calculations for the vaccine groups; n = Number of participants reporting at least 1 occurrence of the event specified.

Note: Groups 1, 3, 5, and 7 received MenABCWY + saline at the first study vaccination and MenABCWY at the second study vaccination; Groups 2, 4, 6, and 8 received Trumenba + MenACWY-CRM at the first study vaccination and Trumenba at the second study vaccination.

Note: One (1) participant who received Trumenba + saline at Vaccination 1 was excluded from the safety reporting in this table and in other safety summary tables.

Note: One (1) participant who received MenABCWY + MenACWY-CRM at Vaccination 1 and Trumenba at Vaccination 2 was included in the MenABCWY group for the Vaccination 1 summaries but was excluded from the Vaccination 2 summaries.

<sup>a</sup> Vaccination phase is from the first study vaccination (Month 0) through 1 month after the second study vaccination (Month 7).

<sup>b</sup> Throughout study is defined as the time from the first study vaccination (Month 0) through 6 months after the second study vaccination (Month 12).

<sup>c</sup> These values were computed by the statistical reviewer.

Source: Adapted from CBER Request AE Tables for Protocol C3511001 submitted to BLA125770/0.8 on February 28, 2023.

### 6.1.12.3 Deaths

There were no deaths reported during the study.

### 6.1.12.4 Nonfatal Serious Adverse Events

Throughout the study, SAEs were reported by 0.6% of participants in either of the MenABCWY (11 participants) and Trumenba + MenACWY-CRM group (4 participants), none of which were considered related to vaccine.

### 6.1.12.5 Adverse Events of Special Interest (AESI)

There were 3 AESIs reported in participants in the MenABCWY group. Two of these events (one case of unconfirmed mild alopecia areata and one case of severe status migrainosus) were considered unrelated to vaccine and one event (severe headache) was considered to be related to vaccine by the applicant. I defer to the clinical reviewers regarding the evaluation of these reported AESIs.

## 7. INTEGRATED OVERVIEW OF EFFICACY

Since the effectiveness evaluation of this BLA is primarily based on the immunogenicity data from one pivotal study, C3511001, an integrated analysis of efficacy is not applicable.



## 8. INTEGRATED OVERVIEW OF SAFETY

Since the safety evaluation of this BLA is primarily based on safety data from one pivotal study, C3511001, an integrated analysis of safety is not applicable.

## 9. ADDITIONAL STATISTICAL ISSUES

### 9.1 Special Populations

Not applicable.

### 9.2 Aspects of the Statistical Evaluation Not Previously Covered

#### 9.2.1 Extended 2-dose Schedule

Study C3511004 was a Phase 2, descriptive study conducted in the U.S. in which a group of participants 11 through 14 years of age received MenABCWY on an extended 2-dose schedule with an interval of 12 months between doses (i.e., on a 0- and 12-month schedule). Participants were naïve to any meningococcal vaccine. The proportions of participants in this group achieving seroresponse in hSBA titer for each of the ACWY test strains and primary MenB test strains (A22, A56, B24, and B44), and composite response in MenB test strains 1 month after the second dose are summarized in Table 12. Following 2 doses of MenABCWY on a 0- and 12-month schedule, 98.2% to 99.1% and 92.9% to 100% of participants achieved seroresponse for groups ACWY and group B, respectively. The group B composite response rate was 96.4% following 2 doses of MenABCWY on a 0- and 12-month schedule.

Table 12: Number (%) of Participants Achieving  $\geq 4$ -fold Rise in hSBA Titer at 1 Month After Second Dose of MenABCWY for MenA, MenC, MenW, MenY, Primary MenB Strains – Post-Vaccination 2 – Evaluable Population

Endpoint Strain	MenABCWY (0- and 12-Month Schedule) n <sup>c</sup> /N <sup>d</sup> (%) (95% CI <sup>e</sup> )
Seroresponse <sup>a</sup>	--
MenA	115/116 (99.1) (95.3, 100.0)
MenC	114/115 (99.1) (95.3, 100.0)
MenW	112/113 (99.1) (95.2, 100.0)
MenY	109/111 (98.2) (93.6, 99.8)
PMB80 (A22)	106/111 (95.5) (89.8, 98.5)
PMB2001 (A56)	115/115 (100.0) (96.8, 100.0)
PMB2948 (B24)	105/113 (92.9) (86.5, 96.9)
PMB2707 (B44)	110/116 (94.8) (89.1, 98.1)
Composite response <sup>b</sup>	106/110 (96.4) (91.0, 99.0)

Abbreviations: hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; LOD=limit of detection; MenA= *Neisseria meningitidis* group A; MenB= *Neisseria meningitidis* group B; MenC= *Neisseria meningitidis* group C; MenW= *Neisseria meningitidis* group W; MenY= *Neisseria meningitidis* Y

Note: LOD = 1:4 for all MenB strains.

Note: LLOQ = 1:16 for A22; 1:8 for A56, B24, and B44.

<sup>a</sup> Seroreponse is defined as hSBA titer fold rise  $\geq 4$  from baseline (blood draw prior to Vaccination 1). The 4-fold rise is defined as follows: (1) For participants with a baseline hSBA titer below the LOD (hSBA titer  $< 1:4$ ), a response is defined as an hSBA titer  $\geq 1:16$ . (2) For participants with a baseline hSBA titer  $\geq$  LOD and  $<$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the LLOQ. (3) For participants with a baseline hSBA titer  $\geq$  LLOQ, a response is defined as an hSBA titer  $\geq 4$  times the baseline titer.

<sup>b</sup> Composite response is defined as hSBA titer  $\geq$  LLOQ for all 4 primary MenB strains.

<sup>c</sup> For hSBA titer fold rise  $\geq 4$  from baseline,  $n$  = number of participants who achieved hSBA titer fold rise  $\geq 4$  from baseline for the given strain. For composite hSBA response (hSBA  $\geq$  LLOQ for all 4 primary strains),  $n$  = number of participants with observed hSBA titer  $\geq$  LLOQ for all 4 primary strains.

<sup>d</sup> For hSBA titer fold rise  $\geq 4$  from baseline,  $N$  = number of participants with valid and determinate hSBA titers for the specified strain at both the specified time point and baseline. For composite hSBA response (hSBA  $\geq$  LLOQ for all 4 primary strains),  $N$  = number of participants with valid and determinate hSBA results for all 4 strains.

<sup>e</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

Source: Tables 15 and 21 in the CSR for Protocol C3511004 submitted to STN 125770/0.

## 9.2.2 Booster Immunogenicity

Study B1971057 was a 2-stage study conducted in U.S. and Europe. Stage 1 was a randomized, active-controlled, observer-blinded, multicenter trial in which participants 10 through 25 years of age received MenABCWY at 0 and 6 months (Group 1 for ACWY-naïve and Group 3 for ACWY-experienced) or Trumenba at 0 and 6 months and MenACWY-CRM at 0 month (Group 2 for ACWY-naïve and Group 4 for ACWY-experienced). All participants were naïve to MenB vaccine. Both ACWY-naïve and ACWY-experienced participants (received 1 dose of MenACWY conjugate vaccine at least 4 years prior to enrollment) were part of the study. Stage 2 was an open-label extension in which a subset of participants from Groups 1 and 3 or from Groups 2 and 4 were followed for 4 years and received a booster dose of MenABCWY or Trumenba + MenACWY-CRM 4 years after primary series completion, respectively. Immunopersistence following the primary series of MenABCWY (on a 0- and 6- month schedule) and immunogenicity of a booster dose of MenABCWY was evaluated in Stage 2. Seroprotections (defined as hSBA titer  $\geq$  LLOQ) and GMTs at 1 month after vaccination 2, before booster vaccination and 1 month after booster vaccination are presented in Table 13 by ACWY-serostatus for MenA, MenC, MenW, and MenY strains and in Table 14 for primary MenB strains. Following the booster dose of MenABCWY or Trumenba + MenACWY-CRM approximately 4 years after primary series completion, proportions of participants achieving protective hSBA titers  $\geq 1:8$  for serogroups A, C, W, and Y rose to 100% in both ACWY-naïve and ACWY-experienced participants. At 1 month after the booster dose, the proportions of MenABCWY recipients and Trumenba + MenACWY-CRM recipients achieving protective hSBA titers  $\geq$  LLOQ for the 4 primary MenB test strains were  $>95\%$  and similar between both vaccine groups.

Table 13: Participants with hSBA Titers  $\geq 1:8$  and GMTs for MenA, MenC, MenW, and MenY – MenABCWY (Groups 1 and 3) and Trumenba + MenACWY-CRM (Groups 2 and 4) – Booster Evaluable Immunogenicity Population

Serogroup Time point endpoint	Group 1 ACWY-naïve MenABCWY	Group 2 ACWY-naïve Trumenba + MenACWY-CRM	Group 3 ACWY-experienced MenABCWY	Group 4 ACWY-experienced Trumenba + MenACWY-CRM
MenA	--	--	--	--
1 month after vaccination 2, N <sup>a</sup>	60	37	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	35 (94.6) (81.8,99.3)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	143.7 (114.3, 180.6)	56.1 (33.9, 93)	315.8 (223.7, 445.9)	236 (136.5, 408)
Before booster vaccination, N <sup>a</sup>	60	36	32	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	47 (78.3) (65.8,87.9)	22 (61.1) (43.5,76.9)	32 (100) (89.1,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	29.9 (21.2, 42)	21 (11.6, 37.8)	125.3 (89.3, 175.8)	122.9 (62, 243.5)
1 month after booster vaccination, N <sup>a</sup>	60	37	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	530.1 (427.6, 657)	1043.4 (728.5, 1494.3)	451.4 (333.1, 611.6)	1024 (687.5, 1525.3)
MenC	--	--	--	--
1 month after vaccination 2, N <sup>a</sup>	60	36	70	51
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	33 (91.7) (77.5,98.2)	70 (100) (94.9,100)	51 (100) (93,100)
GMT (95% CI <sup>d</sup> )	191.8 (143.5, 256.3)	50.8 (30.3, 85.2)	689.1 (531.2, 894)	318.2 (217.8, 464.8)
Before booster vaccination, N <sup>a</sup>	60	37	68	51
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	36 (60) (46.5,72.4)	14 (37.8) (22.5,55.2)	67 (98.5) (92.1,100)	45 (88.2) (76.1,95.6)
GMT (95% CI <sup>d</sup> )	17.1 (11.5, 25.6)	12.1 (7, 21)	130.6 (96.8, 176.3)	91.1 (57.9, 143.4)
1 month after booster vaccination, N <sup>a</sup>	60	37	70	51
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	37 (100) (90.5,100)	70 (100) (94.9,100)	51 (100) (93,100)
GMT (95% CI <sup>d</sup> )	383.6 (286, 514.4)	641.1 (421.8, 974.3)	760.8 (593.8, 974.8)	1272.7 (885.6, 1829)
MenW	--	--	--	--
1 month after vaccination 2, N <sup>a</sup>	60	37	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)

Serogroup Time point endpoint	Group 1 ACWY-naïve MenABCWY	Group 2 ACWY-naïve Trumenba + MenACWY-CRM	Group 3 ACWY-experienced MenABCWY	Group 4 ACWY-experienced Trumenba + MenACWY-CRM
GMT (95% CI <sup>d</sup> )	230.7 (185, 287.7)	84.8 (59.2, 121.4)	779.3 (496.3, 1223.8)	313.9 (141.8, 694.8)
Before booster vaccination, N <sup>a</sup>	59	37	32	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	53 (89.8) (79.2,96.2)	26 (70.3) (53,84.1)	32 (100) (89.1,100)	15 (88.2) (63.6,98.5)
GMT (95% CI <sup>d</sup> )	36.4 (26.4, 50.3)	16 (10.2, 25.1)	159 (94.8, 266.7)	92.4 (35.6, 239.4)
1 month after booster vaccination, N <sup>a</sup>	60	37	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	822.2 (627.1, 1077.9)	1189.6 (796.8, 1776)	631.7 (492.2, 810.7)	943.8 (479.5, 1857.7)
MenY	--	--	--	--
1 month after vaccination 2, N <sup>a</sup>	60	35	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	35 (100) (90,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	297.5 (244, 362.6)	84.4 (54.2, 131.7)	522.9 (348.7, 784.1)	208.8 (103.8, 420)
Before booster vaccination, N <sup>a</sup>	60	37	32	16
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	35 (94.6) (81.8,99.3)	32 (100) (89.1,100)	16 (100) (79.4,100)
GMT (95% CI <sup>d</sup> )	45.3 (34.8, 58.9)	27.5 (18.8, 40.4)	162.4 (105.3, 250.6)	103.1 (55, 193.2)
1 month after booster vaccination, N <sup>a</sup>	60	37	33	17
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	60 (100) (94,100)	37 (100) (90.5,100)	33 (100) (89.4,100)	17 (100) (80.5,100)
GMT (95% CI <sup>d</sup> )	1012.2 (793.6, 1291.1)	1575.5 (1062.3, 2336.7)	522.9 (404.4, 676)	943.8 (538.1, 1655.3)

Abbreviations: GMT=geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenA= *Neisseria meningitidis* group A; MenC= *Neisseria meningitidis* group C; MenW= *Neisseria meningitidis* group W; MenY= *Neisseria meningitidis* Y

Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination, MenABCWY at the second study vaccination, and MenABCWY at the booster vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination, Trumenba at the second study vaccination, and Trumenba + MenACWY-CRM at the booster vaccination.

Note: LLOQ = 1:8 for all MenA, MenC, MenW, and MenY serogroups. Titers below the LLOQ were set to 0.5×LLOQ for analysis of GMTs.

Note: Seroprotection is defined as hSBA titer ≥ LLOQ.

<sup>a</sup> N = number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point. These values are used as the denominators for the percentage calculations.

<sup>b</sup> n = Number of participants who achieved hSBA titer fold rise ≥ LLOQ at the given sampling time point for the given strain.

<sup>c</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

<sup>d</sup> CIs are back transformed from confidence interval based on the student t distribution for the mean logarithm of the concentrations.

*Source: Tables 14 and 15 in the interim CSR for Protocol B1971057 Stage 2 submitted to STN 125770/0.*

Table 14: Table 12: Participants with hSBA Titers  $\geq$ LLOQ and GMTs for Primary MenB Strains – MenABCWY (Groups 1 and 3 Combined) and Trumenba + MenACWY-CRM (Groups 2 and 4 Combined) – Booster Evaluable Immunogenicity Population

Serogroup Time point endpoint	Groups 1+3 MenABCWY	Groups 2 + 4 Trumenba + MenACWY-CRM
PMB80 (A22)	--	--
1 month after vaccination 2, N <sup>a</sup>	129	88
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	122 (94.6) (89.1,97.8)	82 (93.2) (85.7,97.5)
GMT (95% CI <sup>d</sup> )	54.8 (47.1, 63.7)	43.5 (36.2, 52.3)
Before booster vaccination, N <sup>a</sup>	121	83
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	34 (28.1) (20.3,37)	26 (31.3) (21.6,42.4)
GMT (95% CI <sup>d</sup> )	12 (10.5, 13.8)	11.6 (10.1, 13.4)
1 month after booster vaccination, N <sup>a</sup>	122	81
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	116 (95.1) (89.6,98.2)	76 (93.8) (86.2,98)
GMT (95% CI <sup>d</sup> )	85 (70.3, 102.9)	74.7 (60.3, 92.5)
PMB2001 (A56)	--	--
1 month after vaccination 2, N <sup>a</sup>	128	87
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	126 (98.4) (94.5,99.8)	84 (96.6) (90.3,99.3)
GMT (95% CI <sup>d</sup> )	161.6 (134.7, 193.8)	123 (97.5, 155.2)
Before booster vaccination, N <sup>a</sup>	127	86
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	46 (36.2) (27.9,45.2)	25 (29.1) (19.8,39.9)
GMT (95% CI <sup>d</sup> )	8.9 (7.2, 11)	6.6 (5.4, 8)
1 month after booster vaccination, N <sup>a</sup>	124	86
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	124 (100) (97.1,100)	85 (98.8) (93.7,100)
GMT (95% CI <sup>d</sup> )	321.9 (272.3, 380.7)	223.2 (172, 289.7)
PMB2948 (B24)	--	--
1 month after vaccination 2, N <sup>a</sup>	126	87
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	109 (86.5) (79.3,91.9)	68 (78.2) (68,86.3)
GMT (95% CI <sup>d</sup> )	28.8 (23.6, 35.2)	16.9 (13.5, 21.2)
Before booster vaccination, N <sup>a</sup>	126	86
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	44 (34.9) (26.6,43.9)	21 (24.4) (15.8,34.9)
GMT (95% CI <sup>d</sup> )	7 (6, 8.1)	5.9 (5, 7.1)
1 month after booster vaccination, N <sup>a</sup>	123	84
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	117 (95.1) (89.7,98.2)	80 (95.2) (88.3,98.7)
GMT (95% CI <sup>d</sup> )	60.8 (50.9, 72.7)	40.7 (33.1, 49.9)
PMB2707 (B44)	--	--
1 month after vaccination 2, N <sup>a</sup>	130	86
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	128 (98.5) (94.6,99.8)	82 (95.3) (88.5,98.7)
GMT (95% CI <sup>d</sup> )	46.7 (39, 56)	34.1 (27.5, 42.4)
Before booster vaccination, N <sup>a</sup>	129	87
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	23 (17.8) (11.7,25.5)	14 (16.1) (9.1,25.5)
GMT (95% CI <sup>d</sup> )	5.1 (4.6, 5.6)	5 (4.4, 5.7)
1 month after booster vaccination, N <sup>a</sup>	128	86

Serogroup Time point endpoint	Groups 1+3 MenABCWY	Groups 2 + 4 Trumenba + MenACWY-CRM
seroprotection, n <sup>b</sup> (%) (95% CI <sup>c</sup> )	127 (99.2) (95.7,100)	85 (98.8) (93.7,100)
GMT (95% CI <sup>d</sup> )	98.2 (81.3, 118.5)	66.1 (53.3, 81.9)

Abbreviations: GMT=geometric mean titer; hSBA = serum bactericidal assay using human complement; LLOQ = lower limit of quantitation; MenB= *Neisseria meningitidis* group B

Note: Groups 1 and 3 received MenABCWY + saline at the first study vaccination, MenABCWY at the second study vaccination, and MenABCWY at the booster vaccination; Groups 2 and 4 received Trumenba + MenACWY-CRM at the first study vaccination, Trumenba at the second study vaccination, and Trumenba + MenACWY-CRM at the booster vaccination.

Note: LLOQ = 1:16 for A22 and 1:8 for A56, B24, and B44. Titers below the LLOQ were set to 0.5×LLOQ for analysis of GMTs.

Note: Seroprotection is defined as hSBA titer ≥ LLOQ.

<sup>a</sup> N = number of participants with valid and determinate hSBA titers for the specified strain at the given sampling time point. These values are used as the denominators for the percentage calculations.

<sup>b</sup> n = Number of participants who achieved hSBA titer fold rise ≥LLOQ at the given sampling time point for the given strain.

<sup>c</sup> Exact 2-sided CI based upon the observed proportion of participants, using the Clopper and Pearson method.

<sup>d</sup> CIs are back transformed from confidence interval based on the student t distribution for the mean logarithm of the concentrations.

Source: Tables 16 and 17 in the interim CSR for Protocol B1971057 Stage 2 submitted to STN 125770/0.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

Key immunogenicity results are summarized as follows:

- For the MenACWY NI evaluation in ACWY-naïve participants, proportions of subjects achieving seroresponse ranged from 93.3% to 97.8% after 2 doses of MenABCWY and ranged from 52.4% to 95.3% after 1 dose of MenACWY-CRM for the ACWY test strains. The differences in proportions (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from 2.5% to 41.0% across ACWY strains. The LLs of the 2-sided 95% confidence intervals (CIs) for the differences in proportions are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-naïve participants.
- For the MenACWY NI evaluation in ACWY-experienced participants, proportions of subjects achieving seroresponse ranged from 93.0% to 97.1% after 2 doses of MenABCWY and ranged from 93.7% to 96.9% after 1 dose of MenACWY-CRM. The differences in proportions (2 doses of MenABCWY versus 1 dose of MenACWY-CRM) ranged from -3.2% to 0.7% across ACWY strains. The LLs of the 2-sided 95% CIs for the differences in proportions are greater than -10% for all ACWY strains, meeting the NI criteria for 2 doses of MenABCWY compared with 1 dose of MenACWY-CRM in ACWY-experienced participants.
- For the MenB NI evaluation, proportions of subjects achieving seroresponse ranged from 68.1% to 95.9% after 2 doses of MenABCWY and ranged from 57.2% to 94.5%

after 2 doses of Trumenba for the four primary MenB strains. The differences in proportions (2 doses of MenABCWY versus 2 doses of Trumenba) ranged from 1.4% to 10.9% across primary MenB strains. Additionally, proportions of subjects achieving composite response were 78.3% and 68.7% after 2 doses of MenABCWY and Trumenba, respectively, resulting in a difference of 9.6%. The LLs of the 2-sided 95% CIs for the differences in proportions (2 doses of MenABCWY versus 2 doses of Trumenba) are greater than -10% for all 4 primary MenB strains and the composite endpoint, meeting the NI criteria for 2 doses of MenABCWY compared with 2 doses of Trumenba.

The main safety results are summarized as follows:

- Following 2 doses of MenABCWY, the most common local reaction within 7 days was pain at the injection site (89.3% post-Vaccination 1 and 84.4% post-Vaccination 2) and the most common systemic events were fatigue (52.1% post-Vaccination 1 and 47.6% post-Vaccination 2) and headache (46.8% post-Vaccination 1 and 39.8% post-Vaccination 2). Most local reactions and systemic events were mild to moderate in severity.
- During the vaccination phase (from the first study vaccination through 1 months after the second study vaccination), similar percentages of participants in the MenABCWY and Trumenba + MenACWY-CRM groups reported at least 1 AE (20.8% and 20.0%, respectively), related AEs (0.5% and 0.3%, respectively), and severe AEs (0.6% and 0.5%, respectively).
- During the vaccination phase and throughout the study period, similar proportions of participants in the MenABCWY and Trumenba + MenACWY-CRM groups reported SAEs (0.4% and 0%, respectively, during the vaccination phase; 0.6% and 0.6%, respectively, throughout the study period) and MAEs (14.9% and 14.2%, respectively, during the vaccination phase; 19.3% and 18.2%, respectively, throughout the study period). None of the SAEs were considered related to vaccine and a low proportion of participants experienced related MAEs ( $\leq 0.1\%$ ).
- A higher proportion of participants in the MenABCWY group than in the Trumenba + MenACWY-CRM group reported NDCMCs (1.1% and 0.3%, respectively, during the vaccination phase; 1.4% and 0.3%, respectively, throughout the study period).
- There were no immediate AEs reported during the study.
- There were no deaths reported during the study.

## 10.2 Conclusions and Recommendations

In conclusion, there were no statistical issues related to this BLA. Primary immunogenicity and safety results were confirmed by my independent analyses. The primary immunogenicity objectives pre-specified in this pivotal study (i.e., 2 doses of MenABCWY, administered on a 0- and 6-month schedule, induce noninferior immune responses for MenA, MenC, MenW, MenY compared to 1 dose of MenACWY-CRM, and induce noninferior immune response for MenB compared to 2 doses of Trumenba) were achieved and supported approval of the vaccine. The safety profile was generally similar between participants in the MenABCWY and Trumenba + MenACWY-CRM groups except for NDCMCs. I defer to the clinical reviewer on whether the safety profile of MenABCWY supports approval of the vaccine.