BLA Clinical Review Memorandum

Application Type	Efficacy Supplement to Biologics License Application
STN	125701/262
CBER Received Date	July 23, 2024
PDUFA Goal Date	May 23, 2025
Division / Office	DCTR/OVRR
Priority Review (Yes/No)	No
Reviewer Names	Gauri Raval, MD, MPH Clinical Reviewer CRB3, DCTR, OVRR, CBER Robin Wisch, MD Clinical Reviewer CRB3, DCTR, OVRR, CBER
Review Completion Date / Stamped Date	May 23, 2025
Supervisory Concurrence	Rachel Zhang, MD Team Lead CRB3, DCTR, OVRR, CBER Anuja Rastogi, MD, MHS Branch Chief CRB3, DCTR, OVRR, CBER
Applicant	Sanofi Pasteur Inc.
Proper Name	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine
Trade Name	MenQuadfi
Pharmacologic Class	Vaccine
Formulation, including Adjuvants	Each dose (0.5 mL) contains 10 µg each of the meningococcal capsular polysaccharides Serogroup A, C, Y, W and approximately 55 µg of tetanus toxoid protein carrier.
Dosage Forms and Routes of Administration	Dosage form: Solution Route of Administration: Intramuscular
Dosing Regimen	• Infants 2 months of age at first dose: 4-dose series at 2, 4, 6, and between 12 and 18 months of age. The first dose may be given as early as 6 weeks of age. • Infants 6 months through 11 months of age: 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose. • Infants 12 months through 23 months of age: 2-dose series with the second dose administered at least 3 months after the first dose. • Individuals 2 years of age and older: A single dose.
Indication and Intended Populations	Active immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y for use in individuals 6 weeks of age and older.
Orphan Designated (Yes/No)	No

Table of Contents

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	Biologics License Application
CBER	Centers for Biologics Evaluation and Research
CDC	Centers for Disease Control and Preventions
CFR	code of federal regulations
CI	confidence interval
COVID	coronavirus disease
CRF	case report form
CSR	clinical study report
(b) (4)	(b) (4)
ED	emergency department
EEG	electroencephalogram
(b) (4)	(b) (4)
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	full analysis set
FDA	Food and Drug Administration
FHA	filamentous hemagglutinin
GCP	good clinical practices
GMC	geometric mean concentration
GMT	geometric mean titer
hSBA	serum bactericidal activity using human complement
IMD	invasive meningococcal disease
ISS	integrated summary of safety
ITP	idiopathic thrombocytopenic purpura
ITT	intent-to-treat
KD	Kawasaki disease
LLOQ	lower limit of quantitation
MCV4	Meningococcal Conjugate Quadrivalent (Groups A,C,Y,W) Vaccine
MedDRA	Medical Dictionary for Regulatory Activities
Menactra	Meningococcal ACWY Diphtheria Toxoid Conjugate Vaccine
Menveo	Meningococcal ACWY CRM Conjugate Vaccine
Menomune	Meningococcal ACWY Polysaccharide Vaccine
MenQuadfi	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine
MMR	measles, mumps, and rubella vaccine
NI	noninferiority
PPAS	per protocol analyses set
PRN	pertactin
PRP	polyribosyl-ribitol phosphate
PP	per protocol
PT	pertussis toxin
PT	preferred term
PREA	Pediatric Research Equity Act
RCDC	reverse cumulative distribution curves
(b) (4)	(b) (4)
RSV	respiratory syncytial virus
SAE	serious adverse event
SafAS	safety analysis set
SC	subcutaneous

SOC	system organ class
SRR	seroresponse rate
USPI	United States package insert
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1. EXECUTIVE SUMMARY

Sanofi Pasteur, Inc. (the Applicant) has submitted a supplemental Biologics License Application (sBLA) to the United States (U.S.) Food and Drug Administration (FDA) to extend the age indication for use of their Meningococcal (Groups A, C, Y, W) Conjugate Vaccine (trade name MenQuadfi) to include infants 6 weeks through 23 months of age. MenQuadfi is currently indicated for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* (*N. meningitidis)* serogroups A, C, W, and Y in individuals 2 years and older.

To support the safety and effectiveness of MenQuadfi for the intended use in individuals 6 weeks through 23 months of age, the Applicant submitted data from three Phase 3 studies (MET 42, MET41, MET61) and one supportive Phase 2 study (MET39). MET42 evaluated the safety and effectiveness of a 4-dose series of MenQuadfi when concomitantly administered with routine childhood vaccinations recommended by the Advisory Committee on Immunization Practices (ACIP) and approved by the Centers for Disease Control and Prevention (CDC) (hereafter "recommended pediatric vaccines") at 2, 4, 6, and 12 through 18 (hereafter 12-18) months of age. MET41 evaluated the safety of a 4-dose series of MenQuadfi when concomitantly administered with recommended pediatric vaccines at 2, 4, 6, and 12 months of age. MET61 evaluated the safety and effectiveness of a 2-dose series of MenQuadfi when concomitantly administered with recommended pediatric vaccines at 6 through 7 (hereafter 6-7) months and 12 through 13 (hereafter 12-13) months of age, or at 17 through 19 (hereafter 17-19) months and 20 through 23 (hereafter 20-23) months of age. The Phase 2 study, MET39, evaluated the safety and immunogenicity of five different schedules of MenQuadfi administered to infants and toddlers concomitantly with recommended pediatric vaccines.

Immunogenicity Analyses:

Protection against invasive meningococcal disease is conferred mainly by complement-mediated antibody-dependent killing by bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y. Effectiveness of MenQuadfi was evaluated by measuring antibodies with assays that use human complement to assess serum bactericidal activity (hSBA) after vaccination with MenQuadfi as compared to after vaccination with a comparator U.S.-licensed meningococcal A, C, Y, W vaccine (Menveo, GlaxoSmithKline Biologicals SA).

MET42 evaluated the effectiveness of a 4-dose series of MenQuadfi administered at 2, 4, 6, and 12-15 months of age in infants 6 weeks through 2 months of age at enrollment. The primary immunogenicity objectives evaluating the noninferiority of MenQuadfi compared with Menveo were met, based on the percentage of participants achieving hSBA seroresponse[1] after the 4th dose and the percentage of participants with hSBA titers ≥1:8 after the 3rd dose for all four serogroups. Noninferior immune responses to recommended pediatric vaccines administered concomitantly with MenQuadfi compared with Menveo were demonstrated. Descriptive analyses of hSBA responses following the 4th dose of MenQuadfi administered at 12-15 months of age were similar to those elicited when the 4th dose was administered at 15-18 months of age.

1 hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as: if prevaccination (pre-1st dose) hSBA titer < 1:8, then post-4th dose (D30 after 12-month) vaccination titer must be ≥ 1:16; and if prevaccination hSBA titer ≥ 1:8, then post-4th dose vaccination titer must be ≥ 4-fold greater than the prevaccination titer.

MET61 evaluated the effectiveness of a 2-dose series of MenQuadfi administered at 6-7 months and 12-13 months. The primary immunogenicity objective evaluating the noninferiority of MenQuadfi compared with Menveo was met, based on the percentage of participants achieving hSBA seroresponse following the 2nd dose for all four serogroups. Noninferiority of MenQuadfi compared with Menveo was also demonstrated based on the percentage of participants with hSBA titers ≥ 1:8 following the 2nd dose for all four serogroups. MET61 included groups of participants who received a 2-dose series of MenQuadfi or a comparator U.S.-licensed meningococcal A, C, Y, W vaccine (Menactra, Sanofi Pasteur, Inc) administered at 17-19 months and 20-23 months of age. In descriptive analyses, hSBA responses following a 2-dose series of MenQuadfi were similar to those observed after Menactra.

Safety Analyses

Safety data from MET41 and MET42 included 3,807 participants 6 weeks through 2 months of age at enrollment who received at least one dose of a 4-dose series of MenQuadfi. The most frequently reported solicited adverse reactions (ARs) among infant recipients after any dose of a 4-dose series of MenQuadfi in MET42 included: injection site tenderness (38.5%-45.6%), irritability (40.1%-51.9%), crying abnormal (27.3%- 42.1%), and drowsiness (25.1%-43.4%); the reported rates were similar to those observed in Menveo recipients in MET42 and to those observed in MenQuadfi recipients in MET41.

Safety data from MET61 included 466 participants who received at least one dose of a 2-dose series of MenQuadfi administered at 6-7 months and 12-13 months of age (N=370) or at 17-19 months and 20-23 months of age (N=96). The most frequently reported solicited adverse reactions among MenQuadfi recipients after any dose of a 2-dose series at 6-7 months and 12-13 months of age were injection site tenderness (30.1%- 42.7%), crying abnormal (26.6%-35.0%), drowsiness (27.7%- 36.5%), and irritability (40%- 49%). The most frequently reported solicited adverse reactions among MenQuadfi recipients after any dose of a 2-dose series at 17-19 months and 20-23 months were injection site tenderness (34.4%- 41.5%), crying abnormal (25.6%-26.7%), drowsiness (23.2%- 24.4%), and irritability (35.4%- 40%). The reported rates were similar to those observed in comparator MenACWY vaccine recipients.

Overall, across the three studies, the frequencies of solicited ARs after any dose of MenQuadfi were similar to those observed after the comparator vaccines. Rates of unsolicited adverse events (AEs) within 30 days after any dose and serious adverse events (SAEs) through the study duration among MenQuadfi recipients were similar to those reported in the comparator groups. Two SAEs classified under the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of febrile convulsion (hereafter referred to as febrile seizure), both occurring after the 4th dose of MenQuadfi administered at 12 months of age with concomitant recommended pediatric vaccines, were considered possibly related to vaccination with MenQuadfi and will be described in Section 6 of the MenQuadfi Prescribing Information (PI). There was a nominally higher reported rate of febrile seizures after MenQuadfi compared with Menveo within 30 days of vaccination in the clinical studies (0.1% compared with 0%, respectively); however, Menactra recipients had a higher reported rate (1%) than both MenQuadfi and Menveo groups. The Applicant has been requested to conduct enhanced post-marketing surveillance to further assess for the risk of febrile seizure after MenQuadfi.

Concomitant Vaccination

Study MET42 found no evidence of immune interference when MenQuadfi was concomitantly administered with recommended pediatric vaccines.

Pediatric Assessment and Pediatric Research Equity Act

Studies MET41, MET42, and MET61 were submitted to this sBLA to fulfill the deferred post-marketing requirements (PMRs) agreed upon with the initial BLA for use of MenQuadfi in individuals 2 years of age and older. The Pediatric Review Committee at FDA agreed that these PMRs are fulfilled.

Overall Conclusions:

The totality of clinical safety and effectiveness data presented in this application support approval of MenQuadfi for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y in individuals 6 weeks of age and older.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, demographic characteristics were reviewed individually. There were no substantial differences identified in the safety and immunogenicity profiles of the evaluated demographic subgroups.

Prematurity at birth was evaluated in MET41 and MET42. The immunogenicity and safety profiles of MenQuadfi in infants born preterm (31 to <37 weeks gestational age) were generally comparable with those of infants born at term (≥37 weeks gestational age).

1.2 Patient Experience Data

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

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

N. meningitidis is a gram-negative endotoxin-producing diplococcal bacterium responsible for endemic and epidemic invasive meningococcal disease (IMD) worldwide, with the greatest incidence in Sub-Saharan Africa. Meningococci spread through respiratory secretions and require close contact for transmission. Fewer than 1% of people who acquire the bacteria develop disease. Meningococci are classified into serogroups based on the structure and antigenic differences of their capsular polysaccharides. Serogroups B, C, and Y are responsible for most IMD in the U.S.

Meningococcal disease usually presents as bacteremia with or without meningitis or sepsis. Other clinical presentations include pneumonia, arthritis, and pericarditis. Even with prompt antimicrobial therapy, up to 15% of infected individuals will have a fatal outcome (CDC 2024a). Furthermore, up to 20% of survivors will have substantial morbidity including brain damage, deafness, and loss of limbs.

IMD can affect any age group. In Sub-Saharan Africa, the highest rates of disease are among children and adolescents ages 5 through 14 years. In the U.S., the highest incidence rates are among children <1 year of age. In this age group, meningococcal disease may present with nonspecific symptoms (e.g., lethargy, irritability, feeding, fever) and without neck stiffness. CDC reported the overall incidence rate in 2023 to be 0.13 per 100,000 persons, which is higher than incidence rates in 2021 (0.06-0.07 cases per 100,000), after which cases of meningococcal disease have increased (CDC 2024a).

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

Third generation cephalosporins are recommended for empiric treatment. Ampicillin or penicillin may be used for treatment after determination of meningococcal isolate susceptibility. Chemoprophylaxis with antimicrobial agents (e.g., rifampin, ceftriaxone, ciprofloxacin, or azithromycin) may be given to close contacts of individuals with IMD (CDC 2024c).

2.3 Safety and Effectiveness of Pharmacologically Related Products

The ACIP recommends routine vaccination with a quadrivalent meningococcal conjugate vaccine (MenACWY vaccine) for adolescents (first dose at age 11-12 years and booster dose at age 16 years) and individuals ≥2 months of age at increased risk, including individuals at increased risk due to an outbreak (Mbaeyi et al. 2020). Two licensed MenACWY vaccines are available use in the U.S: Menveo approved for individuals 2 months through 55 years of age, and MenQuadfi approved for individuals ages 2 years and older. (Menomune and Menactra were discontinued in the U.S. in 2017 and 2022, respectively) (CDC 2024b). In addition, there are two U.S.-licensed meningococcal A, B, C, W, Y vaccines: Penbraya and Penmenvy, both approved for use in individuals 10 through 25 years of age (CDC 2024b).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

On April 23, 2020, the FDA approved MenQuadfi for use in individuals two years of age and older. MenQuadfi is approved for individuals ages 12 months and older in Australia, Canada, the European Union, European Economic Area countries, and several Latin American countries including Argentina, Brazil, Cuba, and Chile (Sáfadi et al. 2017).

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

The following timeline includes a list of major regulatory activity associated with the submission of this sBLA:

- April 23, 2020: MenQuadfi was originally approved for use in individuals 2 years of age and older. The approval letter included 3 postmarketing requirement (PMR) studies under the Pediatric Research Equity Act (PREA): MET41, MET42, and MET61.
- September 19, 2022: A deferral extension was granted for the 3 PMRs, with a new October 31, 2024, due date for submission of the final clinical study reports for all 3 studies.
- March 8, 2024 (Type B pre-sBLA Meeting): The Applicant sought CBER concurrence on the clinical data supporting the review of the sBLA submission and CBER provided responses to the Applicant's questions.

2.6 Other Relevant Background Information

Immunologic Marker of Protection: Serum Bactericidal Activity[2]
The use of immunogenicity data to support the effectiveness of meningococcal vaccines in children younger than 2 years of age was discussed at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting held on April 6-7, 2011. The committee concluded that serum bactericidal activity with human complement (hSBA) could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children

2 FDA. Vaccines and Related Biological Products Advisory Committee. Rockville, Maryland. April 6-7, 2011.

younger than 2 years of age. In addition, the committee concluded that seroresponse achieved at or above a pre-defined hSBA titer could be considered evidence that the meningococcal-specific functional antibodies measured postvaccination were protective against systemic infection. Due to the characteristics of the applicant's hSBA assays, a threshold titer of ≥ 1:8 was used as one of the criteria used to demonstrate effectiveness following administration of MenQuadfi.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance with Good Clinical Practices and Submission Integrity

Safety and immunogenicity data from three main studies (MET41, MET42, and MET61) were provided in this application to support this efficacy supplement for MenQuadfi and were conducted in accordance with the International Council on Harmonization's Good Clinical Practice (GCP) guidelines. The informed consent form for each study contained all the essential elements as stated in 21 CFR 50.25.

Bioresearch monitoring (BIMO) inspections were issued for 5 clinical study sites that participated in the conduct of studies MET41, MET42, and MET61. The inspections did not reveal substantive issues that impact the data submitted in this application.

3.3 Financial Disclosures

Table 1. Covered Clinical Studies: MET41, MET42, MET61, and MET39

Was a list of clinical investigators provided? Yes
Total number of investigators and sub-investigators identified: 293
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Significant payments of other sorts: N/A Is an attachment provided with details of the disclosable financial interests/arrangements? N/A Is a description of the steps taken to minimize potential bias provided? N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 The sponsor certified that 293 investigators had absence of financial interests and/or arrangements. However, for 12 investigators (2 from MET42 and 10 from MET61), the Applicant reported being unable to obtain complete financial disclosure information and so the financial disclosure is missing or incomplete.

4. SIGNIFICANT EFFECTIVENESS/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The Chemistry, Manufacturing and Controls review of this submission focused on the suitability of serological assays used for the evaluation of immune responses in the clinical studies (see Section 4.2).

4.2 Assay Validation

The immunogenicity-based potency tests for the final drug product, clinical serologic assays, and assays evaluating immune non-interference with concomitant vaccines were adequate to support effectiveness evaluations as determined by CBER Product and Assay reviewers.

4.3 Nonclinical Pharmacology/Toxicology

The CBER Toxicology reviewer considered the nonclinical toxicology data to be adequate to support licensure.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

IMD is caused by the bacterium *N. meningitidis*, a gram-negative diplococcus found exclusively in humans. The presence of bactericidal anti-capsular meningococcal antibodies in serum has been associated with protection from IMD. MenQuadfi induces the production of bactericidal antibodies specific to the capsular polysaccharides of *N. meningitidis* serogroups A, C, W, and Y.

4.5 Statistical

The CBER Statistical reviewer concluded that the datasets and the analyses provided in this application were adequate to assess the safety and effectiveness of MenQuadfi for use in infants 6 weeks through 23 months of age.

4.6 Pharmacovigilance

The CBER pharmacovigilance reviewer concluded that the reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety PMR study. Routine surveillance has not identified other adverse events that should be added to the postmarketing section of the label at this time. Due to the imbalance seen in febrile seizures for MenQuadfi recipients compared with comparator vaccine recipients when considering the full time period of the studies, the Applicant has agreed to conduct enhanced surveillance for febrile seizures. See Section 11.6 and the Pharmacovigilance review memorandum for additional details.

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

5.1 Review Strategy

This BLA included clinical data from 3 main Phase 3 studies (MET42, MET61, and MET41) to support immunogenicity (inferred clinical effectiveness) and safety of MenQuadfi for use:

- As a 4-dose series when administered concomitantly with recommended pediatric vaccines at 2, 4, 6, and 12-18 months of age (MET42, MET 41)
- As a 2-dose series when administered concomitantly with recommended pediatric

vaccines between 6 to <24 months of age (MET 61)

The submission also included the clinical study report from a supportive Phase 2 study (MET39) which described the safety and immunogenicity of MenQuadfi administered at 5 different schedules concomitantly with recommended pediatric vaccines. This study will not be discussed in detail in this review memorandum since the study does not contribute substantially to the overall safety and effectiveness conclusions and no datasets from the study were submitted to the sBLA.

The clinical, labeling, and financial disclosure information sections of the application were reviewed with detailed analyses of the main trials' study reports, pertinent line listings, case report forms, and datasets. ACIP vaccine recommendations for the prevention of meningococcal disease and current meningococcal U.S. surveillance data were also reviewed.

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

The following STN#125701/262 Amendments (Ams), listed by Module, were reviewed:

- Modules 1, 2, and 5: Am 0
- Modules 1 and 5: Ams 13, 14, 15, 16, 17, 18, 24, 25, 26, 28, 29, 34, 36, and 37
- Module 1: Ams 1, 2, 5, 7, 8, 9, 10, 11, 12, 19, 20, 21, 22, 23, 27, 30, 31, 32, 33, 38, 39, 40, 41, 42, and 43

5.3 Overview of Clinical Trials

Table 2. Clinical Trials Submitted in Support of Effectiveness and Safety of MenQuadfi

Study Number	Region	Description	Population	Study Groups: # Enrolled
Trial #1 MET42	U.S.	Phase 3, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate safety and immunogenicity of a 4-dose series of MenQuadfi administered with concomitant vaccines	Healthy infants 42 through 89 days of age at enrollment	MenQuadfi: 1746 Menveo: 881
Trial #2 MET61	U.S., including Puerto Rico	Phase 3, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate the safety and immunogenicity of a 2-dose series of MenQuadfi administered with concomitant vaccines	Healthy infants 6-7 months or 17-19 months of age at enrollment	MenQuadfi: 476 Menveo: 370 Menactra: 104
Trial #3 MET41	U.S., including Puerto Rico	Phase 3, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate the safety of a 4-dose series of MenQuadfi administered with concomitant vaccines	Healthy infants 6 weeks through 2 months of age at enrollment	MenQuadfi: 2099 Menveo: 698
Trial #4 MET39	U.S.	Phase 2 randomized, open-label, multi-center study to evaluate the safety and immunogenicity of MenQuadfi when administered with concomitant vaccines	Healthy infants 42 through 89 days of	MenQuadfi: 472 Comparator (U.S.-licensed pediatric vaccines): 108

Study Number	Region	Description	Population	Study Groups: # Enrolled
			age at enrollment	

Source: FDA-generated table

5.5 Literature Reviewed

American Academy of Pediatrics, Committee on Infectious Diseases (2024). Kawasaki Disease. In D.W. Kimberlin, R. Banerjee, E.D. Barnett, R. Lynfiend & M.H. Sawyer (Eds.), Red Book: 2024–2027 Report of the Committee on Infectious Diseases. https://publications.aap.org/redbook/book/755/chapter/14078740/Kawasaki-Disease?autologincheck=redirected

Cendes, F., & Sankar, R. (2011). Vaccinations and febrile seizures. *Epilepsia*, *52 Suppl 3*, 23–25. https://doi.org/10.1111/j.1528-1167.2011.03032.x

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

Centers for Disease Control and Prevention (2024b). Meningococcal Vaccine Safety https://www.cdc.gov/vaccine-safety/vaccines/meningococcal.html

Centers for Disease Control and Prevention (2024c). Meningococcal Disease CDC Yellow Book 2024. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/meningococcal-disease

Centers for Disease Control and Prevention (2024d). Febrile Seizures and Vaccines. https://www.cdc.gov/vaccine-safety/about/febrile-seizures.html

Cohn, A. C., MacNeil, J. R., Harrison, L. H., Lynfield, R., Reingold, A., Schaffner, W., Zell, E. R., Plikaytis, B., Wang, X., Messonnier, N. E., & Active Bacterial Core Surveillance (ABCs) Team and MeningNet Surveillance Partners (2017). Effectiveness and Duration of Protection of One Dose of a Meningococcal Conjugate Vaccine. *Pediatrics*, 139(2), e20162193. https://doi.org/10.1542/peds.2016-2193

Corwin, M.J. (2020). Acute events in infancy including brief resolved unexplained event (BRUE). UpToDate https://www.uptodate.com/contents/acute-events-in-infancy-including-brief-resolved-unexplained-event-brue?search=BRUE&source=search_result&selectedTitle=1~28&usage_type=default&display_rank=1#H3547546552 Accessed May 21, 2025.

Deng L., Gidding H., Macartney K., Crawford N., Buttery J., Gold M., Richmond P., Wood N. (2019) Postvaccination Febrile Seizure Severity and Outcome. *Pediatrics.* https://doi.org/10.1542/peds.2018-2120

Hauser, W.A. (1994). The prevalence and incidence of convulsive disorders in children. *Epilepsia*. 1994 Apr;35:S1-6.

Mbaeyi, S.A., Bozio CH, Duffy J, et al. (2020). Meningococcal vaccination: recommendations of the advisory committee on immunization practices, United States, 2020. *MMWR. Recommendations and Reports*, *69*. http://dx.doi.org/10.15585/mmwr.rr6909a1

Millichap J. J. (2025) Clinical features and evaluation of febrile seizures. https://www.uptodate.com/contents/clinical-features-and-evaluation-of-febrile-seizures?search=febrile%20seizures&source=search_result&selectedTitle=1~78&usage_type=default&display_rank=1#H750682289

Sáfadi, M. A. P., Valenzuela, M. T., Carvalho, A. F., De Oliveira, L. H., Salisbury, D. M., & Andrus, J. K. (2017). Knowing the scope of meningococcal disease in Latin America. Revista panamericana de salud publica = Pan American journal of public health, 41, e118. https://doi.org/10.26633/RPSP.2017.118

Subcommittee on Febrile Seizures (2011). Febrile seizures: guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics, 127(2); 389-394.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: MET42

NCT03537508: "Immunogenicity and Safety of a Quadrivalent Meningococcal Conjugate Vaccine When Administered Concomitantly With Routine Pediatric Vaccines in Healthy Infants and Toddlers in the US"

Study Overview: MET42 was the main Phase 3 study designed to evaluate the safety and immunogenicity of a 4-dose series of MenQuadfi (given at 2, 4, 6, and 12-18 months of age) in healthy infants and toddlers in comparison to a licensed meningococcal serogroup A,C,Y,W vaccine (Menveo) when both were administered concomitantly with recommended pediatric vaccines. The study enrolled and randomized 2,627 participants and was conducted at 69 centers in the U.S. The study was conducted from April 25, 2018, to September 22, 2023, with a data lock date of March 8, 2024.

6.1.1 Objectives

Primary Objectives/Endpoints

1. To demonstrate the noninferiority (NI) of the serum bactericidal activity using human complement (hSBA) vaccine seroresponse[3] to meningococcal serogroups A, C, Y, and W following the administration of a 4-dose series of MenQuadfi compared with a 4-dose series of Menveo when given concomitantly with recommended pediatric vaccines to infants and toddlers 6 weeks old through 15 months old.

    - **Endpoints**: Meningococcal serogroups A, C, Y, and W hSBA antibody titers before 1st study vaccination on Day 0 and 30 days after the 4th meningococcal vaccination (MenQuadfi versus Menveo).
    - **Hypothesis 1 (H1)**: MenQuadfi was noninferior to Menveo for each of the four serogroups A, C, Y, and W.
    - **Success criterion**: Noninferiority is demonstrated if the lower limit (LL) of the 2-sided 95% confidence interval (CI) of the difference between the percentage of participants achieving seroresponse is > -10% for each serogroup.

2. To demonstrate the noninferiority of the hSBA antibody response to meningococcal serogroups A, C, Y, and W following the administration of 3 doses in infancy of MenQuadfi compared with 3 doses in infancy of Menveo when given concomitantly with recommended pediatric vaccines to infants at 2, 4, and 6 months of age.

    - **Endpoints:** hSBA antibody titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W 30 days after vaccination at 6 months of age (MenQuadfi versus Menveo).
    - **Hypothesis 2 (H2):** MenQuadfi was noninferior to Menveo for each of the four serogroups A, C, Y, and W.
    - **Success criterion:** Noninferiority is demonstrated if the LL of the 2-sided 95% CI of the

3 hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as: if prevaccination (pre-1st dose) hSBA titer < 1:8, then post-4th dose (D30 after 12-month) vaccinations titer must be ≥ 1:16; and if prevaccination hSBA titer ≥ 1:8, then post 4th dose vaccination titer ≥ 4-fold greater than the prevaccination titer.

difference between the percentages of participants achieving hSBA titers ≥ 1:8 is > -10% for each serogroup.

Reviewer Comment:

1. Early clinical trial data evaluating different formulations and schedules of MenQuadfi in infants and toddlers supported late phase clinical trials of the final MenQuadfi formulation when administered as a 4-dose series with recommended pediatric vaccines. The assessment of noninferior serum bactericidal antibody seroresponse from pre-1st dose to one month after the 4th dose at 12-15 months of age as primary objective #1 was considered appropriate to demonstrate the benefit of MenQuadfi in an infant/toddler population following the completion of a 4-dose series administered at 2, 4, 6, and 12-15 months of age.
2. Because the highest incidence of meningococcal disease is during the first year (birth through 12 months) of life, CBER also requested that the Applicant include primary objective #2 to demonstrate noninferior serum bactericidal antibody responses one month after completion of 3 doses at 6 months of age to ensure adequate protection during the first year of life prior to the 4th dose at 12 months of age.
3. During review of the MET42 protocol, CBER communicated to the Applicant concerns associated with the protocol-specified seroresponse definition that was based on baseline pre-Dose 1 hSBA titers (at approximately 2 months of age). CBER commented that the use of pre-Dose 1 antibody titers may obscure the effect of the 4-dose schedule on protection afforded by the vaccine during the first two years of life due to the potential presence of maternal antibodies at 2 months of age. CBER had recommended the Applicant evaluate the response to the 4th dose by measuring the 4-fold response using data from samples drawn just prior to the 4th dose compared with those drawn post-4th dose. Analyses of the percentage of participants with 4-fold rise in hSBA titers from pre-4th dose to post-4th dose for each serogroup was included as a descriptive secondary endpoint (Table 11). In addition, potential differences across participants (at 2 months of age) in baseline pre-Dose 1 hSBA titers were accounted for with the composite seroresponse definition. For participants with baseline hSBA titers <1:8, seroresponse was defined as a post-4th dose hSBA titer ≥1:16; and for participants with baseline hSBA titers ≥1:8, then seroresponse was defined as ≥ 4-fold rise in hSBA titers (compared to baseline). Subgroup descriptive analyses of the primary endpoints evaluating seroresponse rates based on baseline serostatus are reviewed in Section 6.1.11.1.

Secondary Objectives/Endpoints

Concomitant Pediatric Vaccine Endpoints

1. To demonstrate the noninferiority of immune responses of recommended pediatric vaccines administered concomitantly with MenQuadfi as compared with Menveo in infants and toddlers 6 weeks old to 18 months old.

Timepoints for sera collection to support secondary analyses are listed in Timing of Serologic Sample Collection by Study Group. Each endpoint and success criterion are listed by vaccine pathogen/antigenic component.

- Hepatitis B:
  - Endpoint: IgG antibodies against hepatitis B surface antigen (anti-HB) concentrations ≥ 10 milli-international units (mIU) / mL
    - ***Success criterion***: LL of the 2-sided 95% CI of the difference between percentage of participants who achieve ≥ 10 mIU/mL in anti-HB surface antibody concentrations (MenQuadfi – Menveo) is > -10%.
- *H. influenzae b*
  - Endpoint: Anti-polyribosyl-ribitol phosphate (PRP) antibody concentrations ≥ 0.15 micrograms/milliliter (µg / mL)
    - ***Success criterion*:** LL of the 2-sided 95% CI of the difference between the percentage of participants who achieve ≥ 0.15 µg / mL in anti-PRP antibody concentrations (MenQuadfi – Menveo) is > -5%.
  - Endpoint: Anti-PRP antibody concentrations ≥ 1.0 µg/mL
    - ***Success Criterion*:** LL of the 2-sided 95% CI of the difference between the percentage of participants who achieve ≥ 1.0 µg/mL in anti-PRP antibody concentrations (MenQuadfi – Menveo) is > -10%
- Poliovirus
  - Endpoint: Anti-poliovirus types (1, 2, and 3) antibody titers ≥ 1:8
    - ***Success Criterion***: LL of the 2-sided 95% CI of the difference between the percentage of participants who achieve ≥ 1:8 anti-poliovirus antibody titers (MenQuadfi – Menveo) is > - 5% for each type.
- Rotavirus
  - Endpoint: Anti-rotavirus serum IgA antibody concentrations with ≥ 3-fold rise over baseline
    - **Success Criterion:** LL of the 2-sided 95% CI of the difference between the percentage of participants who achieve ≥ 3-fold rise in serum IgA antibody concentrations against rotavirus antigens (serotypes G1, G2, G3, G4, and P1A[8]) over baseline (MenQuadfi – Menveo) is > -10%.
  - Endpoint: Anti-rotavirus serum IgA antibody geometric mean concentrations (GMCs)
    - **Success Criterion**: LL of the 2-sided 95% CI of the ratio of the GMCs of the serum IgA antibodies against the rotavirus antigens (serotypes G1, G2, G3, G4, and P1A[8]) (MenQuadfi/Menveo) is > 2/3.
- Pertussis
  - Endpoint: Anti-pertussis antibody concentrations (PT, FHA, PRN, and FIM) (GMCs)
    - **Success Criterion (post-vaccination at 6 months)**: LL of the 2-sided 95% CI of the ratio of the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) (MenQuadfi/Menveo) is > 2/3.
    - **Success Criterion (post-vaccination at 15 months)**: LL of the 2-sided 95% CI of the difference between the percentages of participants with a pertussis vaccine response[4] for the pertussis antigens (PT, FHA, PRN, and FIM) (MenQuadfi – Menveo) is > -10% for each antigen.

4 Pertussis vaccine response was defined as:
- Pre-4th dose vaccination concentration < lower limit of quantitation (LLOQ), then post-4th dose vaccination concentration should be ≥ 4x the LLOQ

- Pneumococcal
    - Endpoint: Anti-pneumococcal antibody concentrations (for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) (GMCs)
    - **Success Criterion**: LL of the 2-sided 95% CI of the ratio of the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) from the 2 groups (MenQuadfi/Menveo) is > 1/2 for each serotype.
- Measles
    - Endpoint: Anti-measles antibody concentrations ≥ 255 mIU/mL
    - **Success Criterion:** LL of the 2-sided 95% CI of the difference in the percentages of participants who achieved ≥ 255 mIU/mL in anti-measles antibody concentrations (MenQuadfi/Menveo) is > -10%.
- Mumps
    - Endpoint: Anti-mumps antibody concentrations ≥ 10 mumps antibody (Ab) units/mL
    - **Success Criterion**: LL of the 2-sided 95% CI of the difference between the percentages of participants who achieved ≥ 10 mumps Ab units/mL in anti-mumps antibody concentrations (MenQuadfi – Menveo) is > -10%.
- Rubella:
    - Endpoint: Anti-rubella antibody concentrations ≥ 10 IU/mL
    - **Success criterion:** LL of the 2-sided 95% CI of the difference the percentages who achieved ≥ 10 IU/mL in anti-rubella antibody concentrations (MenQuadfi – Menveo) is > -10%
- Varicella:
    - Endpoint: Anti-varicella antibody concentrations ≥ 5 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL
    - **Success criterion:** LL of the 2-sided 95% CI of the difference between the percentage of participants who achieved ≥ 5 gpELISA units/mL in anti-varicella antibody concentrations (MenQuadfi – Menveo) is > -10%

Secondary Objectives 2-6 (Descriptive Analyses Without Hypothesis Testing)

Concomitant Pediatric Vaccine Endpoints and Additional Meningococcal Endpoints

2. To assess the antibody responses against meningococcal serogroups A, C, Y, and W after the administration of the 4th dose of MenQuadfi or Menveo when given concomitantly with recommended pediatric vaccines at 12 months of age
    - Endpoints: hSBA meningococcal serogroups A, C, Y and W antibody titers (≥ 4-fold rise) before and 30 days after the 4th dose at 12 months of age
3. To assess the persistence of bactericidal antibodies at 12 months of age in participants who received 3 doses of MenQuadfi or Menveo in infancy concomitantly with recommended pediatric vaccines at 2, 4, and 6 months of age
    - Endpoint: hSBA meningococcal serogroups A, C, Y, and W antibody titers (≥ 1:4, ≥ 1:8) 30 days after the 6-month and before the 12-month vaccination

- Pre-4th dose vaccination concentration ≥ LLOQ but < 4x the LLOQ, then post-4th dose vaccination concentration had to achieve a 4-fold rise (post-4th vaccination / pre-4th vaccination ≥ 4)
- Pre-4th dose vaccination concentration ≥ 4x the LLOQ, then post-4th dose vaccination concentration had to achieve a 2-fold response (post-4th vaccination / pre-4th vaccination ≥ 2)

4. To describe the antibody responses against the antigens of the recommended pediatric vaccines (Pentacel, Prevnar 13, M-M-R II, Varivax, RotaTeq, and Engerix-B) when administered concomitantly with either MenQuadfi or Menveo.
   - Endpoints:
     - Anti-PRP antibody concentrations (≥ 0.15 µg/mL)
     - Anti-diphtheria antibody concentrations (≥ 0.01 IU/mL, ≥ 0.1 IU/mL)
     - Anti-tetanus antibody concentrations (≥ 0.01 IU/mL, ≥ 0.1 IU/mL)
     - Anti-HBs antibody concentrations (≥ 100 IU/mL)
     - Anti-polio (types 1, 2, and 3) antibody titers (≥1:8)
     - Anti-rotavirus serum IgA antibody concentrations (≥4-fold rise over baseline)
     - Anti-pertussis (PT, FHA, PRN, and FIM) antibody concentrations
     - Anti-pneumococcal antibody concentrations (≥0.35 µg/mL, ≥1 µg/mL)
     - Anti-measles antibody concentrations
     - Anti-mumps antibody concentrations
     - Anti-rubella antibody concentrations
     - Anti-varicella antibody concentrations
5. To describe the antibody responses against meningococcal serogroups A, C, Y, and W when MenQuadfi versus Menveo is administered concomitantly with recommended pediatric vaccines before first vaccination, 30 days after the 3rd dose at 6-month, before and 30 days after the 4th dose at 12 months or 15 months
   - Endpoints:
     - hSBA meningococcal serogroups A, C, Y, and W antibody titers (≥ 1:4, ≥ 1:8, 4-fold rise from pre- to post-4th dose and pre- to post-3rd dose])
     - Titer distribution and reverse cumulative distribution curves (RCDCs)
     - hSBA vaccine seroresponse
6. To describe the antibody responses against meningococcal serogroups A, C, Y, and W when MenQuadfi is administered to children 12-15 months of age versus 15-18 months of age, concomitantly with recommended pediatric vaccines, including the bactericidal antibodies persistence (post-3rd dose and pre-4th dose) and the effect of 4th dose of MenQuadfi
   - Endpoints:
     - hSBA meningococcal serogroups A, C, Y, and W antibody titers (≥ 1:4, ≥ 1:8, 4-fold rise from pre-1st dose to post-4th dose, 4-fold rise from pre-4th dose to post-4th dose)
     - hSBA meningococcal serogroups A, C, Y and W antibody titers ratio
     - hSBA vaccine seroresponse
     - hSBA vaccine seroresponse difference

Observational Objectives:

<u>Safety</u>

1. To describe the safety profile of MenQuadfi and Menveo when administered concomitantly with recommended pediatric vaccines in healthy infants and toddlers.

- Endpoints:
  - Any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
  - Solicited injection (local) site reactions occurring up to Day 7 after each vaccination
  - Solicited systemic reactions occurring up to Day 7 after each vaccination
  - Unsolicited AEs up to Day 30 after each vaccination

- SAEs (including AESIs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination
- Medically attended adverse events (MAAEs) throughout the trial, from Visit 1 to the 6-month follow-up contact after the last vaccination

6.1.2 Design Overview

Study MET42 was a Phase 3, double-blind, randomized, parallel-group, active-controlled, multi-center study in the U.S. in healthy infants 42 days through 89 days of age at enrollment.
A total of 2,628 infants were enrolled and randomized 2:1 to receive a 4-dose series of either MenQuadfi (Group 1) or Menveo (Group 2), along with recommended pediatric vaccines based on the ACIP recommended schedule. Each group was further randomized 2:1 in 2 subgroups based on the schedule of the second year of life analyses (either 30 days after the 12-month vaccination [Subgroups 1a and 2a] or 30 days after the 15-month vaccination [Subgroups 1b and 2b]). Participants were followed for safety through 6 months after the last study vaccination.

The study groups are as follows, and the vaccines administered for each group at each timepoint are detailed in Table 3.

- Group 1 (MenQuadfi):
  - Subgroup 1a: MenQuadfi and recommended pediatric vaccines at 2, 4, 6, and 12-15 months of age
  - Subgroup 1b: MenQuadfi at 2, 4, 6, and 15-18 months of age and recommended pediatric vaccines at 2, 4, 6, 12-15, and 15-18 months of age
- Group 2 (Menveo):
  - Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended pediatric vaccines at 2, 4, 6, 12, and 15-18 months of age
  - Subgroup 2b: Menveo at 2, 4, 6, and 12 months of age and recommended pediatric vaccines at 2, 4, 6, 12, and 15-18 months of age

Table 3. Schedule of Vaccination and Blood Sampling, Study MET42

Group Subgroup	2 MOA Visit 1 Blood Draw‡	2 MOA Visit 1 Vaccines	4 MOA Visit 2 Vaccines	6 MOA Visit 3 Vaccines	7 MOA Visit 4 Blood Draw	12 MOA Visit 5* Blood Draw‡	12 MOA Visit 5* Vaccines	13 MOA Visit 6: 1a† and 2a Blood Draw	15 MOA Visit 6: 1b and 2b Visit 7: 2a Blood Draw‡	15 MOA Visit 6: 1b and 2b Visit 7: 2a Vaccines	16 MOA Visit 7: 1b and 2b Visit 8: 2a Blood Draw
1	X	MenQuadfi Pentacel PCV13 rotavirus hepatitis B§	MenQuadfi Pentacel PCV13 rotavirus	MenQuadfi Pentacel PCV13 rotavirus hepatitis B	X	-	-	-	-	-	-
1a	-	-	-	-	-	X	MenQuadfi MMR varicella PCV13	X	No study visit DTaP-IPV/Hib**	No study visit DTaP-IPV/Hib**	-
1b	-	-	-	-	-	-	MMR varicella PCV13	No study visit	X	MenQuadfi DTaP-IPV/Hib hepatitis A	X
2	X	MENVEO DTaP-IPV/Hib PCV13 rotavirus hepatitis B§	MENVEO DTaP-IPV/Hib PCV13 rotavirus	MENVEO DTaP-IPV/Hib PCV13 rotavirus hepatitis B	X	-	-	-	-	-	-
2a	-	-	-	-	-	X	MENVEO MMR varicella PCV13	X	-	DTaP-IPV/Hib hepatitis A	-
2b	-	-	-	-	-	-	MENVEO MMR varicella PCV13	No study visit	X	DTaP-IPV/Hib hepatitis A	X

Source: Adapted from Applicant Protocol, Study MET42
Abbreviations: MOA=months of age; MMR=measles, mumps, and rubella vaccine
X=blood draw performed
*Visit 5 occurred at 12 months of age for Subgroups 2a and 2b, and at 12-15 months of age for Subgroups 1a and 1b.
† Last study visit for Subgroup 1a. Recommended vaccines could be administered as per standard of care after study procedures were completed. Visit 6 occurred at 13-16 months of age for Subgroup 1a. For Subgroup 2a Visit 6 occurred at 13 months of age.
‡ Blood was drawn prior to vaccinations.
§ The first dose of HB vaccine must have been received at least 28 days prior to the first study vaccination at Visit 1.
**Participants in Subgroup 1a completed the last study visit at 13-16 months of age. DTaP-IPV/Hib was provided by the Applicant to complete the DTaP series with vaccine from the same manufacturer and was administered as per standard of care. The study personnel / investigator were responsible for administering this dose at the recommended age outside of the scope of the study.

6.1.3 Population

Key Inclusion Criteria

- Age at enrollment: 42 through 89 days of age on the day of the first study visit
- Healthy as determined by the investigator's medical history, physical examination, and judgment
- Received the first dose of hepatitis B vaccine at least 28 days before the first study visit

Key Exclusion Criteria

- Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination (except for influenza vaccination, which may be received at a gap of at least 2 weeks before or 2 weeks after any study vaccination)
- Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine
- Previous vaccination against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella; and of *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and/or rotavirus infection or disease
- Receipt of more than 1 previous dose of hepatitis B vaccine
- Receipt of immune globulins, blood, or blood-derived products since birth
- Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks) since birth
- Family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient was demonstrated
- History of any *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically
- History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella; and of *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and/or rotavirus infection or disease
- At high risk for meningococcal infection during the trial (specifically, but not limited to, participants with persistent complement deficiency, with anatomic or functional asplenia, or participants travelling to countries with high endemic or epidemic disease)
- History of intussusception
- History of any neurologic disorders, including any seizures and progressive neurologic disorders
- Receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw
- Chronic illness (including, but not limited to, cardiac disorders, congenital heart disease, chronic lung disease, renal disorders, auto-immune disorders, diabetes, psychomotor diseases, and known congenital or genetic diseases) that in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion

6.1.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc.)

- Dose and route of administration: 0.5mL intramuscular (IM)
- Schedule of administration: 2, 4, 6, and 12-15 months of age (Subgroup 1a) or 15-18 months of age (Subgroup 1b)

- Composition: 10 µg each of meningococcal capsular polysaccharides serogroups A, C, Y, W, and 55 µg tetanus toxoid protein carrier
- Presentation: Solution for injection
- Lot #: UD19643, UD20030, UD20578, UD20579, UD21928, UD22379, UD22548, and U7249AA

Menveo: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GSK Vaccines)

- Dose and route of administration: 0.5 mL IM
- Schedule of administration: 2, 4, 6, and 12 months of age.
- Composition: 10 µg MenA oligosaccharide, 5 µg MenC oligosaccharide, 5 µg MenY oligosaccharide, 5 µg MenW-135 oligosaccharide, 32.7 to 64.1 µg CRM197 protein, ≤0.30 µg residual formaldehyde
- Presentation: Lyophilized powder and liquid components combined to produce a solution
- Lot #: M17030, M17035, AMVA052A, AMVA196A, AMVA321A, AMVA397A, AMVA548A, AMVA655A, and AMVA748A

Pentacel: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur Ltd.)

- Dose and route of administration: 0.5 mL IM
- Schedule of administration: 2, 4, 6, and 15-18 months of age5
- Composition: diphtheria toxoid, tetanus toxoid, acellular pertussis antigens (pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)), inactivated polioviruses [Type 1 (Mahoney), Type 2 (MEF-1), Type 3 (Saukett)], H. influenzae type b (PRP), and Tetanus toxoid (PRP-T).
- Presentation: liquid DTaP-IPV used to reconstitute lyophilized ActHIB
- Lot #: C5461AA, C5515AA, UJ065AAA, UJ601AAA, UJ672AAA, UJ390AAA

Prevnar 13: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals, Inc.)

- Dose and route of administration: 0.5 mL IM
- Schedule of administration: 2, 4, 6, and 12-15 months of age
- Composition: Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, 6B saccharides, CRM197 carrier protein, Polysorbate 80, Succinate buffer, Aluminum as aluminum phosphate adjuvant
- Presentation: single-dose prefilled syringe
- Lot #: AP4719, CM2357, DE8785, DR7167, EY2562, T88778, X16197

RotaTeq: Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp.)

- Dose and route of administration: 2mL oral
- Schedule of administration: 2, 4, and 6 months of age
- Composition: 5 live reassortant rotaviruses: G1 serotype, G2 serotype, G3 serotype, G4 serotype, P1A(8).
- Presentation: oral solution
- Lot #: 1660685, 1660998, 1661000, 1687009, 1741375, 1742420, N021101, N030364,

5 Participants in Subgroup 1a completed the last study visit at 13 through 16 months of age. For participants in Subgroup 1a, the 4th dose of Pentacel, which is administered at 15-18 months of age, was provided by the Applicant for completion of the series and was administered by the investigator outside of the study.

R002805, R016790, S005874, S005878, S013890, S025595, T026932, T034512,

Engerix-B: Hepatitis B Vaccine [Recombinant] (GlaxoSmithKline Biologicals)
- Dose and route of administration: 0.5 mL IM
- Schedule of administration: 2 and 6 months of age
- Composition: 10 µg of hepatitis B virus surface antigen (HBsAg) adsorbed on 0.25 mg aluminum as aluminum hydroxide.
- Presentation: suspension for injection
- Lot #: 34PK5, 3AM2M, 52X7T, 97Y27, K329E, LL5A5, LM992, LX4XP, P7294

M-M-R II: Measles, Mumps, and Rubella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Dose and route of administration: 0.5 mL subcutaneous (SC)
- Schedule of administration: 12-15 months of age
- Composition: Measles virus (derived from Ender's Edmonston strain) propagated in chick embryo cell culture, Mumps virus (Jeryl Lynn™ [B level] strain) propagated in chick embryo cell culture, Rubella virus (Wistar RA 27/3 strain) propagated in WI-38 human diploid lung fibroblasts
- Presentation: suspension for injection
- Lot #: R009955/R022423, R022423/R009955, R022423/S000978, R035701/S008566, R035701/R009955, S012944/S013898, S037497/T005074, T005074/T013724, T013724/U005973, T013724/T022571, T013724//U005973, T013724/T005074, T013724/T022570, U006485/T022571, U006485/T022571, U19291/U004712

Varivax: Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Dose and route of administration: 0.5 mL SC
- Schedule of administration: 12-15 months of age
- Composition: Live, attenuated Oka/Merck varicella virus
- Presentation: suspension for injection
- Lot #: N028746/R023504, R009955/R023504, R023504/N028746, R023504/R009955, R024144/S000978, S005084/S014277, S005084/S015238, S015238/S020159, S020159/S015238, S020159/S021106, S020159/S021196, S020159/R009955, S020159/S014277, S020159/S032591, S020159/T005074, T005074/T010298, T010298/T005074, T032315/U000171, T032315/T020663, T040507/U000171, T040507/U004712, U028164/U004712

Havrix: Hepatitis A vaccine (GlaxoSmithKline Biologicals) (Subgroups 1b, 2a, and 2b only):
- Dose and route of administration: 0.5 mL IM
- Schedule of administration: 15-18 months of age
- Composition: 720 enzyme-linked immunosorbent assay (ELISA) Units (EL.U.) of viral antigen, adsorbed onto 0.25 mg of aluminum as aluminum hydroxide
- Presentation: suspension for injection
- Lot #: 95EJ7, 9PL5M, B23EA, F7X23

6.1.5 Directions for Use

See section 6.1.4

6.1.6 Sites and Centers

The study enrolled and randomized 2,627 participants and was conducted at 69 centers in the United States.

6.1.7 Surveillance/Monitoring

Safety Monitoring

- Clinical Assessments: physical exam before first dose (Day 0) and at Visit 5 (12-15 months of age)
- AE Monitoring:
    - Immediate adverse events (AEs): 30 minutes postvaccination period
    - Solicited adverse reactions (ARs): recorded on diary card from Day 0 through Day 7 after each vaccination
    - Local [6]: injection site tenderness, erythema, swelling
    - Systemic[7]: fever (temperature recorded daily in diary card), vomiting, crying abnormal, drowsiness, appetite lost, irritability
    - Unsolicited AEs[8]: recorded on diary card from Day 0 through Day 30 after each vaccination
    - Medically attended adverse events (MAAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs): collected from the time of vaccination through 6 months after the last vaccination
    - Collected in diary card from time of each vaccination through the next study visit
    - Collected in a memory aid from 30 days post-last vaccination through the 6 months follow-up
    - Protocol-specified AESIs include generalized seizures (non-febrile and febrile), Kawasaki disease, Guillain- Barré syndrome, idiopathic thrombocytopenia purpura

Diary Card: Safety Data Collection

The participant's parent or guardian recorded all daily safety information including solicited adverse reactions and unsolicited AEs using paper diary cards. The diary cards included prelisted terms, intensity scales, and areas for free text to capture additional safety information. Parents/guardians were also provided with rulers to measure injection site reactions and digital thermometers to measure daily temperatures. At specified intervals, the investigator systematically reviewed each entry in the diary card with the parent/guardian, asked clarifying questions about any unclear, missing, or inconsistent information, documented clarifications on the designated "Investigator Comment page" of the diary card, and ensured that any necessary

6 Grading scale for solicited local adverse reactions:

- For tenderness Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced.
- For erythema Grade 1: > 0 to < 25 mm; Grade 2: ≥ 25 to < 50 mm; Grade 3: ≥ 50 mm
- For swelling Grade 1: > 0 to < 25 mm; Grade 2: ≥ 25 to < 50 mm; Grade 3: ≥ 50 mm

7 Grading scale for solicited systemic adverse reactions: .

- For fever, Grade 1: ≥ 38.0°C to ≤ 38.5°C or ≥ 100.4°F to ≤ 101.3°F; Grade 2: > 38.5°C to ≤ 39.5°C or > 101.3°F to ≤ 103.1°F; Grade 3: > 39.5°C or > 103.1°F
- For vomiting, Grade 1: 1 episode per 24 hours; Grade 2: 2– 5 episodes per 24 hours; Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration
- For crying abnormal, Grade 1: < 1 hour; Grade 2: 1 - 3 hours; Grade 3: > 3 hours
- For drowsiness, Grade 1: Sleepier than usual or less interested in surroundings; Grade 2: Not interested in surroundings or did not wake up for a feed / meal; Grade 3: Sleeping most of the time or difficult to wake up
- For appetite lost, Grade 1: Eating less than normal; Grade 2: Missed 1 or 2 feeds / meals completely; Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals
- For irritability, Grade 1: Easily consolable; Grade 2: Requiring increased attention; Grade 3: Inconsolable

8 Grading scale for unsolicited AEs:

- Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

corrections were made by the parent/guardian themselves, as site staff were not permitted to modify diary entries directly. For vaccinations administered at 2 and 4 months of age, investigators collected and reviewed diary cards at the scheduled 4 and 6-month visit, respectively, when the participant returned for the next vaccination. For vaccination administered at 6 and 12-15 or 15-18 months of age, investigators collected and reviewed diary cards at the scheduled visit 30 days post-vaccination. Review and data entry into the web-based electronic case report form (CRF) occurred within 3-5 business days after the subsequent vaccination visit. A memory aid was given to the participant's parents/guardians after the last vaccination to assist in recording events that occur between 30 days post-last vaccination and the 6-month follow-up. The 6- month follow-up was conducted by interviewing the participant's parents/guardians over the telephone using a questionnaire to capture MAAEs, SAEs and AESIs, and the information was transcribed into the CRF.

Reviewer Comment: The Applicant's procedure for collection of participants safety data from source documents (Diary Cards) was employed at all study sites by blinded study staff. As described above, approximately 1-2 months after any vaccination dose, staff would review reported safety information with the parent/guardian by asking clarifying questions. Subsequently parents/guardian would make corrections to the Diary Cards and staff would enter the corrected safety data into the electronic CRF (eCRF).

Although the time elapsed (~1 to 2 months) between the postvaccination reporting period and the study staff review of diary card information may be associated with recall bias, the Applicant indicates that nature/scope of changes made by parent/guardian were limited to unclear, missing, or inconsistent information. Furthermore, because study staff and parents/guardians were blinded to the study group assignment, the impact of potential bias is likely balanced across groups. The Applicant's procedures for collecting and reporting safety data in the CRF will be described in United States Package Insert (USPI), Section 6.

The Applicant's Safety Management Team (SMT) reviewed the data generated from all the ongoing studies with MenQuadfi for any new safety signals or safety concerns. There was no pre-specified early safety data review.

Study withdrawal/discontinuation: For participants who prematurely terminated because of an AE, protocol deviation, or loss of eligibility, all scheduled safety follow ups and contacts were to be completed. For those who terminated early due to lost to follow-up or withdrawal of consent and then indicated that they did not want to be contacted again, the site did not attempt to obtain further safety information. For other participants who withdrew voluntarily, the site attempted to make contact during the 6-month follow up period.

Immunogenicity Monitoring:

- Antibodies to meningococcal antigens: Functional meningococcal antibody activity against serogroups A, C, Y, and W was measured in hSBA. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of (b) (4) All assays were performed at (b) (4) or at a qualified contract laboratory for (b) (4)
- Anti-Rotavirus IgA antibodies: Measured by validated (b) (4) using (b) (4) performed at the (b) (4)
- Anti- Diphtheria, Tetanus, and Pertussis Antibodies: Measured by DTP (Diphtheria, Tetanus, and Pertussis) (b) (4), a multiplexed serological assay. The LLOQ for Diphtheria is (b) (4) the LLOQ for Tetanus is (b) (4) and the LLOQ for Pertussis antigens is (b) (4) (b) (4)

(b) (4)

- Anti-Hepatitis B Antibodies: Measured by (b) (4) using (b) (4) detection technology. The LLOQ is (b) (4)
- Anti-Haemophilus influenza type b (Anti-PRP) Antibodies: Measured using (b) (4) (b) (4) LLOQ of the anti-PRP (b) (4) is (b) (4) (b) (4)
- Anti-Polio (types 1, 2, and 3) Antibodies: Measured by (b) (4) assay. The LLOQ of the anti-poliovirus types 1, 2, and 3 assays is (b) (4) Sanofi Pasteur (Swiftwater, PA).
- Anti-Pneumococcal Antibodies: Measured by the pneumococcal capsular PS (PnPS) IgG (b) (4) assay to quantitate the amount of anti- Streptococcus pneumoniae PS (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F) antibodies in human serum. The LLOQ for all PnPS serotypes is (b) (4) (b) (4)
- Anti-Measles Antibodies; Measured by (b) (4) The clinical endpoint for the measles assay is (b) (4) and the LLOQ is (b) (4) (b) (4)
- Anti-Mumps Antibodies; measured by Mumps (b) (4) (b) (4) is to detect IgG antibody to mumps virus. The clinical endpoint and the LLOQ for the mumps assay is (b) (4) (b) (4) (b) (4)
- Anti-Rubella Antibodies; measured by (b) (4) is to detect total IgG antibody to rubella virus. The clinical endpoint for the rubella assay is (b) (4) and the LLOQ is (b) (4) (b) (4)
- Anti-Varicella Antibodies; Measured by the (b) (4) (b) (4) is to detect IgG antibody to varicella-zoster virus (VZV). The clinical endpoint for the varicella assay is (b) (4) and the LLOQ is (b) (4) (b) (4) (b) (4)

Although Hepatitis A vaccine was administered in the study, its immunologic responses were not measured because not all subgroups received the vaccine.

> Reviewer Comment: These assays were reviewed by the CBER clinical assay reviewers and were determined to be validated and adequate to support evaluation of the pre-specified endpoints.

Timing of Serologic Sample Collection by Study Group:

Sera to assess immunogenicity endpoints evaluating MenQuadfi/Menveo or concomitantly administered recommended pediatric vaccines were collected at the following time points for the listed vaccine pathogens/antigenic components:

- All participants:
    - Day 0 and Day 30 post-6-month vaccination (3rd dose): rotavirus serum IgA, pertussis antibody concentrations (PT, FHA, PRN, FIM), meningococcal serogroups (A, C, Y, W) antibody titers
    - Day 30 post-6-month vaccination (3rd dose): hepatitis B antibody concentrations, *H. influenzae* b (PRP), poliovirus antibody titers, pneumococcal GMCs (serotypes 1,3,4,5,6A,6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), diphtheria antibody concentrations, tetanus antibody concentrations

- For Subgroups 1a and 2a participants:
    - Day 0, Pre- and Day 30 post-12-month vaccination (4th dose): meningococcal serogroups (A, C, Y, W) antibody titers
    - Day 30 post-12-month vaccination (4th dose): measles antibody concentrations, mumps antibody concentrations, rubella antibody concentrations, varicella antibody concentrations, pneumococcal GMCs (serotypes 1,3,4,5,6A,6B, 7F, 9V, 14, 18C, 19A, 19F, 23F)
- For Subgroups 1b and 2b participants:
    - Pre- and Day 30 post-15-month vaccination (4th dose): pertussis antibody concentrations (PT, FHA, PRN, FIM), *H. influenzae* b (PRP), meningococcal serogroups (A, C, Y, W) antibody titers
    - Day 30 post-15-month vaccination (4th dose): poliovirus antibody titers, diphtheria antibody concentrations, tetanus antibody concentrations

6.1.8 Endpoints and Criteria for Study Success

Refer to section 6.1.1 and section 6.1.9.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary Hypothesis 1 – Seroresponse Rate After 4th Dose (at 12-15 Months)

For each of the four meningococcal serogroups A, C, Y, and W, the percentage of participants with hSBA seroresponse (if prevaccination titer < 1:8, the post-vaccination titer was ≥ 1:16, and if prevaccination titer ≥ 1:8, the postvaccination titer was at least 4-fold greater) 30 days after the administration of the 4th dose of MenQuadfi at 12-15 months of age (Subgroup 1a) versus 4th dose of Menveo at 12 months of age (Subgroup 2a) were assessed via the following noninferiority hypothesis:

- (H0): p(men, G1a) - p(men, G2a) ≤-10% versus (H1): p(men, G1a) - p(men, G2a) >-10%
- p(men, G1a) and p(men, G2a) are the percentages of participants who achieve hSBA vaccine seroresponse in Subgroup 1a and Subgroup 2a, respectively.
- Each of the serogroups A, C, Y, and W was tested separately. The overall noninferiority of this objective was demonstrated if all 4 individual null hypotheses are rejected.
- MenQuadfi was considered noninferior to Menveo if the LL of the 2-sided 95% CI of the difference between the 2 percentages is >-10% for each serogroup.

Primary Hypothesis 2- hSBA Titer ≥ 1:8 After 3rd Dose at 6 Months

For each of the four meningococcal serogroups A, C, Y, and W, the percentage of participants with hSBA titers ≥ 1:8 at 30 days after the administration of the 3rd dose of MenQuadfi (Group 1) versus Menveo (Group 2) at 6 months of age were assessed via the following noninferiority hypothesis:

- (H0): p(men, G1) - p(men, G2) ≤-10% versus (H1): p(men, G1) - p(men, G2) >-10%
- p(men, G1) and p(men, G2) are the percentages of participants who achieve hSBA titers ≥ 1:8 in Group 1 and Group 2, respectively.
- Each of the serogroups A, C, Y, and W was tested separately. The overall noninferiority of this objective was demonstrated if all 4 individual null hypotheses are rejected.
- MenQuadfi was considered noninferior to Menveo if the LL of the 2-sided 95% CI of the difference between the 2 percentages is >-10% for each serogroup.

Secondary Hypotheses: Post-3rd Dose at 6-Months

Secondary Hypothesis 1: (Anti-hepatitis B)

The percentage of participants who achieve ≥ 10 mIU/mL in anti-HB surface antibody concentrations 30 days after the 6-month hepatitis B vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis:

- (H0): p(hep, G1) – p(hep, G2) ≤-10% versus (H1): p(hep, G1) – p(hep, G2) >-10%
- p(hep, G1) and p(hep, G2) are the percentages of participants in Group 1 and Group 2, respectively, who achieve ≥ 10 mIU/mL in anti-HB surface antibody concentrations.

Secondary Hypothesis 2: (Anti-PRP ≥ 0.15 µg/mL)

The percentage of participants who achieve ≥ 0.15 µg/mL in anti-PRP antibody concentrations 30 days after the 6-month Pentacel vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis:

- (H0): p(prp, G1) – p(prp, G2) ≤ - 5% versus (H1): p(prp, G1) – p(prp, G2) > - 5%
- p(prp, G1) and p(prp, G2) are the percentages of participants in Group 1 and Group 2 respectively, who achieve ≥ 0.15 µg/mL in anti-PRP antibody concentrations

Secondary Hypothesis 3: (Anti-PRP ≥ 1.0 µg/mL)

The percentage of participants who achieve ≥ 1.0 µg/mL in anti-PRP antibody concentrations 30 days after the 6-month Pentacel vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis:

- (H0): p(prp, G1) – p(prp, G2) ≤-10% versus (H1): p(prp, G1) – p(prp, G2) >-10%
- p(prp, G1) and p(prp, G2) are the percentage of participants in Group 1 and Group 2, respectively, who achieve ≥ 1.0 µg/mL in anti-PRP antibody concentrations

Secondary Hypothesis 4 (Anti-polio):

The percentage of participants who achieve ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3) 30 days after the 6-month Pentacel vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis:

- (H0): p(pol, G1) – p(pol, G2) ≤ - 5% versus (H1): p(pol, G1) – p(pol, G2) > - 5%
- p(pol, G1) and p(pol, G2) are the percentages of participants in Group 1 and Group 2, respectively, who achieve ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3).

Secondary Hypothesis 5: (Anti- rotavirus ≥ 3-fold rise):

The percentage of participants who achieve ≥ 3-fold rise in serum IgA antibody concentrations against the rotavirus antigens (serotypes G1, G2, G3, G4, and P1A[8]) 30 days after the 6-month rotavirus vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis: .

- (H0): p(rota, G1) - p(rota, G2) ≤-10% versus (H1): p(rota, G1) - p(rota, G2) >-10%
- p(rota, G1) and p(rota, G2) are the percentages of participants in Group 1 and Group 2, respectively, who achieve ≥ 3-fold rise in serum anti-rotavirus IgA antibody concentrations (serotypes G1, G2, G3, G4, and P1A[8]).

Secondary Hypothesis 6 (Anti-rotavirus GMC):

The ratio of GMCs of the serum IgA antibodies against rotavirus antigens 30 days after the 6-month rotavirus vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) was assessed via the following noninferiority hypothesis:

- (H0): GMC(rota,G1) / GMC(rota, G2) ≤ 2/3 versus (H1): GMC(rota,G1) / GMC(rota, G2) > 2/3
- GMC(rota, G1) and GMC(rota,G2) are the GMCs of the serum IgA antibodies against the rotavirus antigens (serotypes G1, G2, G3, G4, and P1A[8]) in Group 1 and Group 2, respectively

Reviewer Comment: While the Applicant has included pre-specified endpoints with hypothesis testing for rotavirus, anti-rotavirus IgA titers after live, oral rotavirus vaccine cannot be used to conclude whether immune interference has occurred, and therefore cannot be used to evaluate for immune interference impacting effectiveness of the oral rotavirus vaccine when administered concomitantly with MenQuadfi or Menveo.

Secondary Hypothesis 7 (Anti-pertussis; GMC):

The ratio of GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) for 30 days after the 6-month Pentacel vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) were assessed via the following noninferiority hypothesis.

- (H0): GMC(pert,G1) / GMC(pert, G2) ≤ 2/3 versus (H1): GMC(pert,G1) / GMC(pert, G2) > 2/3
- GMC(pert, G1) and GMC(pert,G2) are the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 1 and Group 2, respectively.

Secondary Hypothesis 8 (Anti-pneumococcal):

The ratio of GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) 30 days after the 6-month Prevnar 13 vaccine administration in the MenQuadfi group (Group 1) compared with the Menveo group (Group 2) were assessed via the following noninferiority hypothesis.

- (H0): GMC(pne, G1) / GMC(pne, G2) ≤ 1/2 versus (H1): GMC(pne, G1) / GMC(pne, G2) > 1/2
- GMC(pne, G1) and GMC(pne, G2) are the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Group 1 and Group 2, respectively.

Secondary Hypotheses: Post-4th Dose at 12 Months

Secondary Hypothesis 9 (Anti- measles):

The percentage of participants who achieve ≥ 255 mIU/mL in anti-measles antibody concentrations 30 days after the 12-month M-M-R II vaccine administration in the MenQuadfi group (Subgroup 1a) compared with the Menveo group (Subgroup 2a) was assessed via the following noninferiority hypothesis.

- (H0): p(mea, G1a) – p(mea, G2a) ≤-10% versus (H1): p(mea, G1a) – p(mea, G2a) >-10%
- p(mea, G1a) and p(mea, G2a) are the percentages of participants in Subgroup 1a and Subgroup 2a, respectively, who achieve ≥ 255 mIU/mL in anti-measles antibody concentrations.

Secondary Hypothesis 10 (Anti-mumps):

The percentage of participants who achieve ≥10 Mumps Ab units/mL in anti-mumps antibody concentrations 30 days after the 12-month M-M-R II vaccine administration in the MenQuadfi group (Subgroup 1a) compared with the Menveo group (Subgroup 2a) was assessed via the following noninferiority hypothesis.

- (H0): p(mum, G1a) – p(mum, G2a) ≤-10% versus (H1): p(mum, G1a) – p(mum, G2a) >-10%
- p(mum, G1a) and p(mum, G2a) are the percentages of participants in Subgroup 1a and Subgroup 2a, respectively, who achieve ≥ 10 Mumps Ab units/mL in anti-mumps antibody concentrations.

Secondary Hypothesis 11 (Anti-rubella):

The percentage of participants who achieve ≥ 10 IU/mL in anti-rubella antibody concentrations 30 days after the 12-month M-M-R II vaccination in the MenQuadfi group (Subgroup 1a) compared with the Menveo group (Subgroup 2a) was assessed via the following noninferiority hypothesis.

- (H0): p(rub, G1a) – p(rub, G2a) ≤-10% versus (H1): p(rub, G1a) – p(rub, G2a) >-10%
- p(rub, G1a) and p(rub, G2a) are the percentage of participants in Subgroup 1a and Subgroup 2a, respectively, who achieve ≥ 10 IU/mL in anti-rubella antibody concentrations.

Reviewer Comment: Although these success criteria for the endpoints of anti-measles, anti-mumps, and anti-rubella antibody concentrations were agreed upon at the time of study initiation, in recent years, CBER has routinely recommended a more stringent noninferiority margin of 5% for percentage difference in participants achieving the associated concentration thresholds, instead of the 10% specified in this protocol.

Secondary Hypothesis 12 (Anti-varicella):

The percentage of participants who achieve ≥ 5 gpELISA units/mL in anti-varicella antibody concentrations 30 days after the 12-month Varivax vaccine administration in the MenQuadfi group (Subgroup 1a) compared with the Menveo group (Subgroup 2a) was assessed via the following noninferiority hypothesis.

- (H0): p(var, G1a) – p(var, G2a) ≤-10% versus (H1): p(var, G1a) – p(var, G2a) >-10%
- p(var, G1a) and p(var, G2a) are the percentages of participants in Subgroup 1a and Subgroup 2a, respectively, who achieve ≥ 5 gpELISA units/mL in anti-varicella antibody Concentrations.

Secondary Hypothesis 13 (Anti-pneumococcal):

The ratio of GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) 30 days after the 12-month Prevnar13 vaccine administration in the MenQuadfi group (Subgroup 1a) compared with the Menveo group (Subgroup 2a) were assessed via the following noninferiority hypothesis.

- (H0): GMC(pne, G1a) / GMC(pne, G2a) ≤ 1/2 versus (H1): GMC(pne, G1a) / GMC(pne, G2a) > 1/2
- GMC(pne, G1a) and GMC(pne, G2a) are the GMCs of antibodies against the pneumococcal antigens (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in Subgroup 1a and Subgroup 2a, respectively. Each of the serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F were tested separately.

Secondary Hypotheses: Post-4th Dose at 15 Months

Secondary Hypothesis 14 (Anti-PRP ≥ 1.0 µg/mL):

The percentage of participants who achieve ≥1.0 µg/mL in anti-PRP antibody concentrations 30 days after the 15-month Pentacel vaccine administration in the MenQuadfi group (Subgroup 1b) compared with the comparator group (Subgroup 2b) was assessed via the following noninferiority hypothesis.

- (H0): p(prp, G2b) – p(prp, G1b) ≤-10% versus (H1): p(prp, G2b) – p(prp, G1b) > -10%
- p(prp, G1b) and p(prp, G2b) are the percentages of participants in Subgroup 1b and Subgroup 2b, respectively, who achieve ≥ 1.0 µg/mL in anti-PRP antibody concentrations.

Secondary Hypothesis 15 (Anti-polio):

The percentages of participants who achieve ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3) 30 days after the 15-month Pentacel vaccine administration in the MenQuadfi group (Subgroup 1b) compared with the comparator group (Subgroup 2b) were assessed via the following noninferiority hypothesis.

- (H0): p(pol, G1b) – p(pol, G2b) ≤ - 5% versus (H1): p(pol, G1b) – p(pol, G2b) > - 5%
- p(pol, G1b) and p(pol, G2b) are the percentages of participants in Subgroup 1b and Subgroup 2b, respectively, who achieve ≥ 1:8 in anti-polio antibody titers (type 1, type 2, and type 3).
- Each of the antigens of type 1, type 2, and type 3 were tested separately.

Secondary Hypothesis 16 (Anti-pertussis; vaccine response rate):

The percentages of participants with a pertussis vaccine response[9] for the pertussis antigens (PT, FHA, PRN, and FIM) 30 days after the 15-month Pentacel vaccine administration in the MenQuadfi group (Subgroup 1b) compared with the comparator group (Subgroup 2b) were assessed with the following noninferiority hypothesis.

- (H0): p(pert, G1b) - p(pert, G2b) ≤-10% versus (H1): p(pert, G1b) - p(pert, G2b) >-10%
- p(pert, G1b) and p(pert, G2b) are the percentages of participants who achieve a pertussis vaccine response in Subgroup 1b and Subgroup 2b, respectively.
- Each of the antigens of PT, FHA, PRN, and FIM were tested separately.

Other Secondary Endpoints (Descriptive Analyses Only):

For analyses of descriptive endpoints, descriptive statistics with point estimates and 95% CIs were generated. The 95% CIs of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions. For GMTs and GMCs, 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

9 Pertussis vaccine response was defined as:

- Pre-booster (4th) vaccination concentration< lower limit of quantitation (LLOQ), then post- booster (4th) vaccination concentration had to be ≥ 4x the LLOQ
- Pre- booster (4th) vaccination concentration ≥ LLOQ but < 4x the LLOQ, then post- booster (4th) vaccination concentration had to achieve a 4-fold rise (post-4th vaccination/ Pre-4th vaccination ≥ 4)
- Pre- booster (4th) vaccination concentration ≥ 4x the LLOQ, then post- booster (4th) vaccination concentration had to achieve a 2-fold response (post-4th vaccination/ Pre-4th vaccination ≥ 2)

Observational Endpoints (Safety): See Section 6.1.1

Impact of COVID-19 pandemic was analyzed as follows:

- Participants impacted by COVID-19 pandemic defined as: at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19
- If more than 10% of participants are impacted as per this definition, baseline and demographic characteristics, and the main immunogenicity and safety endpoints will also be summarized in the subsets of participants impacted/ non-impacted participants to assess the potential impact of COVID-19 situation on study outcome.

Reviewer Comment: Less than 10% of study participants had at least one major/critical protocol deviation due to COVID-19 or did not complete the study due to COVID-19. Therefore, the additional sensitivity analyses specified above were not performed.

Protocol Amendments:

- Version 1.0 (October 20, 2017): Original study protocol
- Version 2.0 (March 28, 2018): Amendment 1
    - Sample size increased from 2,250 to 2,475
    - Each group was randomized 2:1 into 2 subgroups based on time of analysis in the second year of life
    - Second primary objective (and corresponding hypothesis) added to demonstrate noninferiority of hSBA antibody response after the 3rd dose (antibody titers ≥ 1:8);
    - Additional immunogenicity objective (observational) added to describe antibody responses when MenQuadfi is administered at 12-15 months of age versus 15-18 months of age (Subgroup 1a versus Subgroup 1b)
    - Clarification that the 4th dose of Pentacel for Subgroup 1a is to be administered outside of the study by the study site personnel / investigator.
- Version 3.0 (January 25, 2019): Amendment 2; removed criteria requiring participants to be born at full term and with a birth weight ≥ 2.5 kg to allow a broader population to be enrolled that corresponds to healthy children that would be vaccinated under routine care.
- Version 4.0 (June 2, 2021): Amendment 3; sample size increased from 2,475 to 2,628 due to high attrition rates seen during the study conduct, especially during the COVID-19 pandemic. Immunogenicity objectives previously listed as observational were changed to secondary. Added a new section on a conditional sensitivity analysis on the impact of the COVID-19 pandemic. Full Analysis Set (FAS) 3 was added as a subset for evaluation of immunogenicity persistence; a third Per-Protocol Analysis Set (PPAS) was also added; PPAS 2 is now for immunogenicity persistence evaluation and PPAS 3 for 2nd year of life vaccination.
- Version 5.0 (January 26, 2022): Amendment 4; Updated secondary endpoint to assess the effect of the 4th dose of MenQuadfi or Menveo to reflect ≥ 4-fold rise from pre-4th dose (at 12 months of age) to post-dose 4 vaccination, based on CBER recommendations dated September 21, 2021

6.1.10 Study Population and Disposition

A total of 2,627 participants were enrolled and randomized in the study. The first participant, first visit took place on April 25, 2018, and the last participant, last contact took place on September 22, 2023.

6.1.10.1 Populations Enrolled/Analyzed

Safety sets: All participants will have their safety analyzed after each dose according to the vaccine they actually received, and after all 4 doses according to the vaccine received at the first dose.

Overall SafAS (Overall Safety Analysis Set for Any Dose): participants who have received at least one dose of the study vaccines and have any safety data available.

- SafAS1 (Safety Analysis Set for vaccination at 2 months of age): participants who have received the study vaccine at Visit 1 around 2 months of age and have any safety data available.
- SafAS2 (Safety Analysis Set for vaccination at 4 months of age): participants who have received the study vaccine at Visit 2 around 4 months of age and have any safety data available
- SafAS3 (Safety Analysis Set for Vaccination at 6 months of age): participants who have received the study vaccine at Visit 3 at around 6 months of age and have any safety data available
- SafAS4 (Safety Analysis Set for Vaccination at 12 months of age): participants who have received the study vaccine at Visit 5 at around 12-15 months of age and have any safety data available
- SafAS5 (Safety Analysis Set for Vaccination at 15 months of age): participants who have received the study vaccine at around 15-18 months of age and have any safety data available
- SafAS6 (Safety Analysis Set for all 4-Dose Vaccination): participants who have received all 4 doses of the study vaccine (3 doses in infancy and one dose in the 2nd year of life at 12-15 or 15-18 months of age) and have any safety data available.

Full Analysis Set (FAS)

- FAS 1 (for infant vaccination): subset of all randomized participants who received at least 1 dose of the study vaccine infancy (<12 months of age) and have a valid post-vaccination serology result in infancy.
- FAS 2 (For immunogenicity persistence evaluation): subset of all randomized participants who received at least 1 dose of the study vaccine in infancy (<12 months of age) and have a valid prevaccination serology result at Visit 5 before the 12-month vaccination for Subgroups 1a and 2a or visit 6 before 15-month vaccination for Subgroups 1b and 2b
- FAS 3 (for 2nd year of life vaccination): subset of all randomized participants who received at least 1 dose of the study vaccine in the 2nd year of life (≥12 months of age) and have a valid post-vaccination serology result in the 2nd year of life.

Per-Protocol Analysis Set (PPAS): The PPAS will serve as primary population for immunogenicity analyses. Participants with the following protocol deviations are excluded from any PPAS:

- Did not meet all protocol-specified inclusion criteria or met at least one of the protocol specific exclusion criteria
- Received a vaccine other than the one that he/she was randomized to receive
- Did not complete vaccination schedule for infant year of the study (2, 4, 6 months)
- Preparation and/or administration of vaccine not done as per-protocol
- Received a protocol- prohibited therapy, medication, or vaccine
- Had other protocol violations that affected the participant's immune response

- Serology sample did not produce a valid result.

    - PPAS1 (infant vaccination): Subset of FAS1 without any relevant protocol deviations. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded:
    - Did not receive vaccine in a proper time window (Visit 1: 42 to 89 days of age, Visit 2: Visit 1 + 60 days [+14 days], Visit 3: Visit 2 + 60 days [+14 days])
    - Did not provide a post-dose serology sample in the proper time window (Visit 3 + 30 days [+21 days]) or a post-dose serology sample was not drawn
    - PPAS2 (immunogenicity persistence evaluation): Subset of FAS2 with valid prevaccination serology obtained at Visit 5 before 12-month vaccinations for Subgroups1a and 2a or Visit 6 before 15-month vaccinations for Subgroups 1b and 2b. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded:
    - Did not receive vaccine in a proper time window (Visit 1: 42 to 89 days of age, Visit 2: Visit 1 + 60 days [+14 days], Visit 3: Visit 2 + 60 days [+14 days])
    - Pre-dose serology sample at Visit 5 for Subgroups 1a or 2a before 12-month vaccinations or Visit 6 for Subgroups 1b and 2b before 15-month vaccinations was not drawn
    - PPAS3 (2^{nd} year of life vaccination): Subset of FAS3 with no relevant protocol deviations. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded:
    - Did not complete the vaccination schedule including the infant and the second year of the study
        - Subgroups 1a and 2a: up through 12-month vaccinations
        - Subgroups 1b and 2b: up through 15-month vaccinations, including the 12-month vaccinations
    - Did not receive vaccine in the proper time window during the second year of the study:
        - Subgroup 1a: Visit 5: 12-15 months of age
        - Subgroup 1b: Visit 5: 12-15 months of age, Visit 6: 15-18 months of age
        - Subgroup 2a: Visit 5: 12 months of age
        - Subgroup 2b: Visit 5: 12 months of age, Visit 6: 15-18 months of age
    - Did not provide a post-dose serology sample in the proper time window or a post-dose serology sample was not drawn for a given antigen specific analysis
        - Subgroups 1a and 2a: Visit 5 + 30 days (+21 days),
        - Subgroups 1b and 2b: Visit 6 + 30 days (+21 days)

6.1.10.1.1 Demographics

The demographics of participants in the Overall Safety Analysis Set for Any Dose (Overall SafAS) are shown in Table 4. Overall, across both study groups, there was a slightly higher percentage of male participants (52.8%) compared with female participants (47.2%). The median age of participants at enrollment was 64 days. Most participants identified as White (82.0%) and not Hispanic or Latino (51.8%). Only 7.4% of participants overall had a history of prematurity (<37 weeks gestational age). Demographic characteristics of the Overall SafAS were similar to the that of the other Safety Analyses Sets, the Full Analysis Sets, and the Per-Protocol Analysis Sets.

Table 4. Demographic and Baseline Characteristics, Overall Safety Analysis Set, Study MET42

Baseline Characteristic	MenQuadfi Group 1 N=1727	Menveo Group 2 N=867
Sex, n (%)	--	--
Male	911 (52.8)	458 (52.8)
Female	816 (47.2)	409 (47.2)
Age at enrollment (days)	--	--
Median age (min, max)	64.0 (42.0, 89.0)	64.0 (42.0, 89.0)
Race, n (%)	--	--
American Indian or Alaska Native	11 (0.6)	3 (0.3)
Asian	13 (0.8)	10 (1.2)
Black or African American	204 (11.8)	94 (10.8)
Native Hawaiian or Other Pacific Islander	7 (0.4)	6 (0.7)
White	1414 (81.9)	714 (82.4)
Mixed Origin	42 (2.4)	30 (3.5)
Unknown	18 (1.0)	5 (0.6)
Not Reported	18 (1.0)	5 (0.6)
Ethnicity, n (%)	--	--
Hispanic/Latino	831 (48.1)	408 (47.1)
Not Hispanic/Latino	885 (51.2)	454 (52.4)
Unknown	3 (0.2)	3 (0.3)
Not reported	8 (0.5)	2 (0.2)
Born preterm[a]	--	--
Yes	133 (7.7)	58 (6.7)
No	1593 (92.2)	809 (93.3)

Source: Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Tables 8.23. Data cutoff 08MAR2024.
Abbreviations: N=number of participants in overall safety analysis set for any dose; n=number of participants fulfilling the item listed in the first column.
a. Preterm is defined as infant born at gestational age <37 weeks.

Reviewer Comment: Baseline characteristics were balanced across groups. The study included 133 (7.7%) infants born preterm (31 to <37 weeks gestational age) who received at least one dose of MenQuadfi. Among these 133 infants born preterm, the large majority (91%) were born at 34 to <37 weeks of gestation (late preterm). There were 58 (6.7%) infants born preterm who received at least one dose of Menveo, and 81% of these preterm infants were late preterm.

6.1.10.1.2 Participant Disposition

Disposition of the participants who contributed to the immunogenicity analyses are shown in Table 5. Approximately 44%-51% of participants were excluded from each of the Per Protocol Analysis Sets. The most common reasons for exclusion from the Per Protocol Analyses Sets 1 and 2 were due to not receiving the vaccine in the time window, not providing a post-dose serology sample, and not providing a valid blood test result. For Per Protocol Analysis Set 3, the most common reasons for exclusion were not completing the vaccinations schedule, not providing a post-dose serology sample, and not providing a valid blood test.

Table 5. Participant Disposition, Immunogenicity Sets, Study MET42

Population	MenQuadfi Group 1 n (%) N=1746	Menveo Group 2 n (%) N=881
Randomized Set	1746 (100)	881 (100)
Full Analysis Set 1	1339 (76.7)	663 (75.3)
Excluded from Full Analysis Set 1	407 (23.3)	218 (24.7)
Did not receive study vaccine at Visit 1 to Visit 3	19 (1.1)	12 (1.4)
Did not have a valid post-vaccination serology result at Visit 4	407 (23.3)	218 (24.7)
Per Protocol Analysis Set 1	928 (53.2)	460 (52.2)
Excluded from Per Protocol Analysis Set 1	818 (46.8)	421 (47.8)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.3)	6 (0.7)
Did not complete the vaccinations schedule for infant stage from Visit 1 to Visit 3	217 (12.4)	94 (10.7)
Received vaccine other than randomized from Visit 1 to Visit 3	1 (<0.1)	2 (0.2)
Vaccine not prepared/administered as per-protocol from Visit 1 to Visit 3	47 (2.7)	21 (2.4)
Did not receive vaccine in time window	367 (21.0)	189 (21.5)
Did not provide a post-dose serology sample	387 (22.2)	197 (22.4)
Post-dose serology sample not in time window	141 (8.1)	70 (7.9)
Received protocol-prohibited therapy/medication/vaccine	42 (2.4)	11 (1.2)
Did not provide a valid blood test result	407 (23.3)	218 (24.7)
Other protocol deviations	0	0
Full Analysis Set 2	1232 (70.6)	634 (72.0)
Excluded from Full Analysis Set 2	514 (29.4)	247 (28.0)
Did not receive study vaccine at Visit 1 to Visit 3	19 (1.1)	12 (1.4)
Did not have a valid post-vaccination serology result at Visit 5 or Visit 6	514 (29.4)	247 (28.0)
Per Protocol Analysis Set 2	942 (54.0)	486 (55.2)
Excluded from Per Protocol Analysis Set 2	804 (46.0)	395 (44.8)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.3)	6 (0.7)
Did not complete the vaccinations schedule for infant stage from Visit 1 to Visit 3	217 (12.4)	94 (10.7)
Received vaccine other than randomized	1 (<0.1)	2 (0.2)
Vaccine not prepared/administered as per-protocol	47 (2.7)	21 (2.4)
Did not receive vaccine in time window	367 (21.0)	189 (21.5)
Did not provide a post-dose serology sample	493 (28.2)	240 (27.2)
Received protocol-prohibited therapy/medication/vaccine	6 (0.3)	3 (0.3)
Did not provide a valid blood test result	514 (29.4)	247 (28.0)
Other protocol deviations	0	1 (0.1)
Full Analysis Set 3	1194 (68.4)	591 (67.1)
Excluded from Full Analysis Set 3	552 (31.6)	290 (32.9)
Did not receive study vaccine at Visit 5 to Visit 7	335 (19.2)	173 (19.6)
Did not have a valid post-vaccination serology result at Visit 6 or Visit 7	552 (31.6)	290 (32.9)
Per Protocol Analysis Set 3	983 (56.3)	434 (49.3)
Excluded from Per Protocol Analysis Set 3	763 (43.7)	447 (50.7)
Did not meet all protocol-specified inclusion/exclusion criteria	5 (0.3)	6 (0.7)
Did not complete the vaccinations schedule for infant year and the second year of the study	385 (22.1)	192 (21.8)
Received vaccine other than randomized	1 (<0.1)	2 (0.2)
Vaccine not prepared/administered as per-protocol	60 (3.4)	29 (3.3)
Did not receive vaccine in time window	37 (2.1)	97 (11.0)

Population	MenQuadfi Group 1 n (%) N=1746	Menveo Group 2 n (%) N=881
Did not provide a post-dose serology sample	530 (30.4)	287 (32.6)
Post-dose serology sample not in time window	146 (8.4)	65 (7.4)
Received protocol-prohibited therapy/medication/vaccine	14 (0.8)	12 (1.4)
Did not provide a valid blood test result	552 (31.6)	290 (32.9)
Other protocol deviations	0	1 (0.1)

Source: Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Tables 8.15, 8.16, 8.17. Data cutoff 08MAR2024.
Abbreviations: N=total number of participants randomized in each study group; n=number of participants fulfilling the item listed; percentages based on N. Note: Participants may have been excluded for more than 1 reason.

Reviewer Comment: The proportions of participants excluded from each of the Per Protocol Analysis Sets and the reasons for exclusion were generally similar across the study groups, with the exception of PPAS3, for which a lower percentage of participants were excluded from the MenQuadfi versus Menveo groups (43.7% versus 50.7%, respectively). This was primarily due to a higher percentage of participants in the Menveo group who did not receive the vaccine in the time window (11.0%, compared with 2.1% in the MenQuadfi group).

There was a higher percentage of participants excluded from the immunogenicity analyses due to protocol deviations when compared to studies that enroll adult populations. However, the study enrolled an infant/toddler study population and the study design included multiple vaccination visits over a prolonged study period with many protocol specified immunogenicity assessments requiring sera collection, which are not easily obtained from young infants. The study also was conducted during the beginning of the COVID-19 pandemic with lock-down restrictions. Despite the reported protocol deviations, the proportion of participants to support the per protocol analyses sets were sufficient to assess key immunogenicity endpoints.

Disposition of the participants who contributed to the safety analyses are shown in Table 6. Overall, approximately 80% of all participants received all 4 doses of MenQuadfi or Menveo. A slightly lower percentage of participants in the MenQuadfi group withdrew from the study compared with the Menveo group (24.1% versus 29.8%, respectively), which was also reflected in the slightly higher percentage of MenQuadfi recipients who completed at least 6 months of follow-up post-last vaccination compared with Menveo recipients (80.0% versus 75.8%, respectively). Study withdrawal due to AEs were rare and balanced across the two groups.

Table 6. Participant Disposition, Safety Analysis Sets, Study MET42

Population	MenQuadfi Group 1 n (%) N=1727	Menveo Group 2 n (%) N=867
Overall safety analysis set for any dose	1727 (100)	867 (100)
Safety analysis set for vaccinations at 2 months of age (SafAS1)	1727 (100)	867 (100)
Safety analysis set for vaccinations at 4 months of age (SafAS2)	1620 (93.8)	827 (95.4)
Safety analysis set for vaccinations at 6 months of age (SafAS3)	1542 (89.3)	794 (91.6)
Safety analysis set for vaccinations at 12 months of age (SafAS4)	1410 (81.6)	708 (81.7)
Safety analysis set for vaccinations at 15 months of age (SafAS5)	444 (25.7)	644 (74.3)
Safety analysis set for all 4-dose vaccination* (SafAS6)	1375 (79.6)	705 (81.3)
Participants withdrawn from study	396 (22.9)	245 (28.3)

Population	MenQuadfi Group 1 n (%) N=1727	Menveo Group 2 n (%) N=867
Reason for withdrawal	--	--
Adverse event[a]	2 (0.1)	1 (0.1)
Lost to follow-up	86 (5.0)	60 (6.9)
Protocol deviation	61 (3.5)	45 (5.2)
Withdrawal by parent/guardian	247 (14.3)	139 (16.0)
Completed at least 6 months of safety follow-up after the last dose	1382 (80.0)	657 (75.8)

Source: Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Table 8.18 and 8.12 and from Additional Analysis submitted to Amendment 5. Data cutoff 08MAR2024.
Abbreviations: n=number of participants fulfilling the item listed; N = number of participants in overall safety analysis set for any dose; percentages based on N
Notes: Participants may have been withdrawn for more than 1 reason
* All 4-dose vaccinations received in a series (without vaccinations window restrictions) should be either all MenQuadfi or all Menveo
a. Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is < Grade 1 according to the Applicant.

Reviewer Comment: The proportion of participants who contributed to each safety analysis set was generally balanced across the two groups. The differences observed for SafAS5 (post-15-month vaccination) was due to the study design as participants randomized to MenQuadfi Subgroup 1a did not have a vaccination visit at 15 months and thus would not be eligible to contribute to the SafAS5. Withdrawals from study by parent/guardian were most commonly due to relocation, time commitment constraints, and difficulty or concerns with continued study visits during the COVID-19 pandemic. The percentage of participants withdrawn from study by parent/guardian (14.3-16.0%) is not unexpected for a study in young infants with a study duration of 16 to 22 months (depending on the randomized group) for each individual participant.

6.1.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Vaccine effectiveness is inferred from serologic immune endpoints to assess the response to study vaccines as discussed in section 6.1.1.

Analyses of Primary Immunogenicity Objectives

Primary objective #1: Noninferiority of vaccine seroresponse following a 4-dose series of MenQuadfi compared with Menveo

Primary objective #1 evaluated the noninferiority of hSBA vaccine seroresponse 30 days after the 4th dose of MenQuadfi administered at 12-15 months of age compared with the 4th dose of Menveo administered at 12 months of age. Seroresponse was defined as: if prevaccination (pre-1st dose) hSBA titer < 1:8, then post-4th dose vaccinations titer must be ≥ 1:16; and if prevaccination hSBA titer ≥ 1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer. The pre-specified noninferiority success criterion of the LL of the 95% CI of the difference in seroresponse rate (MenQuadfi – Menveo) >-10% was met for all 4 serogroups (Table 7).

Table 7. hSBA Vaccine Seroresponse Rate at 30 Days After the 4th Dose of MenQuadfi or Menveo, PPAS3, Study MET42

Serogroup	MenQuadfi Subgroup 1a[a] SRR % (95% CI)[c] N1=501-540	Menveo Subgroup 2a[b] SRR % (95% CI)[c] N1=223-250	Difference in SRR [MenQuadfi-Menveo] % (95% CI)[d]
A	79.4% (75.6, 82.9)	77.6% (71.5, 82.9)	1.86 (-4.4, 8.6)
C	97.0% (95.1, 98.3)	88.2% (83.4, 92.0)	8.75 (4.8, 13.6)
Y	96.4% (94.4, 97.8)	92.3% (88.1, 95.4)	4.09 (0.7, 8.4)
W	97.6% (95.9,98.7)	96.4% (93.3, 98.3)	1.19 (-1.2, 4.5)

Source: Adapted from STN 125701/262 Amendment 2, Study Met42 Clinical Study Report, Tables 8.35. Data cutoff 08MAR2024.
Abbreviations: PPAS3=Per protocol analysis set 3 (2nd year of life vaccination); CI=confidence interval; N1=number of participants with available data for the relevant endpoint;
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer <1:8, then post-4th dose vaccinations titer must be ≥1:16; and if prevaccination hSBA titer ≥1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer.
a. Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. Seroresponse rate based on hSBA titer obtained 30 days post-4th dose of MenQuadfi administered at 12-15 months of age.
b. Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Seroresponse rate based on hSBA titer obtained 30 days post-4th dose of Menveo administered at 12 months of age.
c. 95% CI of the single proportion calculated from the exact binomial method;
d. 95% CI of the seroresponse difference calculated from the Wilson Score method without continuity correction.
Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups

Primary objective #2: Noninferiority of hSBA antibody response after the 3rd dose of MenQuadfi compared with Menveo

Primary objective #2 evaluated the noninferiority of the hSBA antibody response (titers ≥1:8) 30 days after the 3rd dose (administered at 6 months) of MenQuadfi compared with Menveo. The pre-specified noninferiority success criterion of the LL of the 95% CI of the difference in percentage of participants who achieved hSBA titers ≥1:8 (MenQuadfi – Menveo) >-10% was met for all 4 serogroups (Table 8).

Table 8. Percentage of Participants with hSBA Titers ≥1:8 at 30 Days after the 3rd Dose of MenQuadfi or Menveo, PPAS1, Study MET42

Serogroup	MenQuadfi Group 1 % with hSBA ≥1:8 (95% CI)[a] N1=835-883	Menveo Group 2 % with hSBA ≥1:8 (95% CI)[a] N1=409-438	Difference in % with hSBA ≥1:8 [MenQuadfi-Menveo] (95% CI)[b]
A	77.9% (75.0, 80.7)	67.7% (63.0, 72.2)	10.2% (5.0; 15.6)
C	99.0% (98.1, 99.6)	91.2% (88.1, 93.7)	7.83% (5.3, 11.0)
Y	98.3% (97.1, 99.0)	91.7% (88.7, 94.2)	6.53% (4.0, 9.6)
W	98.6% (97.6, 99.3)	92.9% (90.1, 95.1)	5.72% (3.4, 8.6)

Source: Adapted from STN 125701/262 amendment 2, Study MET42 Clinical Study Report, Tables 8.37. Data cutoff 08MAR2024.
Abbreviations: PPAS1=per protocol analysis set 1, hSBA=serum bactericidal activity using human complement, CI=confidence interval, N1=number of participants with available data for the relevant endpoint.
Notes: Group 1: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-18 months of age. hSBA titer obtained 30 days post-3rd dose of MenQuadfi administered at 6 months of age.
Group 2: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. hSBA titer obtained 30 days post-3rd dose of Menveo administered at 6 months of age.
a 95% CI of the single proportion calculated from the exact binomial method;
b 95% CI of the difference calculated from the Wilson Score method without continuity correction. Noninferiority is demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

Reviewer Comment:

1. The primary analyses evaluating meningococcal-specific functional antibody responses met the protocol specified statistical noninferiority criteria for success, demonstrating the effectiveness of MenQuadfi compared with a licensed meningococcal vaccine when administered as a 4-dose series to infants/toddlers, with sufficient immune responses also demonstrated following the 3rd dose administered at 6 months of age.
2. Analyses of primary objective #2 demonstrated a greater percentage of MenQuadfi recipients achieving hSBA antibody titers ≥1:8 compared with Menveo recipients after the 3rd dose at 6 months of age for all 4 serogroups; however, it is unclear if these differences would translate to clinical meaningful differences in protection against meningococcal disease.
3. The criterion for achieving seroresponse after the 4th dose was dependent on the participant's hSBA titers prior to Dose 1 at approximately 2 months of age. To assess for potential differences in seroresponse rates based on pre-Dose 1 hSBA titers, descriptive subgroup analyses of the seroresponse rate (SRR) post-4th dose were performed based on participants with baseline hSBA titers. As discussed in Section 6.1.11.1, the majority of study participants had hSBA titers <1:8 prior to Dose 1, suggesting minimal anti-meningococcal maternal antibodies prior to initiation of the 4-dose series. Overall, the percentages of participants achieving seroresponse after the 4th dose compared to baseline were similar or higher in the MenQuadfi group compared with the Menveo group, irrespective of pre-Dose 1 hSBA titer level.

Analyses of Secondary Immunogenicity Objectives

The same or similar study endpoints were evaluated as part of multiple secondary objectives. Results of these analyses are grouped below by endpoints evaluated. Study endpoints considered integral to the assessment are presented below.

Descriptive analyses of hSBA titers and seroresponse after 4th dose of MenQuadfi when administered at 12-15 months or 15-18 months of age (Secondary Objective #6:)

Comparisons of the post-4th dose hSBA GMTs and seroresponse rates between participants who received the 4th dose of MenQuadfi at 12-15 months of age (Subgroup 1a) and those who received the 4th dose of MenQuadfi at 15-18 months of age (Subgroup 1b) were descriptively analyzed (Table 9). The GMTs for serogroups A, C, and Y were similar across the two subgroups; for serogroup W, the post-4th dose GMTs were higher in the participants who received the 4th dose of MenQuadfi at 15-18 months compared with those who received the dose at 12-15 months. The percentage of participants who achieved hSBA titers ≥1:8 and who had achieved seroresponse were similar across the two subgroups.

Table 9. hSBA GMTs, Percentage of Participants with hSBA titer ≥1:8, and Seroresponse Rate 30 Days After 4th dose of MenQuadfi when Administered at 12-15 Months or 15-18 Months of Age, PPAS3, Study MET42

Sero-group	Endpoint	MenQuadfi Subgroup 1a[a] 4th Dose at 12-15 Months N=501-655	MenQuadfi Subgroup 1b[b] 4th Dose at 15-18 Months N=223-295
A	GMT (95% CI)[c]	67.1 (58.1, 77.5)	78.0 (64.4, 94.5)
C	GMT (95% CI)[c]	678 (606, 758)	654 (555, 770)

Sero-group	Endpoint	MenQuadfi Subgroup 1a[a] 4th Dose at 12-15 Months N=501-655	MenQuadfi Subgroup 1b[b] 4th Dose at 15-18 Months N=223-295
Y	GMT (95% CI)[c]	296 (268, 327)	369 (321, 425)
W	GMT (95% CI)[c]	387 (352, 426)	823 (693, 977)
A	% with hSBA ≥1:8 (95% CI)[d]	87.7% (84.9, 90.1)	92.6% (88.9, 95.3)
C	% with hSBA ≥1:8 (95% CI)[d]	99.4% (98.4, 99.8)	99.3% (97.5, 99.9)
Y	% with hSBA ≥1:8 (95% CI)[d]	99.1% (98.0, 99.7)	99.3% (97.6, 99.9)
W	% with hSBA ≥1:8 (95% CI)[d]	99.4% (98.4, 99.8)	100% (98.7, 100)
A	Seroresponse Rate, % (95% CI)[d]	79.4% (75.6, 82.9)	84.3% (78.9, 88.8)
C	Seroresponse Rate, % (95% CI)[d]	97.0% (95.1, 98.3)	97.9% (95.2, 99.3)
Y	Seroresponse Rate, % (95% CI)[d]	96.4% (94.4, 97.8)	98.3% (95.7, 99.5)
W	Seroresponse Rate, % (95% CI)[d]	97.6% (95.9, 98.7)	98.8% (96.4, 99.7)

Source: Adapted from STN 125701/262, Study Met42 Clinical Study Report, Table 8.127, 8.129, 8.135
Abbreviations: N=number of participants with valid serology results for the particular serogroup and time point; GMT=geometric mean titer; hSBA=serum bactericidal activity using human complement; M=number of participants with valid serology results for the particular serogroup.
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer < 1:8, then post-4th dose vaccinations titer must be ≥ 1:16; and if prevaccination hSBA titer ≥ 1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer.
a Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. hSBA titers assessed 30 days after the 4th dose of MenQuadfi administered at 12-15 months.
b Subgroup 1b: MenQuadfi at 2, 4, 6, and 15-18 months of age and recommended vaccines at 2, 4, 6, 12-15 months of age. hSBA titers assessed 30 days after the 4th dose of MenQuadfi administered at 15-18 months.
c 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
d. 95% CI of the single proportion calculated from the exact binomial method;

Participants in Subgroups 1a and 1b had similar hSBA titers post-3rd dose (results not shown). Before the 4th dose, hSBA GMTs were similar across the two subgroups for serogroups A (1a: 10.6, 1b: 8.02), Y (1a: 43.5, 1b: 42.4), and W (1a: 57.9, 1b: 57.7), and slightly lower in Subgroup 1b compared with Subgroup 1a for serogroup C (1a: 61.3, 1b: 41.3). The percentage of participants with hSBA titers ≥1:8 pre-dose 4 were similar across the two subgroups for serogroups A, Y and W and slightly lower in Subgroup 1b compared with Subgroup 1a for serogroup C (results not shown). Both MenQuadfi subgroups had higher GMTs and percentage with hSBA titers ≥1:8 pre-dose 4 compared with Menveo recipients (Table 10, Menveo Subgroup 2a, Pre-4th Dose).

Reviewer Comments:

1. The timing of the 4th dose administration at 12-15 months of age was based on data generated from early phase studies, including Study MET39 (see Section 6.4). The Applicant included an assessment of a 4th dose administered at 15-18 months to generate data to support flexibility in dosing with recommended pediatric vaccines. Post-4th dose immune responses were generally similar when administered at 12-15 months compared with 15-18 months of age, except for hSBA GMTs for serogroup W. Higher serogroup W hSBA GMTs were observed in participants who received the 4th dose at 15-18 months (Subgroup 1b) compared with those who received the 4th dose at 12-15 months (Subgroup 1a). However, the clinical significance of this difference is unclear since the percentage of seroresponders and participants who achieved hSBA titers ≥1:8 were similar across the two subgroups, including against serogroup W.

   Although pre-4th dose GMTs and percentage of participants with hSBA titers ≥ 1:8 were slightly lower for serogroup C among participants receiving the 4th dose of MenQuadfi at

15-18 months compared with those receiving the 4th dose at 12-15 months of age, the pre-4th dose hSBA responses in this subgroup for serogroup C were higher than those observed prior to the 4th dose among participants in Subgroup 2a who received Menveo at 12 months of age (Table 10).

Overall, these data are reassuring with regard to the durability of immune response through 15-18 months of age (prior to receipt of 4th dose) and the robust immune response generated when the 4th dose is given between 12-18 months, thus supporting the wider age range for administration of the 4th dose MenQuadfi.

2. Subgroup 1a and Subgroup 1b included an overlapping age range of participants 15 to <16 months of age at the time of the receipt of the 4th dose. Only 13 out of the 675 participants in Subgroup 1a (1.9%) were 15 to <16 months of age at the time of receipt of the 4th dose of MenQuadfi. The remaining participants in Subgroup 1a were 12 to <15 months of age at the time of the 4th dose. A sensitivity analysis was performed excluding the 13 participants who were 15 to <16 months of age at 4th dose from Subgroup 1a, and the results were similar to those from the original analysis displayed in Table 9 above.

Descriptive Analyses of hSBA Titers Pre- and Post-4th Dose (Secondary Objective #2, Secondary Objective #3, Secondary Objective #5):

hSBA GMTs and percentage of participants with hSBA titers ≥1:8 pre-4th dose and at 30 days after the 4th dose of MenQuadfi administered at 12-15 months of age or Menveo administered at 12 months of age are shown in Table 10. The pre-4th dose GMTs were higher in the MenQuadfi group compared with the Menveo group for all 4 serogroups. For all 4 serogroups, a higher percentage of participants in the MenQuadfi group compared with the Menveo groups had hSBA titers ≥1:8 before the 4th dose. At 30 days post-4th dose, the hSBA GMTs were comparable across the two groups for serogroup A and higher in the MenQuadfi group as compared with the Menveo group for serogroups C, Y, and W. The percentage of participants with hSBA titers ≥1:8 after the 4th dose were similar across the MenQuadfi and Menveo groups for all serogroups except for serogroup C, for which the rates were higher among MenQuadfi recipients compared with Menveo recipients.

A similar pattern for pre- and post-4th dose hSBA titers was observed when assessing for hSBA titers ≥1:4 (results not shown).

Table 10. hSBA GMTs and Percentage of Participants With hSBA Titers ≥1:8 Before the 4th Dose and at 30 Days After the 4th Dose of MenQuadfi or Menveo, PPAS3, Study MET42

Sero-group	Endpoint	Pre-4th Dose MenQuadfi Subgroup 1a[a] N=607-619	Pre-4th Dose Menveo Subgroup 2a[b] N=282-288	Post-4th Dose MenQuadfi Subgroup 1a[a] N=607-655	Post-4th Dose Menveo Subgroup 2a[b] N=282-305
A	GMT (95% CI)[c]	10.6 (9.5, 11.8)	6.6 (5.7, 7.7)	67.1 (58.1, 77.5)	56.9 (46.7, 69.5)
C	GMT (95% CI)[c]	61.3 (54.4, 69.0)	4.5 (3.9, 5.1)	678 (606, 758)	90.9 (75.7, 109)
Y	GMT (95% CI)[c]	43.5 (39.7, 47.6)	10.0 (8.7, 11.4)	296 (268, 327)	186 (158, 219)
W	GMT (95% CI)[c]	57.9 (52.7, 63.7)	9.0 (7.9, 10.3)	387 (352, 426)	175 (149, 206)
A	% with hSBA ≥1:8 (95% CI)[d]	62.8% (58.8, 66.6)	46.5% (40.5, 52.5)	87.7% (84.9, 90.1)	88.2% (83.9, 91.6)

Sero-group	Endpoint	Pre-4th Dose MenQuadfi Subgroup 1a[a] N=607-619	Pre-4th Dose Menveo Subgroup 2a[b] N=282-288	Post-4th Dose MenQuadfi Subgroup 1a[a] N=607-655	Post-4th Dose Menveo Subgroup 2a[b] N=282-305
C	% with hSBA ≥1:8 (95% CI)[d]	93.1% (90.8, 95.0)	30.6% (25.3, 36.4)	99.4% (98.4, 99.8)	93.3% (89.9, 95.9)
Y	% with hSBA ≥1:8 (95% CI)[d]	96.2% (94.4, 97.6)	67.9% (62.2, 73.3)	99.1% (98.0, 99.7)	98.6% (96.6, 99.6)
W	% with hSBA ≥1:8 (95% CI)[d]	97.1% (95.4, 98.3)	61.5% (55.6, 67.1)	99.4% (98.4, 99.8)	99.0% (97.2, 99.8)

Source: Adapted from STN 125701/262, Study Met42 Clinical Study Report, Table 8.113, 8.115. Data cutoff 08MAR2024.
Abbreviations: hSBA=serum bactericidal activity using human complement; PPAS3=Per Protocol Analysis Set 3; GMT=geometric mean titer; N=number of participants in relevant per protocol analysis set with valid serology results for the particular serogroup and time point
Notes:
a Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. hSBA titers assessed before and 30 days after the 4th dose of MenQuadfi administered at 12-15 months.
b Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. hSBA titers assessed before and 30 days after the 4th dose of Menveo administered at 12 months.
c 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
d 95% CI of the single proportion calculated from the exact binomial method.

The percentages of participants with ≥4-fold rise in hSBA titers from pre- to post-4th dose were similar across the two groups for serogroups A and C, and higher in the Menveo groups compared with the MenQuadfi group for serogroups Y and W (Table 11).

Table 11. Percentage of Participants with 4-Fold Rise in hSBA Titers from Pre-4th Dose to 30 Days Post- 4th Dose of MenQuadfi or Menveo, PPAS3, Study MET42

Serogroup	MenQuadfi Subgroup 1a[a] % with 4-fold rise (95% CI) N1=587-602	Menveo Subgroup 2a[b] % with 4-fold rise (95% CI) N1=272-285
A	66.3% (62.3, 70.1)	73.2% (67.5, 78.3)
C	90.3% (87.7, 92.6)	87.1% (82.6, 90.8)
Y	80.2% (76.8, 83.4)	93.1% (89.5, 95.8)
W	80.4% (77.0, 83.5)	91.9% (88.1, 94.8)

Source: Adapted from STN 125701/262, Study Met42 Clinical Study Report, Table 8.67. Data cutoff 08MAR2024.
Abbreviations: hSBA=serum bactericidal activity using human complement; PPAS3=Per Protocol Analysis Set 3; N1=number of participants in relevant per protocol analysis set with valid serology results for the particular serogroup and time point.
a Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. hSBA titers assessed before and 30 days after the 4th dose of MenQuadfi administered at 12-15 months.
b Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. hSBA titers assessed before and 30 days after the 4th dose of Menveo administered at 12 months.
d 95% CI of the single proportion calculated from the exact binomial method.

Reviewer Comment: As described in section 6.1.1, the Applicant included descriptive analyses of 4-fold rise in hSBA titers from pre-4th dose to post-4th as per CBER request. A higher percentage of Menveo recipients compared with MenQuadfi recipients achieved ≥4-fold rise in hSBA titers from pre- to post-4th dose for serogroups Y and W. As shown in Table 10, the pre-4th dose GMTs for these serogroups were higher for MenQuadfi recipients compared with Menveo recipients; thus, achieving the requisite ≥4-fold rise from pre-4th to post-4th dose in antibody response was more challenging. The post-4th dose hSBA GMTs for serogroups Y and W were higher in the MenQuadfi group compared with the Menveo group, despite the lower percentage of MenQuadfi recipients who achieved a 4-fold rise for these 2 serogroups compared with Menveo recipients. Overall, a 4-dose series of MenQuadfi elicited similar or higher hSBA titers against the 4 meningococcal serogroups compared with

a 4-dose series of Menveo. These results support the primary analysis of hSBA seroresponse post-4th dose relative to baseline.

Descriptive Analyses of hSBA Titers and Seroresponse Rates Post- 3rd Dose (Secondary Objective #3 and Secondary Objective #5):

hSBA GMTs and seroresponse rates 30 days after the 3rd dose (administered at 6 months of age) of MenQuadfi or Menveo are shown in Table 12. For all 4 serogroups, the hSBA GMTs and seroresponse rates after the 3rd dose were higher in the MenQuadfi group compared with the Menveo group. Analyses of these endpoints based on the PPAS2 (not shown) are similar to those based on PPAS1.

Table 12. hSBA Geometric Mean Titers and Vaccine Seroresponse Rate at 30 Days After the 3rd Dose of MenQuadfi or Menveo, PPAS1, Study MET42

Serogroup	Endpoint	MenQuadfi Group 1 N=682-883	Menveo Group 2 N=322-438
A	GMT (95% CI)[a]	25.3 (22.7, 28.3)	15.1 (13.0, 17.5)
C	GMT (95% CI)[a]	391 (356, 428)	53.0 (45.9, 61.1)
Y	GMT (95% CI)[a]	88.1 (81.1, 95.7)	40.6 (35.8, 46.0)
W	GMT (95% CI)[a]	98.1 (91.1, 106)	48.7 (43.1, 55.1)
A	Seroresponse rate % (95% CI)[b]	64.4% (60.6, 68.0)	50.6% (45.0, 56.2)
C	Seroresponse rate % (95% CI)[b]	96.4% (94.7, 97.6)	82.8% (78.4, 86.7)
Y	Seroresponse rate % (95% CI)[b]	88.7% (86.2, 91.0)	81.8% (77.4, 85.8)
W	Seroresponse rate % (95% CI)[b]	92.8% (90.7, 94.6)	85.6% (81.6, 89.1)

Source: Adapted from STN 125701/262, Study Met42 Clinical Study Report, Table 8.103, 8.109 Data cutoff 08MAR2024.
Abbreviations: hSBA=serum bactericidal activity using human complement; PPAS1=Per Protocol Set 1; GMT=geometric mean titer; N=number of participants in relevant per protocol analysis set with valid serology results for the particular serogroup and time point
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer < 1:8, then post-3rd dose vaccinations titer must be ≥1:16; and if prevaccination hSBA titer ≥ 1:8, then post-3rd dose vaccination titer ≥4-fold increase from prevaccination titer.
Group 1: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-18 months of age. hSBA titer obtained 30 days post-3rd dose of MenQuadfi administered at 6 months of age.
Group 2: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. hSBA titer obtained 30 days post-3rd dose of Menveo administered at 6 months of age.
a 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
b 95% CI of the single proportion calculated from the exact binomial method.

Reviewer Comment**:** The higher post-3rd dose geometric mean titer (GMT) and seroresponse rates observed in the MenQuadfi group compared with the Menveo group support the primary analyses. The numerically higher hSBA titers post-3rd dose (Table 8) and pre-4th dose (Table 10) in the MenQuadfi group compared with the Menveo group for all 4 serogroups (most prominently for serogroups C, W, and Y), provides evidence that MenQuadfi likely elicits durable immune responses following the 3rd dose at 6 months of age until the 2nd year of life dose.

Concomitant Pediatric Vaccine Analyses

Non -Inferiority Analyses-Concomitant Pediatric Vaccines (Secondary Objective #1):

Hepatitis B, H. influenzae b, Poliovirus, Rotavirus, Pertussis, and Pneumococcal Antigens

Noninferior immune responses of the concomitantly administered vaccines were demonstrated 30 days after the 6- month vaccinations for anti-hepatitis B surface antigen antibody (Ab), anti-PRP Ab, anti-poliovirus (Types 1, 2 and 3) Ab, anti-rotavirus serum IgA Ab, anti-pertussis Ab, and anti-pneumococcal Ab for all 13 serotypes (Table 13).

Table 13. Concomitant Vaccination Response Rates[#] and GMCs, 30 Days after 6-Month Vaccination, PPAS1, Study MET42

Antigen and Associated Endpoint	MenQuadfi Group 1 % (95% CI) GMC (95% CI) N=663-906	Menveo Group 2 % (95% CI) GMC (95% CI) N=321-444	Difference [MenQuadfi – Menveo] (95% CI) GMC Ratio [MenQuadfi/Menveo] (95% CI)	MET Non-Inferiority* (Yes/No)
Hepatitis B	--	--	--	--
% ≥10 mIU/mL	98.6 (97.4, 99.3)	98.0 (95.9, 99.2)	0.57 (-0.95, 2.75)	Yes
PRP	--	--	--	--
% ≥0.15 µg/mL	99.0 (98.1, 99.5)	96.4 (94.2, 98.0)	2.55 (0.89, 4.84)	Yes
% ≥1.0 µg/mL	91.3 (89.2, 93.0)	85.7 (82.0, 88.9)	5.56 (1.90, 9.60)	Yes
Polio	--	--	--	--
Type 1 % ≥1.8	100 (99.6, 100)	100 (99.1, 100)	0 (-0.46, 0.92)	Yes
Type 2 % ≥1.8	100 (99.6, 100)	100 (99.1, 100)	0 (-0.46, 0.94)	Yes
Type 3 % ≥1.8	100 (99.6, 100)	100 (99.1, 100)	0 (-0.45, 0.92)	Yes
Rotavirus	--	--	--	--
% ≥3-fold rise	91.0 (88.5, 93.0)	92.8 (89.4, 95.4)	-1.88 (-5.26, 2.00)	Yes
GMC	272 (244, 303)	308 (264, 360)	0.881 (0.728, 1.07)	Yes
Pertussis	--	--	--	--
PT GMC	75.8 (72.2, 79.6)	78.6 (72.8, 84.9)	0.964 (0.880, 1.06)	Yes
FHA GMC	95.7 (90.9, 101)	98.6 (91.7, 106)	0.970 (0.887, 1.06)	Yes
PRN GMC	39.4 (36.8, 42.3)	42.1 (37.9, 46.6)	0.938 (0.830, 1.06)	Yes
FIM GMC	309 (291, 330)	311 (284, 341)	0.996 (0.892, 1.11)	Yes
Pneumococcal	--	--	--	--
Serotype 1 GMC	2.26 (2.13, 2.40)	1.93 (1.77, 2.12)	1.17 (1.05, 1.30)	Yes
Serotype 3 GMC	0.607 (0.577, 0.638)	0.544 (0.505, 0.585)	1.12 (1.02, 1.22)	Yes
Serotype 4 GMC	1.46 (1.40, 1.53)	1.33 (1.24, 1.42)	1.10 (1.01, 1.19)	Yes
Serotype 5 GMC	1.54 (1.46, 1.63)	1.26 (1.15, 1.37)	1.23 (1.11, 1.36)	Yes
Serotype 6A GMC	4.01 (3.82, 4.22)	3.34 (3.09, 3.62)	1.20 (1.09, 1.32)	Yes
Serotype 6B GMC	2.47 (2.29, 2.67)	1.97 (1.75, 2.21)	1.26 (1.09, 1.44)	Yes
Serotype 7F GMC	3.48 (3.32, 3.64)	3.40 (3.18, 3.63)	1.02 (0.946, 1.11)	Yes
Serotype 9V GMC	1.88 (1.78, 1.99)	1.61 (1.48, 1.74)	1.17 (1.06, 1.29)	Yes
Serotype 14 GMC	6.95 (6.53, 7.41)	7.17 (6.58, 7.81)	0.970 (0.870, 1.08)	Yes
Serotype 18C GMC	1.95 (1.86, 2.04)	1.82 (1.69, 1.96)	1.07 (0.983, 1.16)	Yes
Serotype 19A GMC	2.21 (2.10, 2.32)	2.00 (1.86, 2.14)	1.10 (1.01, 1.20)	Yes
Serotype 19F GMC	3.36 (3.21, 3.52)	2.98 (2.77, 3.21)	1.13 (1.03, 1.23)	Yes
Serotype 23F GMC	1.59 (1.49, 1.69)	1.30 (1.18, 1.44)	1.22 (1.09, 1.37)	Yes

Source Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Tables 8.39, 8.41, 8.43, 8.45, 8.47, 8.49, 8.51. Data cutoff 08MAR2024. Abbreviations: #: Percentage of participants achieving the endpoint specific antibody level. N=number of participants in per-protocol analysis set 1, for infant vaccinations; CI=confidence interval, GMC=geometric mean concentration; PPAS1: per protocol analysis set 1. Notes: Group 1: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-18 months of age. Immune responses obtained 30 days post-3rd dose of MenQuadfi concomitantly administered with recommended vaccines at 6 months of age. Group 2: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Immune responses obtained 30 days post-3rd dose of Menveo concomitantly administered with recommended vaccines at 6

months of age. 95% CI is calculated by the exact binomial method for the single proportion, the Wilson Score method without continuity correction for the difference, and normal distribution on log10(concentration) following by antilog transformation for GMC. *Non-inferiority criterion for each antigen: Measles, mumps, rubella and varicella: the lower limit of the 2-sided 95% CI is > -10%; Pertussis: the lower limit of the 2-sided 95% CI is > 2/3 for all four antigens; Pneumococcal: the lower limit of the 2-sided 95% CI is >1/2 for all thirteen serotypes.

Reviewer Comment:

1. Following the 3rd dose of Prevnar 13 (PCV13) when administered with MenQuadfi compared with Menveo, noninferior anti-pneumococcal GMCs were demonstrated for all 13 pneumococcal serotypes tested, including serotypes 6B and 23F. The current Menveo USPI includes description of a study evaluating Menveo administered as a 4-dose series (2, 4, 6, and 12 months) when concomitantly administered with recommended infant vaccinations (RIVs), including Prevnar 7 (PCV7). Section 14.3 (Immunogenicity of Concomitantly Administered Vaccines) of the Menveo USPI states that immune interference was suggested for pneumococcal serotypes 6B and 23F when PCV7 was administered concomitantly with Menveo after the 3rd dose, but that interference was not observed following the 4th dose. Because Menveo was the comparator group used in study MET42, potential immune interference between Menveo and serotypes 6B/23F of PCV13 (shared serotypes in PCV7) may limit the interpretability of the noninferiority immunogenicity analyses of MenQuadfi with PCV13. However, for both pneumococcal serotypes 6B and 23F, GMCs were numerically higher after the 3rd dose in the MenQuadfi group compared with the Menveo group, which supports the lack of immune interference.
2. The immune responses following 3 doses of a rotavirus vaccine when administered with MenQuadfi compared with when administered with Menveo met the noninferiority success criteria. However, because serum IgA immune responses are not considered adequate to evaluate for immune interference, the significance of this analysis on the effectiveness of rotavirus vaccine is not known. These data regarding concomitant vaccination with the rotavirus vaccine will not be described in Section 14.3 of the MenQuadfi PI.

Measles, Mumps, Rubella, Varicella, and Pneumococcal Antigens

Noninferior immune responses of the concomitantly administered vaccines were demonstrated 30 days after the 12- month vaccinations for anti-measles Ab, anti-mumps Ab, anti-rubella Ab, anti-varicella Ab, and anti-pneumococcal Ab for all 13 serotypes (Table 14).

Table 14. Concomitant Vaccination Response Rates# and GMCs, 30 Days after 12-Month Vaccinations, PPAS 3, Study MET42

Antigen and Associated Endpoint	MenQuadfi Subgroup 1a[a] % (95% CI) GMC (95% CI) N=649-797	Menveo Subgroup 2a[b] % (95% CI) GMC (95% CI) N=298-391	Difference [MenQuadfi – Menveo] % (95% CI) GMC Ratio [MenQuadfi/Menveo] (95% CI)	Met Non-Inferiority* (Yes/No)
Measles	--	--	--	--
% ≥255 mIU/mL	97.6 (96.1, 98.6)	97.3 (94.8, 98.8)	0.24 (-1.73, 2.90)	Yes
Mumps	--	--	--	--
% ≥10 mumps Ab units/mL	95.5 (93.6, 96.9)	97.7 (95.3, 99.1)	-2.22 (-4.44, 0.53)	Yes
Rubella	--	--	--	--
% ≥10 IU/mL	97.9 (96.5, 98.8)	98.0 (95.7, 99.3)	-0.12 (-1.89, 2.32)	Yes

Antigen and Associated Endpoint	MenQuadfi Subgroup 1a[a] % (95% CI) GMC (95% CI) N=649-797	Menveo Subgroup 2a[b] % (95% CI) GMC (95% CI) N=298-391	Difference [MenQuadfi – Menveo] % (95% CI) GMC Ratio [MenQuadfi/Menveo] (95% CI)	Met Non-Inferiority* (Yes/No)
Varicella	--	--	--	--
% ≥5 gpELISA units/mL	96.4 (94.7, 97.7)	94.7 (91.5, 96.9)	1.69 (-0.96, 5.05)	
Pneumococcal	--	--	--	--
Serotype 1 GMC	3.81 (3.56, 4.08)	3.44 (3.12, 3.81)	1.11 (0.980, 1.25)	Yes
Serotype 3 GMC	0.771 (0.728, 0.817)	0.751 (0.690, 0.818)	1.03 (0.927, 1.14)	Yes
Serotype 4 GMC	2.08 (1.95, 2.22)	2.00 (1.83, 2.18)	1.04 (0.933, 1.16)	Yes
Serotype 5 GMC	2.70 (2.53, 2.88)	2.46 (2.25, 2.69)	1.10 (0.980, 1.23)	Yes
Serotype 6A GMC	9.65 (9.09, 10.2)	9.51 (8.72, 10.4)	1.01 (0.912, 1.13)	Yes
Serotype 6B GMC	7.41 (6.92, 7.93)	6.37 (5.77, 7.03)	1.16 (1.03, 1.31)	Yes
Serotype 7F GMC	5.40 (5.08, 5.73)	6.04 (5.56, 6.55)	0.894 (0.806, 0.992)	Yes
Serotype 9V GMC	3.53 (3.31, 3.77)	3.62 (3.30, 3.96)	0.976 (0.871, 1.09)	Yes
Serotype 14 GMC	7.80 (7.26, 8.38)	9.20 (8.37, 10.1)	0.847 (0.752, 0.954)	Yes
Serotype 18C GMC	2.60 (2.44, 2.78)	2.92 (2.68, 3.19)	0.890 (0.799, 0.992)	Yes
Serotype 19A GMC	6.19 (5.82, 6.59)	5.86 (5.32, 6.45)	1.06 (0.945, 1.18)	Yes
Serotype 19F GMC	6.49 (6.11, 6.90)	6.01 (5.45, 6.62)	1.08 (0.967, 1.21)	Yes
Serotype 23F GMC	3.88 (3.60, 4.17)	3.41 (3.09, 3.78)	1.14 (0.999, 1.29)	Yes

Source Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Tables 8.53, 8.55, 8.57. Data cutoff 08MAR2024.
Abbreviations: #: Percentage of participants achieving the endpoint specific antibody level N=number of participants in per-protocol analysis set 3, for 2nd year of life vaccinations; CI=confidence interval, GMC=geometric mean concentration.
Notes: a- Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. Immune responses assessed 30 days after the 4th dose of MenQuadfi administered concomitantly with recommended vaccines at 12-15 months.
b- Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Immune responses assessed 30 days after the 4th dose of Menveo administered concomitantly with recommended vaccines at 12 months.
*Non-inferiority criterion for each antigen: measles, mumps, rubella and varicella: the lower limit of the 2-sided 95% CI is > -10%; Pneumococcal: the lower limit of the 2-sided 95% CI is > 1/2 for all thirteen serotypes.
95% CI is calculated by the exact binomial method for the single proportion, the Wilson Score method without continuity correction for the difference, and normal distribution on log10(concentration) following by antilog transformation for GMC.

Reviewer Comment: Non-inferiority criterion for the measles, mumps, and rubella and varicella was the lower limit of the 2-sided 95% CI >-10%, which was met for all three endpoints. Notably, if the more stringent CBER recommended criterion was applied (i.e., >-5%), then noninferiority would also have been met.

H.influenzae b, Poliovirus, Pertussis

Noninferior immune responses of the concomitantly administered vaccines were demonstrated 30 days after the 15- month vaccinations for anti-PRP Ab, anti-poliovirus (types 1, 2, and 3) Ab, and anti-pertussis Ab (Table 15).

Table 15. Concomitant Vaccination Response Rates[#], 30 Days after 15-Month Vaccinations, Per-Protocol Analysis Set 3, Study MET42

Antigen and Associated Endpoint	MenQuadfi Subgroup 1b[a] % (95% CI) N=273-297	Menveo Subgroup 2b[b] % (95% CI) N=121-125	Difference [MenQuadfi – Menveo] % (95% CI)	MET Non-Inferiority* (Yes/No)
PRP	--	--	--	--
% ≥1.0 µg/mL	98.3 (96.1, 99.5)	98.4 (94.3, 99.8)	-0.08 (-2.57, 4.08)	Yes
Polio	--	--	--	--
Type 1 % ≥1.8	100 (98.7, 100)	100 (97.0, 100)	0 (-1.33, 3.05)	Yes
Type 2 % ≥1.8	100 (98.7, 100)	100 (97.0, 100)	0 (-1.30, 3.05)	Yes
Type 3 % ≥1.8	100 (98.7, 100)	100 (97.0, 100)	0 (-1.31, 3.05)	Yes
Pertussis[c]	--	--	--	--
PT response %[a]	98.5 (96.3, 99.6)	98.3 (94.2, 99.8)	0.19 (-2.35, 4.46)	Yes
FHA response %[a]	96.7 (93.8, 98.5)	96.7 (91.8, 99.1)	0.01 (-3.48, 5.14)	Yes
PRN response %[a]	96.3 (93.4, 98.2)	97.5 (92.9, 99.5)	-1.18 (-4.55, 3.67)	Yes
FIM response %[a]	98.2 (95.8, 99.4)	97.5 (92.9, 99.5)	0.65 (-2.24, 5.32)	Yes

Source Adapted from STN 125701/262, Study MET42 Clinical Study Report, Tables 8.59, 8.61, 8.63. Data cutoff 08MAR2024.
Abbreviations: #: Percentage of participants achieving the endpoint specific antibody level, N=number of participants in per-protocol analysis set 3, for 2nd year of life vaccinations; CI=confidence interval, GMC=geometric mean concentration.
Notes: Per protocol analysis set 3 included all randomized participants with no relevant protocol deviations who received ≥ 1 dose of the study vaccine in the 2nd year of life (≥12 months of age) and had a valid post-vaccination serology result in the 2nd year of life. 95% CI is calculated by the exact binomial method for the single proportion and the Wilson Score method without continuity correction for the difference.
a. Subgroup 1b: MenQuadfi at 2, 4, 6, and 15-18 months of age and recommended vaccines at 2, 4, 6, 12-15 months of age. Immune responses assessed 30 days after the 4th dose of MenQuadfi administered concomitantly with recommended vaccines at 15-18 months
b. Subgroup 2b: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Participants in Group 2b received the 4th dose of Menveo at 12 months of age; these data reflect immune responses after routine vaccine administration alone at 15-18 months.
c. Pertussis response is defined as a participant with a pre-4th dose vaccinations < LLOQ, then post-4th dose vaccinations should be ≥4x the LLOQ.
*Non-inferiority criterion for each antigen: PRP: the lower limit of the 2-sided 95% CI is > -10%; Polio: the lower limit of the 2-sided 95% CI is > -5% for all three serotypes; Pertussis: the lower limit of the 2-sided 9% CI is > -10% for all four antigens.

Reviewer Comment: Each of the 16 hypothesis-tested secondary analyses evaluating immune interference met their noninferiority criteria for success. These data will be included in Section 14.3 of the MenQuadfi PI to support concomitant administration with routinely recommended pediatric vaccines.

Subgroup 1b received MenQuadfi at 15 months of age along with DTaP-IPV/Hib and Hepatitis A vaccines, while Subgroup 1b received only DTaP-IPV/Hib and Hepatitis A at the 15 month visit. Therefore, the immune responses to DTaP-IPV/Hib when administered concomitantly with Hepatitis A and the 4th dose of MenQuadfi at 15 months were compared to DTaP-IPV/Hib administered with Hepatitis A but without Menveo. This analysis was a more direct assessment for immune interference compared with a noninferiority comparison against the same concomitant vaccines when administered with Menveo.

Descriptive Analyses of Concomitant Pediatric Vaccines GMC Responses and Seroresponse (Secondary Objective #4):

The antibody (GMC) responses for each antigen in the concomitant vaccines were assessed 30 days after the 6-month vaccination (*H.influenzae b,* diphtheria, tetanus, hepatitis B, poliovirus, rotavirus, pertussis, pneumococcal), 30 days after 12-month vaccination (measles, mumps, rubella, varicella, pneumococcal), and 30 days after the 15-month vaccination (*H.influenzae b*, diphtheria, tetanus, poliovirus, pertussis). The antibody responses of concomitant

recommended pediatric vaccines administered with MenQuadfi or Menveo in infants and toddlers were comparable across groups.

Tetanus and Diphtheria

- Anti-diphtheria antibody concentrations (including ≥ 0.01 IU/mL and ≥ 0.1 IU/mL) were assessed at the following time points:
    - Post 3rd dose (6-month vaccinations for Group 1 and Group 2):
    - GMCs were similar across MenQuadfi and Menveo recipients and 100% of participants in both groups achieved anti-diphtheria Ab concentrations ≥ 0.01 IU/mL. 98.7% of MenQuadfi recipients and 98.6% of Menveo recipients achieved Ab concentrations ≥ 0.1 IU/mL.
    - Post 4th dose (15-month vaccinations for Subgroups 1b and 2b):

      GMCs were comparable across MenQuadfi recipients and those receiving concomitant vaccines only (DTaP-IPV/Hib and Hepatitis A), and 100% of participants in both groups achieved anti-diphtheria Ab concentrations ≥ 0.01 IU/mL. The percentages of participants with Ab concentrations ≥ 1.0 IU/mL were similar across groups (MenQuadfi: 96.7% and concomitant vaccines alone: 96.8%).
- Anti-tetanus antibody concentrations (including ≥ 0.01 IU/mL, ≥ 0.1 IU/mL) were assessed at the following timepoints:
    - Post 3rd dose (6-month vaccinations for Group 1 and Group 2):
    - GMCs were comparable across groups and 100% of participants in both groups achieved anti-tetanus Ab concentrations ≥ 0.01 IU/mL. 99.7% of MenQuadfi recipients and 100% of Menveo recipients achieved Ab concentrations ≥ 0.1 IU/mL.
    - Post 4th dose (15-month vaccinations for Subgroups 1b and 2b):
    - GMCs were similar across groups. The percentages of participants with anti-tetanus Ab concentrations ≥ 0.1 IU/mL and ≥ 1.0 IU/mL were similar (MenQuadfi: 99.7% and 98.7%, respectively; concomitant vaccines alone: 100% and 97.6%, respectively).

  Reviewer Comment: MenQuadfi contains tetanus toxoid protein carrier conjugated to the meningococcal polysaccharide antigens. Anti-tetanus antibody GMCs and the percentage of participants with anti-tetanus antibody concentrations ≥0.01 IU/mL or ≥0.1 IU/mL were similar among participants who received DTaP-IPV/Hib administered with MenQuadfi compared with participants who received DTaP-IPV/Hib concomitantly administered with Menveo or participants who received DTaP-IPV/Hib without MenQuadfi or Menveo. These data indicate that the tetanus toxoid conjugate did not have substantial impact on anti-tetanus antibody levels or lead to immune interference.

6.1.11.1 Subgroup Analyses

Immunogenicity results were comparable across groups for male and female participants and participants of different races.

Subgroup Analyses Based on Baseline Pre-Dose 1 hSBA Titers (<1:8 and ≥1:8)

The percentage of participants with pre-dose 1 hSBA titers <1:8 (baseline) was comparable across the MenQuadfi and Menveo groups. The percentage of all PPAS3 study participants with serogroup specific hSBA titers <1:8 at baseline included the following:

- Serogroup A: 85.1%- 86.6%

- Serogroup C: 89.3- 89.4%
- Serogroup Y: 84.4%- 85.4%
- Serogroup W: 88.1%- 89.6%

Table 16 provides the percentage of participants achieving hSBA vaccine seroresponse based on pre-dose 1 hSBA titers <1:8 or ≥1:8. For all serogroups, seroresponse rates were lower in participants with pre-dose 1 titers ≥1:8 compared to those with pre-dose 1 titers <1:8. For participants with pre-dose 1 hSBA titers <1:8, seroresponse rates were similar for Serogroups A, Y, W across MenQuadfi and Menveo groups, and higher in MenQuadfi recipients for Serogroup C. For participants with pre-dose 1 hSBA titers ≥1:8, seroresponse rates similar across MenQuadfi and Menveo recipients for all 4 serogroups.

Table 16. Descriptive Analyses of Vaccine Seroresponse Rate 30 Days After the 4th Dose, by Pre-Dose 1 hSBA Titer (<1:8 and ≥1:8), PPAS3, MET42

Sero-group	MenQuadfi Subgroup 1a Pre-Dose 1 hSBA Titer <1:8 SRR % (95% CI) N=426-480	Menveo Subgroup 2a Pre-Dose 1 hSBA Titer <1:8 SRR % (95% CI) N =193-225	MenQuadfi Subgroup 1a Pre-Dose 1 hSBA Titer ≥1:8 SRR % (95% CI) N =56-82	Menveo Subgroup 2a Pre-Dose 1 hSBA Titer ≥1:8 SRR % (95% CI) N =25-34
A	82.4 (78.4, 85.9)	81.3 (75.1, 86.6)	62.7 (50.7, 73.6)	53.3 (34.3, 71.7)
C	99.2 (97.9, 99.8)	90.6 (85.8, 94.1)	78.6 (65.6, 88.4)	69.2 (48.2, 85.7)
Y	98.9 (97.4, 99.6)	97.0 (93.6, 98.9)	82.9 (73.0, 90.3)	64.7 (46.5, 80.3)
W	99.2 (97.9, 99.8)	97.8 (94.9, 99.3)	85.0 (73.4, 92.9)	84.0 (63.9, 95.5)

Source: STN 125701/262, Amendment 40, Table 2.1, 2.2
Abbreviations: N =number of participants with valid serology results; PPAS3=per protocol analysis set 3; hSBA=serum bactericidal activity using human complement; SRR=seroresponse rate
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer <1:8, then post-4th dose vaccinations titer must be ≥1:16; and if prevaccination hSBA titer ≥1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer.
Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. Immune responses assessed 30 days after the 4th dose of MenQuadfi administered concomitantly with recommended vaccines at 12-15 months.
Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Immune responses assessed 30 days after the 4th dose of Menveo administered concomitantly with recommended vaccines at 12 months.

Reviewer Comment:
As described above, the vast majority of enrolled 2-month-old infants had hSBA titer levels <1:8 prior to receipt of dose 1, suggesting minimal anti-meningococcal maternal antibodies for these participants. A minority of participants across groups had hSBA titers at baseline ≥1:8, potentially suggestive of fetal transmission of maternal antibodies. Across both the MenQuadfi and Menveo groups, infants with baseline hSBA titers <1:8 achieved seroresponse (post-4th dose hSBA titers ≥1:16) at higher rates compared with infants with hSBA titers ≥1:8, which required at least 4-fold rise in hSBA titer levels post-4th dose from pre-dose 1.

Irrespective of baseline status, MenQuadfi vaccine effectiveness against each serogroup was demonstrated in the primary analyses evaluating the percentage of participants who achieved an hSBA titer ≥1:8 following the 3rd dose administered at 6 months of age when compared to Menveo (Table 8). Descriptive analyses of this endpoint following the 4th dose administered at either 12-15 months or 15-18 months (Table 9) show that hSBA titers of ≥1:8 were achieved by ~87% to 93% of participants against serogroup A, and ~99% to 100% of participants against serogroups C, Y, and W.

Subgroup Analyses *for Preterm Infants*

Descriptive subgroup analyses of the primary immunogenicity endpoints (seroresponse rate after the 4th dose and hSBA titers ≥1:8 after the 3rd dose) showed no notable differences between the preterm infants and full-term infants (Table 17 and Table 18).

Table 17. Subgroup Analyses of hSBA Vaccine Seroresponse Rate After the 4th Dose, by Preterm and Full-Term MenQuadfi Recipients, PPAS3, MET42

Serogroup	Participants Born Preterm MenQuadfi Subgroup 1a N=27-35 SRR % (95% CI)	Participants Born Full-term MenQuadfi Subgroup 1a N=474-505 SRR % (95% CI)
A	77.8 (57.7; 91.4)	79.5 (75.6; 83.1)
C	97.1 (84.7; 99.9)	97.0 (95.1; 98.3)
Y	100 (89.4; 100)	96.1 (94.0; 97.6)
W	100 (90.0; 100)	97.4 (95.6; 98.6)

Source: STN 125701/262, MET 42 Appendix 15, Table 65
Abbreviations: N=number of participants with valid serology results; PPAS3=per protocol analysis set 3; hSBA=serum bactericidal activity using human complement;
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer <1:8, then post-4th dose vaccinations titer must be ≥1:16; and if prevaccination hSBA titer ≥1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer.
Group 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. Seroresponse rate based on hSBA titer obtained 30 days post-4th dose of MenQuadfi administered at 12-15 months of age.
Preterm: born at gestational age <37 weeks; full-term: born at gestational age ≥37 weeks
For one participant, gestational age was not collected.

Table 18. Subgroup Analyses of Percentage of Participants With hSBA Titer ≥1.8, by Preterm and Full-Term MenQuadfi Recipients, 30 Days After the 3rd Dose, PPAS1, MET42

Serogroup	Participants Born Preterm MenQuadfi Group 1 N=55-63 % with hSBA ≥1:8 (95% CI)	Participants Born Full-term MenQuadfi Group 1 N=769-819 % with hSBA ≥1:8 (95% CI)
A	76.4 (63.0; 86.8)	78.0 (75.0; 80.8)
C	100 (93.7; 100)	99.0 (98.0; 99.6)
Y	98.3 (91.1; 100)	98.3 (97.1; 99.0)
W	96.8 (89.0; 99.6)	98.8 (97.8; 99.4)

Source: STN 125701/262, MET 42 Appendix 15, Table 55
Abbreviations: N=number of participants with valid serology results for the particular serogroup; hSBA=serum bactericidal activity using human complement; M=number of participants with valid serology results for the particular serogroup; PPAS1=Per protocol analysis set 1.
Notes: Group 1: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-18 months of age. hSBA titer obtained 30 days post-3rd dose of MenQuadfi administered at 6 months of age.
Preterm: born at gestational age <37 weeks; full-term: born at gestational age ≥37 weeks
For one participant, gestational age was not collected.

Reviewer Comment: Although there were no notable differences in the immunogenicity data across the preterm and term infants, the sample sizes of preterm infants included in the relevant per protocol analysis sets were small and limit the interpretation of these results. In addition, the majority of the preterm infants were late preterm, limiting the generalizability of these immunogenicity results to all infants born preterm, especially infants born <31 weeks of gestational age since this population was not included in the study.

6.1.12 Safety Analyses

The Overall Safety Analysis Set for Any Dose (SafAS) included 1,727 participants who received MenQuadfi and 867 participants who received Menveo, of whom 80% and 75.8%, respectively,

completed at least 6 months of safety follow-up post-last vaccination. 1,375 MenQuadfi recipients and 705 Menveo recipients received a full 4-dose series.

6.1.12.1 Methods

See section 6.1.2 above.

6.1.12.2 Overview of Adverse Events

Table 19 summarizes solicited ARs and unsolicited AEs reported in the study for the MenQuadfi and Menveo groups. Rates of solicited ARs within 7 days and unsolicited AEs within 30 days were generally comparable across study groups. Through the entire study period of 6 months after the last dose, the percentages of participants reporting any MAAEs and AEs leading to discontinuation were balanced across the two groups. Through the entire study period, AESIs and SAEs were reported by 0.8% and 5.7% of MenQuadfi recipients, respectively, compared with 0.6% and 4.4% of Menveo recipients, respectively.

Table 19. Percentages of Participants Reporting at Least One Adverse Event Following Vaccination, Overall Safety Analysis Set, Any Dose*, Study MET42

AE Type: Monitoring Period[a]	MenQuadfi Group 1 N=1727 % (n/N1)	Menveo Group 2 N=867 % (n/N1)
Immediate AE*: within 30 minutes	<0.1 (1/1727)	0.1 (1/867)
Solicited local AR[b] at injection site of MenQuadfi or Menveo: within 7 days	71.7 (1176/1641)	71.0 (590/831)
Grade 3 solicited local AR	9.4 (154/1641)	9.0 (75/831)
Solicited systemic AR[c]: within 7 days	80.0 (1313/1642)	81.9 (681/831)
Grade 3 solicited systemic AR	18.3 (300/1642)	17.9 (149/831)
Unsolicited AEs* within 30 days	53.9 (930/1727)	53.9 (467/867)
Severe AEs	4.2 (73/1727)	3.9 (34/867)
Related[d] AEs	5.4 (94/1727)	6.3 (55/867)
MAAEs: Entire study period	60.8 (1050/1727)	60.7 (526/867)
Related[d] MAAEs	0.3 (6/1727)	0.3 (3/867)
AESIs: Entire study period	0.8 (13/1727)	0.6 (5/867)
Related[d] AESIs	<0.1 (1/1727)[e]	0 (0/867)
SAEs: Entire study period	5.7 (99/1727)	4.4 (38/867)
Related[d] SAEs	<0.1 (1/1727)	0.1 (1/867)
Deaths: Entire study period	<0.1 (1/1727)	0 (0/867)
Related[d] deaths	0 (0/1727)	0 (0/867)
AEs leading to withdrawal: Entire study period	0.1 (2/1727)	0.1 (1/867)

Source: Adapted from STN 125701/262.2, Study MET42 Clinical Study Report, Tables 8.137, 8.144, 8.250, 8.306, 8.320, 8.329, 8.332. Data cutoff 08MAR2024.
Abbreviations: AE=adverse event; AR=adverse reaction; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=number of participants in overall safety analysis set for any dose; N1=number of participants with available data for the relevant endpoint; n=number of participants experiencing the endpoint listed in the first column; percentages based on N1.
Notes:
*AEs include all unsolicited events, including events classified as unsolicited AR
b. Solicited local reactions included injection site tenderness, erythema and swelling.
c. Solicited systemic reactions included fever, vomiting, crying abnormal, drowsiness, appetite lost, irritability.
d. Relatedness to study vaccine as determined by principal investigator
e. This AESI was initially assessed as related by the investigator. After the data cutoff, the final investigator assessment was changed to unrelated.
Participants were allocated to the vaccine groups as received at the first dose.

6.1.12.3 Solicited Adverse Reactions *(ARs)*

As described in section 6.1.7, solicited local and systemic ARs through 7 days postvaccination were collected via diary cards and entered into the case report form (CRF) after investigator review of the diary card with the parent/guardian at the subsequent study visit, approximately 1-2 months after each vaccination. In the MenQuadfi group, 71.7% of participants reported one or more solicited local AR within 7 days after any dose and 80% experienced one or more solicited systemic AR within 7 days after any dose. The percentage of participants in the Menveo group reporting one or more solicited local and systemic ARs were comparable.

Solicited Local Adverse Reactions

Table 20 provides the reported rates of solicited local adverse reactions (at the MenQuadfi or Menveo injection site) in the 7 days following each study dose. The rates of solicited local ARs were generally comparable between MenQuadfi and Menveo recipients and similar across the 4 doses of the 4-dose series. The majority of solicited ARs reported were Grade 1 in severity. Tenderness was the most common local AR, reported by 67.2% of MenQuadfi recipients after any dose.

In both the MenQuadfi and Menveo groups, solicited local ARs had onset within the first 3 days after vaccination and had a duration of 1-3 days.

Table 20. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction# Within 7 Days Following Vaccination, by Maximum Severity, Relevant Safety Analysis Set*, Study MET42

Solicited Local Adverse Reaction	MenQuadfi Dose 1 Group 1 N1=1623-1625	Menveo Dose 1 Group 2 N1=823-825	MenQuadfi Dose 2 Group 1 N1=1514-1520	Menveo Dose 2 Group 2 N1=784-786	MenQuadfi Dose 3 Group 1 N1=1453-1456	Menveo Dose 3 Group 2 N1=746-749	MenQuadfi Dose 4 (12-15 Months)** Subgroup 1a N1=863-864	Menveo Dose 4 (12 Months) Subgroup 2a N1=437-438	MenQuadfi Dose 4 (15-18 Months)** Subgroup 1b N1=400-401	Pentacel (15-18 Months), Subgroup 2b N1= 199	Havrix (15-18 Months), Subgroup 2b N1=199
Any local adverse reaction, %	49.7	46.5	48.4	48.3	48.0	46.3	42.5	45.4	46.1	42.7	40.7
Grade 1	31.9	29.5	33.6	31.8	33.2	33.1	29.7	32.9	33.9	30.2	30.2
Grade 2	13.4	13.6	11.4	13.0	11.7	10.7	10.3	10.3	10.0	8.0	8.0
Grade 3	4.4	3.5	3.4	3.6	3.2	2.5	2.4	2.3	2.2	4.5	2.5
Tenderness[a], %											
Any	45.6	43.3	43.6	43.9	42.4	40.6	38.5	40.6	40.8	39.7	37.7
Grade 1	28.5	26.5	29.0	28.1	28.0	27.8	26.3	28.3	29.5	28.6	28.1
Grade 2	12.7	13.4	11.3	12.5	11.3	10.4	10.1	10.0	9.5	8.0	7.5
Grade 3	4.4	3.4	3.4	3.3	3.2	2.4	2.2	2.3	1.8	3.0	2.0
Erythema[b], %											
Any	12.5	11.4	18.3	16.3	19.5	19.7	16.2	20.6	18.7	16.1	12.1
Grade 1	12.0	10.8	18.2	15.4	19.3	19.0	15.8	20.1	17.7	13.6	11.6
Grade 2	0.5	0.5	<0.1	0.6	0.2	0.5	0.3	0.5	0.5	1.5	0
Grade 3	0	0.1	0	0.3	0	0.1	0.1	0	0.5	1.0	0.5
Swelling[b], %											
Any	9.6	9.0	12.3	10.1	12.7	13.0	10.2	15.1	12.3	14.6	11.1
Grade 1	9.0	8.4	12.1	9.2	12.4	12.1	10.1	15.1	12.3	13.1	9.5
Grade 2	0.5	0.6	0.1	0.6	0.3	0.8	0	0	0	0.5	1.0
Grade 3	<0.1	0	<0.1	0.3	0	0.1	0.1	0	0	1.0	0.5

Source Adapted from STN 125701/262, Amendment 36, Study MET42 Clinical Study Report, Tables 8.145, 8.146, 8.147, 8.148, 8.149, 8.166, 8.167, 8.168, 8.169,8.170. Data cutoff 08MAR2024.

Abbreviations: N1=number of participants in relevant safety analysis set with available data for the relevant endpoint

Notes: Concomitant vaccines administered: Pentacel was given at 2, 4, 6, and at 15 through 18 months of age; Prevnar 13 was given at 2, 4, 6, and 12 months of age; RotaTeq was given at 2, 4, and 6 months of age; Engerix- B was given at 2 and 6 months of age (first dose given 28 days prior to study); M-M-R II and Varivax were given at 12 months of age; and Havrix was given at 15 through 18 months of age.

Solicited local adverse reaction at the injection site for MenQuadfi or Menveo. For Subgroup 2b who received concomitant vaccines only at 15-18 months, these are the solicited injection site reactions for Pentacel or Havrix.

* Relevant SafAS for each dose were: SafAS1 (Dose 1), SafAS2 (Dose 2), SafAS3 (Dose 3), SafAS4 (Dose 4 for Subgroup 1a and 2a), SafAS5 (Dose 4 for Subgroup 1b and 2b).

** Both Subgroups 1a and 1b included participants who received a 4th dose of MenQuadfi at 15 to <16 months of age. In the relevant safety analysis sets, 2.2% of participants in Subgroup 1a, compared with 72.1% of participants in Subgroup 1b, were 15 to <16 months of age at the time of receipt of the 4th dose.

a. For tenderness, Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced.

b. For erythema and swelling, Grade 1: >0 to <25 mm; Grade 2: ≥25 to <50 mm; Grade 3: ≥50 mm

Solicited Systemic Adverse Reactions

Table 21 provides the rates for solicited systemic adverse reactions reported within 7 days following each vaccination. The rates of solicited systemic ARs were generally comparable between MenQuadfi and Menveo recipients. The majority of solicited ARs reported were Grade 1 or 2 in severity. For MenQuadfi recipients, the most commonly reported systemic ARs after any dose were irritability (70.3%), abnormal crying (62.4%), and drowsiness (59.4%). Fever was reported by 33.4% of MenQuadfi recipients and 35.2% of Menveo recipients after any dose. Grade 3 fever (> 39.5°C) was rare, reported by 1.7% and 2.1% of MenQuadfi and Menveo recipients, respectively, after any dose.

Percentages of participants reporting solicited ARs of vomiting, crying abnormal, drowsiness, and irritability decreased with each subsequent dose. The percentages of participants reporting appetite lost were similar across the 4 doses. Fever was most frequently reported after Dose 2, followed by Dose 3 and Dose 4 at 12-15 months. Percentages of participants reporting fever were lowest after the first dose at 2 months of age.

The rates of solicited systemic ARs were all slightly higher after the 4th dose of MenQuadfi at 12-15 months of age as compared with the 4th dose of MenQuadfi at 15-18 months of age, but comparable to the 4th dose of Menveo at 12 months of age. The percentages of participants who reported systemic ARs after the 4th dose MenQuadfi at 15-18 months of age was comparable to that of participants who received recommended vaccines (DTaP-IPV/Hib and Hepatitis A vaccines) alone at 15-18 months of age.

Most solicited systemic ARs started within the first 3 days after vaccination and resolved after 1-3 days.

Table 21. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, Relevant Safety Analysis Set*, Study MET42

Solicited Local Adverse Reaction	MenQuadfi Dose 1 Group 1 N1=1552-1627	Menveo Dose 1 Group 2 N1=789-824	MenQuadfi Dose 2 Group 1 N1=1456-1521	Menveo Dose 2 Group 2 N1=743-786	MenQuadfi Dose 3 Group 1 N1=1391-1460	Menveo Dose 3 Group 2 N1=701-748	MenQuadfi Dose 4 (12-15 Months)** Subgroup 1a N1=798-863	Menveo Dose 4 (12 Months) Subgroup 2a N1=419-439	MenQuadfi Dose 4 (15-18 Months)** Subgroup 1b N1=383-401	Pentacel and Havrix# at 15-18 Months Subgroup 2b N=184-199
Any systemic reaction, n (%)	64.8	63.3	62.9	63.5	57.9	57.9	55.2	58.5	50.1	46.2
Grade 1	30.2	30.8	28.5	28.5	26.4	28.1	29.8	28.0	28.7	29.6
Grade 2	27.4	26.1	26.3	27.2	25.2	25.1	19.6	24.8	17.2	12.1
Grade 3	7.3	6.4	8.1	7.8	6.4	4.7	5.8	5.7	4.2	4.5
Fever[a]										
Any	7.8	6.6	17.6	17.9	15.2	16.5	14.8	14.3	11.0	8.2
Grade 1	6.1	4.9	11.3	11.8	9.4	10.6	10.8	6.9	7.6	6.0
Grade 2	1.7	1.6	5.6	5.2	5.1	5.7	3.5	6.2	2.3	1.6
Grade 3	<0.1	0	0.6	0.8	0.7	0.3	0.5	1.2	1.0	0.5
Vomiting[b]										
Any	13.2	10.9	9.7	8.5	9.5	6.7	4.6	5.7	3.5	2.0
Grade 1	8.1	7.0	6.1	5.3	6.3	4.5	3.0	4.3	2.8	1.5
Grade 2	4.6	3.6	3.3	2.7	2.9	1.6	1.5	1.1	0.5	0.5
Grade 3	0.5	0.2	0.3	0.5	0.3	0.5	0.1	0.2	0.3	0
Crying abnormal[c]	--	--	--	--	--	--	--	--	--	--
Any	40.9	39.4	42.1	41.5	37.6	36.6	32.1	35.2	27.3	27.3
Grade 1	25.1	24.5	26.4	23.4	22.6	22.5	20.6	23.3	18.8	19.7
Grade 2	13.0	12.6	12.1	15.3	12.1	12.4	8.6	9.4	7.3	5.6
Grade 3	2.8	2.3	3.6	2.8	3.0	1.7	2.9	(2.5)	1.3	2.0
Drowsiness[d]										
Any	43.4	42.3	38.2	38.8	35.3	34.5	33.6	34.2	25.1	25.3
Grade 1	31.8	30.5	26.8	27.4	24.2	23.9	24.7	26	19.5	19.7
Grade 2	9.1	9.1	9.6	9.0	9.1	8.4	6.7	7.1	4.5	3.5
Grade 3	2.5	2.7	1.9	2.4	2.0	2.1	2.2	1.1	1.0	2.0
Appetite lost[e]	--	--	--	--	--	--	--	--	--	--
Any	20.5	20.4	19.9	22.9	18.9	19.0	21.8	21.5	17.3	17.7
Grade 1	15.1	14.7	14.2	17.4	13.1	14.0	16.7	16.9	14.8	14.6
Grade 2	4.5	5.0	5.1	4.6	4.9	4.1	4.2	2.5	1.8	1.5
Grade 3	0.9	0.7	0.6	0.9	1.0	0.8	0.9	2.1	0.8	1.5

Solicited Local Adverse Reaction	MenQuadfi Dose 1 Group 1 N1=1552-1627	Menveo Dose 1 Group 2 N1=789-824	MenQuadfi Dose 2 Group 1 N1=1456-1521	Menveo Dose 2 Group 2 N1=743-786	MenQuadfi Dose 3 Group 1 N1=1391-1460	Menveo Dose 3 Group 2 N1=701-748	MenQuadfi Dose 4 (12-15 Months)** Subgroup 1a N1=798-863	Menveo Dose 4 (12 Months) Subgroup 2a N1=419-439	MenQuadfi Dose 4 (15-18 Months)** Subgroup 1b N1=383-401	Pentacel and Havrix# at 15-18 Months Subgroup 2b N=184-199
Irritability[f]	--	--	--	--	--	--	--	--	--	--
Any	51.9	51.0	51.4	50.9	47.4	46.3	46.9	47	40.1	38.9
Grade 1	26.6	28.2	26.4	26.0	25.1	25.1	26.8	25.8	25.1	25.3
Grade 2	21.5	20.0	20.4	19.7	18.0	18.4	16.0	18.3	13.0	9.6
Grade 3	3.9	2.8	4.7	5.2	4.3	2.7	4.2	3.0	2.0	4.0

Source Adapted from STN 125701/262 Amendment 31, Study MET42 Clinical Study Report, Tables 8.145, 8.146, 8.147, 8.148, 8.149, 8.208, 8.209, 8.210, 8.211, 8.212. Data cutoff 08MAR2024.

Abbreviations: N1=range of participants with available data for the relevant endpoint; SafAS=Safety Analysis Set

Notes: Concomitant vaccines administered: Pentacel was given at 2, 4, 6, and at 15 through 18 months of age; Prevnar 13 was given at 2, 4, 6, and 12 months of age; RotaTeq was given at 2, 4, and 6 months of age; Engerix- B was given at 2 and 6 months of age (first dose given 28 days prior to study); M-M-R II and Varivax were given at 12 months of age; and Havrix was given at 15 through 18 months of age.

* Relevant SafAS for each dose were: SafAS1 (Dose 1), SafAS2 (Dose 2), SafAS3 (Dose 3), SafAS4 (Dose 4 for Subgroup 1a and 2a), SafAS5 (Dose 4 for Subgroup 1b and 2b).

** Both Subgroups 1a and 1b included participants who received a 4th dose of MenQuadfi at 15 to <16 months of age. In the relevant safety analysis sets, 2.2% of participants in Subgroup 1a, compared with 72.1% of participants in Subgroup 1b, were 15 to <16 months of age at the time of receipt of the 4th dose.

a. For fever, Grade 1: ≥38.0°C to ≤38.5°C or ≥100.4°F to ≤101.3°F; Grade 2: >38.5°C to ≤39.5°C or >101.3°F to ≤103.1°F; Grade 3: >39.5°C or >103.1°F

b. For vomiting, Grade 1: 1 episode per 24 hours; Grade 2: 2– 5 episodes per 24 hours; Grade 3: ≥6 episodes per 24 hours or requiring parenteral hydration

c. For crying abnormal, Grade 1: <1 hour; Grade 2: 1 - 3 hours; Grade 3: >3 hours

d. For drowsiness, Grade 1: Sleepier than usual or less interested in surroundings; Grade 2: Not interested in surroundings or did not wake up for a feed / meal; Grade 3: Sleeping most of the time or difficult to wake up

e. For appetite lost, Grade 1: Eating less than normal; Grade 2: Missed 1 or 2 feeds / meals completely; Grade 3: Refuses ≥3 feeds / meals or refuses most feeds / meals

f. For irritability, Grade 1: Easily consolable; Grade 2: Requiring increased attention; Grade 3: Inconsolable

Compared with earlier doses, the rates of late onset fever (fever starting Day 4- Day 7 postvaccination) after dose 4 were slightly higher across both the MenQuadfi and Menveo groups, though generally still low. Fever with onset starting on Day 4-7 was reported by 2.6% of MenQuadfi recipients after the 4th dose administered at 12-15 months, compared to 0.6%-0.7% after the first 3 doses. Participants in Subgroup 1b who received recommended pediatric vaccines only at 12-15 months, without MenQuadfi, had a similar higher rate of delayed onset fever (3.0%). Delayed onset fever was reported by 1.8% of MenQuadfi recipients who received the 4th dose of MenQuadfi at 15-18 months.

Reviewer Comments:

3. Overall, the reactogenicity profile for infants/toddlers vaccinated with MenQuadfi did not identify any safety signals. The rates of severe solicited systemic ARs were low and generally comparable across groups. Grade 3 (severe) fever after dose 1 administered at 2 months of age was reported by <0.1% of MenQuadfi recipients, which is reassuring as high fever in young infants often necessitates emergency room visits or hospitalizations for fever evaluation, diagnosis, and treatment. Slightly higher rates of solicited systemic adverse reactions were seen with the 4th dose of MenQuadfi when given at 12-15 months of age, compared with when the 4th dose was given at 15-18 months of age. As described above, the 12-month visit included concomitant administration of measles, mumps, and rubella vaccine (MMR), varicella, and PCV13, while the 15-18 month visit included concomitant administration of DTaP-IPV/Hib and Hepatitis A.

4. Rates of late onset fever (starting Day 4-7 postvaccination) were similar in participants receiving the 4th dose of MenQuadfi with recommended pediatric vaccines at 12-15 months of age and those who received only recommended pediatric vaccines at 12-15 months of age, suggesting that the delayed onset of fever may be related to concomitant MMR vaccination, which is known to cause delayed onset of fever.

5. The rates of fever observed in MenQuadfi recipients (7.8% to 17.6% as a range across the 4-dose series) were similar to those seen in Menveo recipients (6.6% to 17.9%) and similar to those reported in clinical trials of other approved infant vaccines administered as a 4-dose series, such as PCV15 (13.3%- 20.4%) and PCV 20 (10.3%- 17.3%).

6. Both Subgroups 1a (MenQuadfi 4th dose at 12-15 months of age) and Subgroup 1b (MenQuadfi 4th dose at 15-18 months of age) included participants who received a 4th dose of MenQuadfi at 15 to <16 months of age. In the relevant safety analysis sets, only 2.2% of participants in Subgroup 1a were 15 to <16 months of age at the time of receipt of the 4th dose and therefore this subgroup is mainly representative of participants who received a 4th dose of MenQuadfi at 12 to <15 months. In comparison, 72.1% of participants in Subgroup 1b were 15 to <16 months at the time of the receipt of the 4th dose. Subgroup 1a and 1b each had a different comparator subgroup (Subgroup 2a and 2b, respectively). Therefore, this age overlap at the time of receipt of 4th dose is unlikely to impact the interpretation of the safety data.

6.1.12.4 Unsolicited AEs

Immediate Unsolicited AEs

There was one participant in each group who experienced an immediate AE within 30 minutes post-vaccination. In the MenQuadfi group, one participant experienced infantile spitting up after the Dose 2, and in the Menveo Group, one participant experienced a rash without other symptoms after the 15 months vaccinations. Neither event was assessed as severe.

> Reviewer Comment: No participant in either the MenQuadfi or Menveo group experienced anaphylaxis or other immediate AEs concerning for a severe systemic allergic reaction.

Unsolicited AEs Within 30 Days After Vaccination

The percentage of participants with at least one unsolicited AE within 30 days after any vaccination was balanced across the MenQuadfi and Menveo groups (53.9% in both groups). The most frequently reported events by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) were *Infections and infestations* (MenQuadfi: 34.6%, Menveo: 35.2%), *General disorders and administration site conditions* (MenQuadfi: 16.9%, Menveo: 17.9%), and *Gastrointestinal disorders* (MenQuadfi: 17.5%, Menveo: 17.6%). By MedDRA PT, the most frequently reported AEs were upper respiratory tract infection (MenQuadfi: 12.4%, Menveo: 15.0%), injection site bruising (MenQuadfi 10.7%, Menveo 10.1%), and teething (MenQuadfi 6.1%, Menveo 7.2%).

Unsolicited AEs within 30 days after any dose which were assessed by the investigator as related to study vaccine were reported by 5.4% of MenQuadfi recipients and 6.3% of Menveo recipients. By MedDRA Preferred Term (PT), the most commonly reported AE assessed as related was injection site bruising, reported by 5.0% and 5.7% of MenQuadfi and Menveo recipients, respectively.

> Reviewer Comment: The reported rates and types of unsolicited adverse events were balanced across the study groups and represent medical conditions that are occur commonly in infants and toddlers. The majority of unsolicited AEs assessed as related to study vaccine were events representative of vaccine reactogenicity.

Medically Attended Adverse Events (MAAEs)

Within 30 days after any dose, MAAEs were reported by 39.9% of MenQuadfi recipients and 42.4% of Menveo recipients. Through the entire study duration of 6 months after the last vaccination, MAAEs were reported by 60.8% of MenQuadfi recipients and 60.7% of Menveo recipients. By MedDRA PT, the most commonly reported MAAEs were upper respiratory tract infection (MenQuadfi: 27.7%, Menveo 30.6%), otitis media acute (MenQuadfi 13.7%, Menveo 13.5%), and otitis media (MenQuadfi 13.7%, Menveo 15.0%). MAAEs considered related by the investigator were reported by 0.3% of participants in both the MenQuadfi and Menveo groups. The 6 MAAEs assessed as related by the investigator in the MenQuadfi group were upper respiratory tract infection, rash, urticaria, pyrexia, injection site mass, and injection site urticaria.

> Reviewer Comment: Rates and types of MAAEs were balanced across the study groups and represent illnesses that are common in infants and toddlers. The majority of MAAEs assessed as related to MenQuadfi were events representative of vaccine reactogenicity.

6.1.12.5 Deaths

Through study duration (6 months after the last vaccination dose), there was one death reported in the MenQuadfi group and no deaths reported in the Menveo group. The death occurred in a 10-week-old full-term male participant (b) (6) days after receipt of MenQuadfi dose 1, DTaP-IPV/Hib vaccine, PCV13, rotavirus vaccine, and hepatitis B vaccine. The infant was diagnosed with a cardiac arrest after being found unresponsive, not breathing, and cyanotic after being left alone in a swing by his father. Despite resuscitation efforts, the participant passed away 2 days later. The case was referred for examination by the coroner due to clinical findings suggestive of non-accidental trauma, including shoulder bruising, retinal hemorrhages, and an abnormal head CT. An autopsy was not done. His past medical history included vomiting with feeds, sometimes forcefully, that was not associated with abnormal gastrointestinal clinical findings or other symptoms (e.g., cyanosis, perspiration). The participant had no cardiac history and was gaining weight well. He had no family history of sudden cardiac death or other cardiac conditions. The death was assessed by the investigator as unrelated to the study vaccination.

> Reviewer Comment: The clinical reviewer agrees with the investigator's assessment that the death of this 10-week-old infant was most likely unrelated to the study vaccine. Although the event occurred (b) (6) days following receipt of concomitantly administered pediatric vaccines and MenQuadfi, other etiologies are supported by the events that preceded the death, in addition to the clinical physical exam findings. Sudden Unexplained Infant Death Syndrome is considered a potential cause of death because of the infant's young age (10 weeks) and history of being left unsupervised in a swing for an unknown time that plausibly contributed to airway obstruction and asphyxia. Developmentally, infants do not develop full head/neck control until approximately 4 months of age. Alternatively, the physical exam findings suggest non-accidental trauma, which was the rationale for referral of this infant's death to the coroner's office. However, some of these physical findings could be sequelae associated with resuscitation efforts. Therefore, based on the case history and clinical findings, it is unlikely that vaccination contributed to this infant's death.

6.1.12.6 Nonfatal Serious Adverse Events

Within 7 days after vaccination, SAEs were reported in 0.6 % of MenQuadfi recipients (12 events in 10 participants) and in 0.7% of the Menveo group (7 events in 6 participants). SAEs experienced by participants were most frequently reported under the MedDRA SOC *Infections and infestations* (MenQuadfi: 0.3%, Menveo: 0.3%). Within 30 days after any vaccination, SAEs were reported by 2.3% of MenQuadfi recipients (49 events in 39 participants) and 1.3% of Menveo recipients (15 events in 11 participants).

During the entire study duration of 6 months after the last vaccination, the percentages of participants with at least 1 SAE was 5.7% in the MenQuadfi group (140 events in 99 participants) and 4.4% in the Menveo group (53 events in 38 participants). SAEs experienced by participants were most frequently reported under the MedDRA SOC *Infections and infestations* (MenQuadfi: 3.7%, Menveo: 2.8%). The three most frequently reported SAEs by MedDRA PT across both groups were bronchiolitis (MenQuadfi: 0.9%, Menveo: 0.5%), respiratory syncytial virus (RSV) bronchiolitis (MenQuadfi: 0.5%, Menveo: 0.5%), and RSV infection (MenQuadfi: 0.4%, Menveo: 0.7%).

During the study, SAEs which were assessed as related to the study vaccine by the investigator included the following: 1) one event of febrile seizure in a MenQuadfi recipient, which the Applicant reports the investigator later assessed as not related and which the clinical review team did not assess as possibly related and is described in section 6.1.12.7.1and 2) one event

of fever in a Menveo recipient. The Menveo recipient was a 2-month-old male participant hospitalized due to fever that occurred 8 hours after vaccination with Menveo, DTaP-IPV/Hib vaccine, PCV13, rotavirus vaccine, and hepatitis B vaccine. The participant had a rectal temperature at 103°F and was admitted to the hospital for evaluation, with no infectious source for fever identified, and was discharged home after 2 days.

Reviewer Comment: The most frequently reported SAEs across both groups are common illnesses reported in infant/toddler populations. The clinical review team agrees with the investigator conclusions that the reported SAEs in the MenQuadfi recipients were most likely not related to the study intervention, based on a review of the narratives for all SAEs.

The clinical review team agrees with the investigator that the SAE of fever in a 2-month-old male Menveo recipient with onset 8 hours after vaccination with no alternative etiology for the fever and close temporal relationship to vaccination is likely related to vaccination. However, it is not possible to determine if the fever may have been related to administration of Menveo and/or one of the other concomitant vaccines.

6.1.12.7 Adverse Events of Special Interest (AESIs)

Protocol specified AESIs included generalized seizures (febrile and non-febrile), Kawasaki disease, Guillain-Barré syndrome, and Idiopathic thrombocytopenic purpura (ITP). Within 7 days after any vaccination, 1 participant (<0.1%) reported 1 AESI (event of febrile seizure) in the MenQuadfi group and no participants reported an AESI in the Menveo group. Within 30 days after any vaccination, 3 participants (0.2%) reported 3 AESIs in the MenQuadfi group and no participants reported an AESI in the Menveo group. The three MenQuadfi recipients who reported an AESI (also classified as SAEs) that occurred within 30 days of vaccination were: 16-month-old with febrile seizure associated with bronchiolitis and acute otitis media; 14-month-old with febrile seizure associated with pyelonephritis; and 4-month-old with a seizure. Clinical review of these two febrile seizure events is provided in section 6.1.12.7.1 and the event of seizure in a 4-month-old is summarized below.

A 4-month-old participant was reported to have a seizure without concurrent fever 15 days after the second dose of MenQuadfi administered concomitantly with DTaP-IPV/Hib vaccine, PCV13 vaccine, and rotavirus vaccine. The 20 second episode occurred while the nursing and the infant was reported to be limp and unresponsive with eye deviation, unequal pupils, and he had decreased movement of the right side for an hour after the event. Upon hospital admission, EEG, MRI, and laboratory testing were normal. The participant continued in the study and received the 3rd and 4th doses of study vaccine and did not have any further reported seizure events.

Throughout the study, 13 participants (0.8%) experienced 17 AESIs In the MenQuadfi group and 5 participants (0.6%) experienced 6 AESIs in the Menveo group. Of the 17 AESIs reported in the MenQuadfi group, 11 were febrile seizures, 4 were seizures, 1 was infantile spasms, and 1 was seizure-like phenomena. Of the 6 AESIs in the Menveo group, 4 were febrile seizures, 1 was a seizure, and 1 was epilepsy.

One AESI across both groups was initially assessed as related to the study vaccine by the investigator (febrile seizure in 16-month-old MenQuadfi recipient, see clinical review in section 6.1.12.7.1).

Reviewer Comment: A review of the narratives for all AESIs accrued in the study did not identify any events assessed by the clinical review team as causally related to

MenQuadfi. The clinical review team agrees with the investigator that the reported seizure in the 4-month-old participant described above is likely not related to MenQuadfi vaccination given that the event occurred 15 days after vaccination, resolved quickly with a nonrevealing workup, and the infant experienced no further seizure episodes including after receiving 2 more doses of study vaccine. Based on the history provided in the case narrative, the presentation may be consistent with a BRUE (brief resolved unexplained event), possibly precipitated by feeding and reflux. A BRUE is a sudden, brief, now resolved episode in an infant that can include a marked change in tone and altered level of responsiveness; BRUEs are usually less than one minute and typically <20 to 30 seconds (Corwin 2020).

6.1.12.7.1 Febrile Seizures

Within 7 days after any vaccination, <0.1% of MenQuadfi participants (1 participant reporting 1 event) reported a febrile seizure, and no Menveo participants reported a febrile seizure. Within 30 days, 0.2% of MenQuadfi participants (2 participants reporting 2 events) reported a febrile seizure, and no Menveo recipients reported a febrile seizure. During the entire study period, 0.5% of MenQuadfi participants (8 participants reporting 11 events) reported a febrile seizure, compared with 0.3% of Menveo recipients (3 participants reporting 4 events).

The two MenQuadfi participants who reported a febrile seizure within 30 days of vaccination are described below. Neither was considered related to MenQuadfi by the investigator on final assessment or by the clinical review team.

1. A 16-month-old female MenQuadfi recipient in Subgroup 1b experienced an SAE (also classified as AESI) of febrile seizure 13 days after receipt of the 4th dose MenQuadfi concomitantly with DTaP-IPV/Hib and Hepatitis A vaccines. During the first 7 days after vaccination, the maximum reported temperature was 100.1°F on Day 5 after vaccination. The febrile seizure occurred on Day 13 in the setting of a fever to 102.5°F and diagnosis of otitis media and bronchiolitis by the participant's healthcare provider. The participant was treated with antibiotics and the fever resolved after a few days.

   This was the participant's third reported febrile seizure; she had a history of 2 prior febrile seizures (also classified as SAEs and AESIs) during the study. The first febrile seizure occurred at 11 months of age (149 days after the third dose of MenQuadfi administered concomitantly with DTAP-IPV/Hib, PCV13, rotavirus, and Hepatitis B vaccines), and the second febrile seizure occurred at 12 months of age (174 days after the third dose of MenQuadfi and these same concomitant vaccines). Both of these first two febrile seizures were assessed as unrelated to MenQuadfi. After the third febrile seizure described above, the participant was referred to a neurologist. Prior to neurology evaluation, she went on to have a fourth febrile seizure when 16 months of age (32 days after the fourth dose of MenQuadfi and concomitant vaccines described above), in the setting of a diagnosis of a viral infection. This febrile seizure was assessed by the investigator as unrelated to MenQuadfi. Following this episode, the participant had an EEG which showed a few occasions of spikes in the right frontal central region. Evaluation by a neurologist noted a possible diagnosis of atypical febrile seizures and recommended genetic testing to rule out Dravet syndrome if the participant began having afebrile seizures and developmental regression.

   This SAE of febrile seizure (the 3rd reported febrile seizure) was initially assessed as related to MenQuadfi by the investigator and assessed as unrelated by the Applicant, though the

Applicant reported that the final investigator assessment was assessed as unrelated.

Reviewer Comment: Of this participant's four febrile seizures which occurred during the study period, the first, second, and fourth febrile seizures are not likely related to MenQuadfi given the lack of close temporal relationship to vaccination. In addition, based on the available information, the third febrile seizure (occurring 13 days after the 4th dose of MenQuadfi), is also less likely to be related to MenQuadfi due to plausible alternative sources for fever including bronchiolitis and otitis media, particularly as the fever resolved with antibiotic administration. In addition, the participant had a known history of recurrent febrile seizures with ongoing evaluation by a neurologist. Therefore, a causal relationship between MenQuadfi and the occurrence of this SAE is less likely, and this event will not be described in Section 6 of the MenQuadfi prescribing information.

2. A 14-month-old female MenQuadfi recipient in Subgroup 1a experienced febrile seizure 6 days post 4th dose of MenQuadfi in the setting of acute pyelonephritis. This participant did not receive any concomitant vaccines with the MenQuadfi dose. Five days after the 4th dose of MenQuadfi, she was febrile, reported to have acute pyelonephritis, and received antipyretics. The next day (Day 6), she had a febrile seizure in the setting of temperature to 40.2°C and was transported to the local emergency department (ED) via ambulance. She was discharged home the same day with antibiotics after resolution of the seizure. The next day, she presented with emesis, decreased in urine output, and persistent fever to 40.5°C. She was admitted to the hospital with diagnosis of acute pyelonephritis and received intravenous antibiotics for three days and was then discharged home on oral antibiotics. The investigator assessed this event as unrelated to the study vaccine.

   Reviewer Comment: There was some inconsistency in the sequence of events described in the case narrative of the 14-month-old with febrile seizure, as she was reported to have acute pyelonephritis 5 days after vaccination but did not appear to have had a diagnosis made on that day or antibiotics administered until the next day. Nonetheless, based on the clinical presentation described including timing of fever in relationship to vaccination and fever resolution only after adequate antibiotic treatment of pyelonephritis, the clinical review team agrees with the investigator's assessment that the participant's fever and resultant febrile seizure were likely secondary to acute pyelonephritis rather than receipt of MenQuadfi, although contribution of MenQuadfi cannot be ruled out given the temporal onset of this event after vaccination.

See section 8 Integrated Overview of Safety for additional assessment and discussion of febrile seizures after MenQuadfi across the clinical studies.

6.1.12.8 Discontinuation due to AE

Rates of discontinuation due to AE were low and similar across groups. Within 30 days of any vaccination, 1 participant (0.1%) discontinued in the MenQuadfi group due to cardiac arrest (see narrative in section 6.1.12.5 Deaths) and 1 participant (0.1%) discontinued in the Menveo group due to congenital absence of bile ducts. Neither event was assessed as related to the study vaccine by the investigator.

6.1.12.9 Subgroup Analyses

Descriptive subgroup analyses of the safety data show a comparable safety profile between male and female participants and participants of different races across the study groups.

Preterm Infants

In general, there were no notable differences in the solicited or unsolicited safety profile between participants born preterm and those born at term.

Reviewer Comment: Overall, these data support the safety of MenQuadfi administration in infants born preterm at 31 to <37 weeks gestational age. However, the sample size for preterm infants in the study was small, and the majority of the preterm infants had estimated gestational ages that were late preterm. See the section 8 Integrated Overview of Safety for additional safety data in infants born preterm across the clinical studies.

6.1.13 Study Summary and Conclusions

Study MET42 was designed to demonstrate the safety and immunogenicity (inferred effectiveness) of a 4-dose series of MenQuadfi as compared with Menveo in healthy infants. The study met the predefined statistical criteria for successful demonstration of the two co-primary objectives: immunologic noninferiority of hSBA seroresponses to serogroups A, C, Y, and W when 4 doses of MenQuadfi versus Menveo were administered concomitantly with recommended pediatric vaccines, and the noninferiority of the percentage of participants with hSBA Ab titers ≥ 1:8 for the same serogroups after 3 doses of MenQuadfi versus Menveo when concomitantly administered with recommended pediatric vaccines. The secondary objective of the noninferiority of immune responses of the recommended pediatric vaccines administered concomitantly with MenQuadfi versus Menveo was also demonstrated. The safety profile of MenQuadfi was generally comparable to that of Menveo. Within 30 days, 0.2% of MenQuadfi recipients and no Menveo recipient reported a febrile seizure. No febrile seizures in MenQuadfi recipients were assessed by the clinical review team as related to vaccination. For clinical reviewer analysis of febrile seizures across all studies, see the Integrated Overview of Safety in section 8.4.3. The data from this study support the safety and effectiveness of MenQuadfi for use as a 4-dose series administered at 2, 4, 6, and 12-18 months in infants.

6.2 Trial #2: MET61

NCT03691610: “Immunogenicity and Safety Study of a Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly With Routine Pediatric Vaccines in Healthy Infants and Toddlers”

Study Overview: MET61 was a Phase 3 study designed to evaluate the safety and immunogenicity (inferred effectiveness) of a 2-dose series of MenQuadfi administered to healthy infants at 6-7 months of age and 12-13 months of age when compared with Menveo, and a 2-dose series of MenQuadfi administered to healthy toddlers 17-19 months of age and 20-23 months of age when compared with Menactra. The study enrolled and randomized 870 participants 6-7 months of age and 200 participants 17-19 months of age and was conducted at 47 sites in the U.S. and Puerto Rico. The study was conducted from October 4, 2018 to October 23, 2023 with a database lock date of January 8, 2024.

6.2.1 Objectives/Endpoints

Primary Objective/Endpoint

1. To demonstrate the noninferiority of the vaccine seroresponse[10] to meningococcal serogroups A, C, Y, and W following administration of 2 doses of MenQuadfi compared with 2 doses of Menveo when given concomitantly with recommended pediatric vaccines to infants and toddlers at 6-7 months of age and 12-13 months of age.

   - **Endpoint**: Meningococcal serogroups A, C, Y, and W hSBA antibody titers before the first study vaccination and 30 days after the 2nd dose administered at 12-13 months of age (MenQuadfi versus Menveo).
   - **Hypothesis 1 (H1)**: MenQuadfi was noninferior to Menveo for each of the four serogroups A, C, Y, and W.
   - **Success criterion**: noninferiority is demonstrated if the LL of the 2-sided 95% CI of the difference in percentage of participants achieving response is > -10% for each serogroup.

Secondary Objectives/Endpoints

1. To demonstrate the noninferiority of the percentage of participants with hSBA titers to meningococcal serogroups A, C, Y, and W ≥ 1:8 following administration of 2 doses of MenQuadfi compared with 2 doses of Menveo when given concomitantly with recommended pediatric vaccines to infants and toddlers at 6-7 months of age and 12-13 months of age.
   - **Endpoint**: Meningococcal serogroups A, C, Y and W hSBA titers ≥1:8 at 30 days after the 2nd dose (MenQuadfi versus Menveo)
   - **Hypothesis 2 (H2)**: MenQuadfi was noninferior to Menveo for each of the four serogroups A, C, Y, and W.
   - **Success criterion**: noninferiority is demonstrated if the LL of 2-sided 95% CI of the difference in percentage of participants achieving hSBA titers ≥ 1:8 is > -10% for each serogroup.

     Reviewer Comment: Noninferiority hypothesis testing was only conducted for participants receiving the 2-dose series of MenQuadfi or Menveo at 6-7 months and 12-13 months of age. Noninferiority hypothesis testing was not done for older participants receiving the 2-dose series of MenQuadfi or Menactra at 17-19 months and 20-23 months of age. For these participants, descriptive analyses were performed comparing immune responses across groups. In addition, although MenQuadfi and Menveo were administered concomitantly with recommended pediatric vaccines in participants receiving the 2-dose series at 6-7 months and 12-13 months, the study did not include hypothesis testing or descriptive analyses for immune interference. This was considered acceptable as noninferiority testing for immune interference with recommended pediatric vaccines was already assessed in study MET42 for the same age groups.

Secondary Objectives 2-5 (Descriptive Analyses Without Hypothesis Testing)

2. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 12-13 months of age with MenQuadfi or Menveo
   - Endpoints:

10 hSBA vaccine seroresponse was defined as: For a participant with a prevaccination (pre-dose 1) titer < 1:8, the post-vaccination titer must be ≥ 1:16; for a participant with a prevaccination titer ≥ 1:8, the post-vaccination titer must be ≥ 4-fold greater than the prevaccination titer

- hSBA meningococcal serogroup A, C, Y, and W antibody titers (including ≥ 1:4, ≥ 1:8, and ≥ 4-fold rise from prevaccination [pre-dose 1] to postvaccination)
- Titer distribution and reverse cumulative distribution curves (RCDCs)

3. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the first vaccination at 6-7 months of age with MenQuadfi or Menveo
   - Endpoints:
     - hSBA meningococcal serogroups A, C, Y, and W antibody titers (including ≥ 1:4, ≥ 1:8, and ≥ 4-fold rise from prevaccination [pre-dose 1] to postvaccination)
     - titer distribution and RCDCs
     - hSBA vaccine seroresponse

4. To describe the antibody response against meningococcal serogroups A, C, Y, and W 6 months after the first vaccination at 6-7 months of age (pre-2nd dose) with MenQuadfi or Menveo
   - Endpoints:
     - hSBA meningococcal serogroups A, C, Y, and W antibody titers (including ≥ 1:4, ≥ 1:8, and ≥ 4-fold rise from prevaccination [pre-dose 1] to postvaccination)
     - titer distribution and RCDCs
     - hSBA vaccine seroresponse

5. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 20-23 months of age with MenQuadfi or Menactra
   - Endpoints:
     - hSBA meningococcal serogroups A, C, Y, and W antibody titers (including ≥ 1:4, ≥ 1:8, and ≥ 4-fold rise from prevaccination [pre-dose 1] to postvaccination)
     - titer distribution and RCDCs
     - hSBA vaccine seroresponse

Observational Objectives

Safety

1. To describe the safety profile of MenQuadfi and Menveo when administered concomitantly with recommended pediatric vaccines in healthy infants and toddlers
2. To describe safety profile of MenQuadfi and Menveo administered in toddlers

Endpoints:

- Occurrence, nature (MedDRA PT), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study, of any:
  - Unsolicited systemic AEs reported within 30 minutes after each vaccination
  - Unsolicited AEs up to 30 days after each vaccination.

    - SAEs (including AESIs) throughout the study from Visit 1 through the 6-month follow-up contact after the last vaccination.
    - MAAEs throughout the study from Visit 1 through the 6-month follow-up contact after the last vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of any:
    - Solicited injection site reactions occurring through 7 days after each vaccination.
    - Solicited systemic reactions occurring through 7 days after each vaccination.

6.2.2 Design Overview

Study MET61 was a Phase 3, randomized, parallel group, active-controlled, multi-center study in the U.S. and Puerto Rico in healthy infants (6-7 months of age at enrollment) and toddlers (17-19 months of age at enrollment). A total of 950 participants were enrolled; 750 infant participants were randomized 1:1 to receive a 2-dose series of MenQuadfi (Group 1) or Menveo (Group 2), and 200 toddler participants were randomized 1:1 to receive either MenQuadfi (Group 3) or Menveo (Group 4). The study was double-blind within each age group (i.e., between Group 1 and Group 2 and between Group 3 and Group 4). Participants were followed for safety through 6 months after the last study vaccination.

The study groups and the vaccines administered for each group at each timepoint are detailed in Table 22.

Table 22. Schedule of Vaccination and Blood Sampling, Study MET61

Group	6-7 MOA Visit 1 Blood Draw*	6-7 MOA Visit 1 Vaccines†	7-8 MOA Visit 2 Blood Draw‡	12 MOA Visit 3 Blood Draw§	12 MOA Visit 3 Vaccines	13 MOA Visit 4 Blood Draw	13 MOA Visit 4 Vaccines**	17-19 MOA Visit 1 Blood Draw*	17-19 MOA Visit 1 Vaccine	20-23 MOA Visit 2 Vaccine	21-24 MOA Visit 3 Blood Draw
1	X	MenQuadfi, DTaP, IPV, Hib, PCV13, Rotavirus, HB	X	X	MenQuadfi, MMR, Varicella	X	PCV13, Hib	-	-	-	-
2	X	MENVEO, DTaP, IPV, Hib, PCV13, Rotavirus, HB	X	X	MENVEO, MMR, Varicella	X	PCV13, Hib	-	-	-	-
3	-	-	-	-	-	-	-	X	MenQuadfi	MenQuadfi	X
4	-	-	-	-	-	-	-	X	Menactra	Menactra	X

Source: Sponsor
Abbreviations: MOA=months of age;
*Blood was drawn prior to vaccinations
† Routine pediatric vaccines recommended at this age are to be given as per standard of care, and will not be provided by the Sponsor.
‡ Blood sample at Visit 2 is applicable only to approximately the first 50% of the participants in Group 1 and Group 2
§ Blood sample at Visit 3 is applicable only to the participants in Group 1 and Group 2 who did not provide a blood sample at Visit 2 (approximately 50% in each group).
**PCV13 and Hib may be given as per standard of care outside of the study during the last study visit after completing the study procedures (Visit 4). PCV13 and Hib will not be provided by the Sponsor.

- Group 1: MenQuadfi and recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
- Group 2: Menveo and recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
- Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age
- Group 4: Menactra at 17-19 months of age and 20-23 months of age

Recommended pediatric vaccines concomitantly administered for Group 1 and Group 2 were:

- At 6-7 months of age: PCV13, rotavirus vaccine, and either (depending on previous vaccination regimen received):
  - DTaP-IPV/Hib vaccine and hepatitis B vaccine OR
  - DTaP-IPV-HepB vaccine and Hib vaccine*
    *For participants immunized with PedvaxHIB at 2 and 4 months of age, a 3rd dose of Hib vaccine at 6 months is not required
- At 12-13 months of age: MMR and varicella vaccines

6.2.3 Population

Key Inclusion Criteria:

1. 6-7 months (168 to 224 days) or 17-19 months of age on the day of the first visit
2. For participants 6-7 months of age at enrollment, documented history of having received 2 doses of DTaP, Hib, IPV, pneumococcal, hepatitis B (for children who received Pediarix at 2 and 4 months of age, prior receipt of 3 doses of hepatitis B), and rotavirus vaccines
3. For participants to be enrolled at 17-19 months of age, documented history of having received all routine pediatric vaccines recommended by ACIP up to the age of enrollment

Key Exclusion Criteria:

1. Receipt of any vaccine in the 4 weeks preceding the first trial vaccination or planned receipt of any vaccine in the 4 weeks before and/or following any trial vaccination except for influenza vaccination, which may be received at least 2 weeks before or 2 weeks after any study vaccination
2. Previous vaccination against meningococcal disease with either the trial vaccine or another vaccine
3. For participants enrolled at 6-7 months of age (Group 1 and Group 2), prior receipt of more than 2 doses of rotavirus vaccine (Rotateq), DTaP, Hib, IPV, pneumococcal, hepatitis B; for children who received Pediarix at 2 and 4 months of age, prior receipt of more than 3 doses of hepatitis B vaccine
4. For participants enrolled at 6-7 months of age, receipt of 2 doses of rotavirus vaccine, Rotarix, at 2 and 4 months of age
5. Known or suspected congenital or acquired immunodeficiency or receipt of immunosuppressive therapy
6. Family history of congenital or hereditary immunodeficiency, until the immune competence of the potential vaccine recipient is demonstrated
7. History of any Neisseria meningitidis infection, confirmed clinically, serologically, or microbiologically
8. History of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella; and of *Haemophilus influenzae* type b, Streptococcus pneumoniae, and /or rotavirus infection or disease

9. At high risk for meningococcal infection during the trial (including those with persistent complement deficiency, with anatomic or functional asplenia, or those travelling to countries with high endemic or epidemic disease)
10. History of intussusception
11. History of any neurologic disorders, including any seizures and progressive neurologic disorders
12. History of Arthus-type hypersensitivity reaction after a previous dose of tetanus toxoid containing vaccine
13. History of Guillain-Barré syndrome
14. Chronic illness that might interfere with trial conduct or completion

6.2.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc.)

- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration:
    - Group 1: 6-7 months of age and 12-13 months of age
    - Group 3: 17-19 months of age and 20-23 months of age
- Batch numbers: U6142AA, U7249AA, UD19648, UD21375, UD21467, UD21951, UD22378, and UD23177

Menveo: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GSK Vaccines)

- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration:
    - Group 2: 6-7 months of age and 12-13 months of age
- Batch numbers: AMVA128A, AMVA223A, AMVA321A, AMVA414A, AMVA548A, AMVA655A, AMVA748A, M17088, and UD6142AA

Menactra: Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Sanofi Pasteur Inc.)

- Dose and route of administration: 0.5mL IM
- Schedule of administration: Group 4: 17-19 months of age and 20-23 months of age
- Composition: 4 µg each of serogroups A, C, Y, W, and 48 µg diptheria toxoid protein carrier
- Presentation: Solution for injection
- Batch numbers: AMVA052A, U6560BA, U6575AB, U6785AA, U6877BA, U7087AA, and U7268AA

For the following concomitant vaccines administered, only one product per indication was to be used. As per ACIP guidelines, the third dose of each recommended vaccine (administered at 6 to 7 months of age) was preferentially chosen to come from the same manufacturer as the doses administered at 2 and 4 months of age.

Pentacel: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur Ltd.)

- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age

- Batch numbers: Commercial batches

Pediarix: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine (GlaxoSmithKline)

- Dose and route of administration: 0.5mL IM
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Composition: Diphtheria toxoid, Tetanus toxoid, Acellular pertussis antigens: Inactivated PT, FHA, PRN, HBsAg, Inactivated polioviruses: Type 1 (Mahoney), Type 2 (MEF-1), Type 3 (Saukett)
- Presentation: single-dose prefilled syringe containing suspension for injection
- Batch number: commercial batches

ActHIB: *Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate) (Sanofi Pasteur Inc.)

- Dose and route of administration: 0.5 mL IM
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Composition: Haemophilus influenzae type b polysaccharide (PRP), Conjugated to tetanus toxoid as carrier protein, Sucrose
- Presentation: solution for injection
- Batch number: commercial batches

Hiberix: *Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate) (GlaxoSmithKline Biologicals)

- Dose: 0.5 mL IM
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Composition: Haemophilus influenzae type b polysaccharide (PRP), Conjugated to tetanus toxoid as carrier protein, lactose, residual formaldehyde
- Presentation: solution for injection
- Batch number: commercial batches

PedvaxHIB: *Haemophilus b* Conjugate Vaccine (Meningococcal Protein Conjugate) (Merck Sharp & Dohme Corp.)

- Dose: 0.5 mL IM
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Composition: Haemophilus influenzae type b polysaccharide (PRP), Neisseria meningitidis outer membrane protein complex, aluminum as amorphous aluminum hydroxyphosphate sulfate, sodium chloride
- Presentation: solution for injection
- Batch number: commercial batches

Prevnar 13: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals, Inc.)

- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Batch number: Commercial batches

RotaTeq: Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp.)

- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Batch number: Commercial batches

Engerix-B: Hepatitis B Vaccine [Recombinant] (GlaxoSmithKline Biologicals)
- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Batch number: Commercial batches

Recombivax HB: Hepatitis B Vaccine (recombinant) (Merck & Co, Inc)
- Dose and route of administration: 0.5 mL IM
- Schedule of Administration: Group 1 and Group 2: 6-7 months of age
- Composition: 5µg of HBsAg adsorbed onto approximately 0.5 mg of aluminum (provided as amorphous aluminum hydroxyphosphate sulphate)
- Presentation: suspension for injection
- Batch number: Commercial batches

M-M-R II: Measles, Mumps, and Rubella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 12-13 months of age
- Batch number: Commercial batches

Varivax: Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Refer to section 6.1.4 for Dose, Composition, and Presentation
- Schedule of Administration: Group 1 and Group 2: 12-13 months of age
- Batch number: Commercial batches

6.2.5 Directions for Use

Refer to section 6.2.4.

6.2.6 Sites and Centers

MET61 enrolled and randomized 950 participants and was conducted at 47 centers that enrolled and randomized participants in the United States, including Puerto Rico.

6.2.7 Surveillance/Monitoring

Safety Monitoring
- Clinical Assessments: physical exam for Groups 1 and 2 at Visit 1 (6-7 months of age) and Visit 3 (12-13 months of age) and for Groups 3 and 4, at Visit 1 (17-19 months of age).
- AE monitoring was the same as in Study MET42, see section 6.1.7.

Reviewer Comment: See section 6.1.7 and associated reviewer comments regarding the procedures for recording of safety data in the diary cards and the review process by the investigator before entry of the safety data into the CRF.

The Applicant's internal Safety Management Team (SMT) reviewed the data from all ongoing studies of MenQuadfi at regular intervals for any new safety signals or concerns. No Early Safety Data review was done.

Study withdrawal/discontinuation: The reason for withdrawal or dropout was documented and the investigator determined whether voluntary withdrawal to safety concerns was the reason, in which case the reason for discontinuation was noted as Adverse Event.

Immunogenicity Monitoring:

Antibodies to meningococcal antigens: Functional meningococcal antibody activity against serogroups A, C, Y, and W was measured in hSBA. The lower limit of quantitation (LLOQ) of the hSBA assay is a titer of 1:4. All assays were performed at GCI, Swiftwater, Pennsylvania (PA) or at a qualified contract laboratory for GCI.

Timing of Serologic Sample Collection by Study Group:

Sera to assess immunogenicity endpoints evaluating MenQuadfi, Menveo or Menactra were collected at the following time points:

- Group 1 and Group 2:
    - Day 0, Day 30 post-1st dose at 6-7 months, and pre- and Day 30 post-2nd dose at 12-13 months: meningococcal serogroups (A, C, Y, W) antibody titers
    - Blood draw at Day 30 post-1st dose (Visit 2) is only applicable to the first 50% of participants in Group 1 and Group 2. The remaining 50% of participants will get blood draw at pre-2nd dose (Visit 3).
- Group 3 and Group 4:
    - Day 0 and Day 30 post-2nd dose at 20-23 months: meningococcal serogroups (A, C, Y, W) antibody titers

6.2.8 Endpoints and Criteria for Study Success

Refer to section 6.2.1 and section 6.2.9.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Primary Hypothesis- *seroresponse rate after the 2nd dose:*

For each of the four meningococcal serogroups A, C, Y and W, the percentage of participants with an hSBA vaccine seroresponse (if prevaccination titer < 1:8, the postvaccination titer was ≥ 1:16, and if prevaccination titer ≥ 1:8, the post-vaccination titer was at least 4-fold greater) 30 days after the administration of the 2nd dose of MenQuadfi (Group 1) or Menveo (Group 2) at 12 months of age were assessed via the following noninferiority hypothesis.

- (H0): p(men, G1) - p(men, G2) ≤ -10% versus (H1): p(men, G1) - p(men, G2) > -10%
- p(men, G1) and p(men, G2) are the percentages of participants who achieve hSBA vaccine seroresponse in Group 1 and Group 2, respectively.
- Each of the serogroups A, C, Y, and W was tested separately. The overall noninferiority of this objective was demonstrated if all 4 individual null hypotheses are rejected.
- MenQuadfi was considered noninferior to Menveo if LL of the 2-sided 95% CI of the difference between the 2 percentages is > -10% for each serogroup.

Secondary Hypothesis - *hSBA titer ≥ 1:8 after the 2nd dose:*

For each of the four meningococcal serogroups A, C, Y and W, the percentage of participants that achieve hSBA titers ≥ 1:8 at 30 days after the 2nd dose of MenQuadfi (Group 1) or Menveo (Group 2) at 12 months of age were assessed via the following noninferiority hypothesis.

- (H0): p(men, G1) - p(men, G2) ≤ -10% versus (H1): p(men, G1) - p(men, G2) > -10%
- p(men, G1) and p(men, G2) are the percentages of participants who achieve hSBA ≥1:8

in Group 1 and Group 2 respectively.
- Each of the serogroups A, C, Y, and W was tested separately. The overall noninferiority of this objective was demonstrated if all 4 individual null hypotheses are rejected.
- MenQuadfi was considered noninferior to Menveo if the LL of the 2-sided 95% CI of the difference between the 2 percentages is > -10% for each serogroup.

Observational Safety Endpoints: See section 6.2.1.

For Secondary Objectives 2, 3, 4, and 5 and Observational Objectives, no hypothesis was tested, and descriptive statistics was used.

Impact of COVID-19 pandemic was analyzed as follows:
- Participants impacted by COVID-19 pandemic situation was defined as those with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19.
- If more than 10% of participants are impacted as per this definition, baseline and demographic characteristics and the main immunogenicity and safety endpoints was summarized in the subset of participants impacted / not-impacted to assess the potential impact of COVID-19 situation on study outcome.

Reviewer Comment: Because less than 10% of participants were directly impacted by the COVID-19 pandemic, the additional sensitivity analyses specified were not performed.

Protocol Amendments
- Version 1.0 (May 31, 2018) – not submitted to IEC/IRB
- Version 2.0 (June 6, 2018)- Original study protocol (first version used in the study)
- Version 3.0 (March 4, 2021)- Protocol Amendment 1
    - Increased sample size from 940 to 1,070 infants
    - Made all four immunogenicity objectives secondary (initially were observational)
    - Clarified the age of infants at first visit to start from 164 to 168 days
    - Added COVID-19 sensitivity analysis
- Version 4.0 (May 12, 2022) – Protocol Amendment 2
    - Due to high attrition rates during the study (especially during the COVID-19 pandemic year 2020-2021), the time window for the postvaccination blood samples was increased from 14 to 21 days.

6.2.10. Study Population and Disposition

A total of 950 participants were enrolled in the study. The first participant, first visit took place on 04 October 2018 and the last participant, last contact took place on 23 October 2023.

Populations Enrolled/Analyzed
- Safety sets: All participants will have their safety analyzed after each dose according to the vaccine the participant actually received, and after both doses according to the vaccine received at the first dose.
    - Overall SafAS (Safety Analysis Set for Any Dose): participants who have received at least one dose of the study vaccines and have any safety data available

  - SafAS 1: participants who received the study vaccine at Visit 1 (Groups 1 and 2) around 6-7 months of age
  - SafAS 2: participants who received the study vaccine at Visit 3 (Groups 1 and 2) around 12-13 months of age
  - SafAS 3: participants who received the study vaccine at Visit 1 (Groups 3 and 4) around 17-19 months of age
  - SafAS 4: participants who received the study vaccine at Visit 2 (Groups 3 and 4) around 20-23 months of age

- Full Analysis Sets (FAS): Exploratory immunogenicity analyses were performed on the FAS. All participants were analyzed according to the treatment group to which they were randomized.
  - FAS 1 (Infant vaccination): all randomized participants who received at least 1 dose of study vaccine in infancy (<12 months of age) and have a valid postvaccination serology result in infancy at 30 days after the 1st dose
  - FAS 2 (second year of life vaccination): all randomized participants who received at least 1 dose of the study vaccine in the second year of life (≥ 12 months of age) and have a valid post-vaccination serology result in the second year of life.
  - FAS 3 (persistence after infant vaccination): all randomized participants who received at least 1 dose of study vaccine in infancy (<12 months of age) and have a valid pre-Dose 2 serology.

- Per-Protocol Analyses Sets (PPAS): The PPAS are subsets of the FAS and will serve as the primary population for immunogenicity analyses. Participants with the following protocol deviations are excluded from any PPAS:
  - Not meeting all protocol-specified inclusion criteria or meeting at least one of the exclusion criteria
  - Receiving a vaccine other than the one he was randomized to received
  - Preparation/administration of vaccine was not done as per-protocol
  - Receiving a protocol-prohibited therapy/medication/vaccine
  - Other protocol violations that affected the immune response
  - Serology sample not producing a valid result

  - PPAS1 (Infant vaccination; Groups 1 and 2 only): subset of FAS 1 without any relevant protocol deviations. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded:
    - Not completing the vaccination schedule
    - Not receiving the vaccine in the proper time window (Visit 1: 24 to 32 weeks of age)
    - Not providing a post-dose serology sample in the proper time window (Visit 1 + 30 days [± 21 days]) or a post-dose serology sample not drawn

  - PPAS2 (Second year of life vaccination; all Groups): subset of FAS 2 without any relevant protocol deviations. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded:
    - Not completing the vaccination schedule including the infant and second year of the study: for Groups 1 and 2, through the 12-13-month vaccinations (including the infant schedule); for Groups 3 and 4, through 23-month vaccinations

- Not receiving the vaccine in the proper time window: for Groups 1 and 2, Visit 3: 12-13 months of age; for Groups 3 and 4, Visit 2: 20-23 months of age
- Not providing a post-dose serology sample in the proper time window (see below), or a post-dose serology sample not drawn
  - Groups 1 and 2: Visit 4 (Visit 3 + 30 days [± 21 days])
  - Groups 3 and 4: Visit 3 (Visit 2 + 30 days [± 21 days])

- PPAS 3 (persistence 6 months after infant vaccination; Groups 1 and 2 only): subset of FAS 3 without any relevant protocol deviations. In addition to those listed for all PPAS, participants with the following protocol deviations will also be excluded.
  - Not completing the vaccination schedule
  - Not receiving the vaccine in the proper time window (Visit 1: 24 to 32 weeks of age).
  - Not providing a pre-dose 2 serology sample in the proper time window or a pre-dose 2 serology sample not drawn at Visit 3

6.2.10.1 Demographics

The demographics of participants in the Overall SafAS are shown in Table 23. Overall, there was a slightly higher percentage of male than females participants in Group 1 (52.4% versus 47.6%) and Group 2 (54.0% versus 46.0%), while the percentage of male and female participants were similar in Groups 3 and 4. The median age of participants at enrollment was 6 months for Groups 1 and 2 and 18 months for Group 3 and 4. Across all groups, most participants identified as White (71.2%- 83.5%) and Not-Hispanic or Latino (54.1% - 67.7%). Demographics of the SafAS were generally similar to the other safety analyses sets and the Per-Protocol Analysis Sets.

Table 23. Demographic and Baseline Characteristics, Overall SafAS, Study MET61

Baseline Characteristic	MenQuadfi Group 1 N=370	Menveo Group 2 N=361	MenQuadfi Group 3 N=96	Menactra Group 4 N=103
Sex, n (%)	--	--	--	--
Male	194 (52.4)	195 (54.0)	48 (50.0)	51 (49.5)
Female	176 (47.6)	166 (46.0)	48 (50.0)	52 (50.5)
Age (months)[a]	--	--	--	--
Median age (min, max)	6.00 (5.00, 7.00)	6.00 (5.00, 7.00)	18.0 (17.0, 19.0)	18.0 (17.0, 19.0)
Race, n (%)	--	--	--	--
American Indian or Alaska Native	0	1 (0.3)	0	0
Asian	6 (1.6)	6 (1.7)	2 (2.1)	1 (1.0)
Black or African American	63 (17.0)	66 (18.3)	11 (11.5)	11 (10.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	274 (74.1)	257 (71.2)	79 (82.3)	86 (83.5)
Mixed Origin	14 (3.8)	20 (5.5)	4 (4.2)	5 (4.9)
Unknown	3 (0.8)	7 (1.9)	0	0
Not Reported	10 (2.7)	4 (1.1)	0	0
Ethnicity, n (%)	--	--	--	--
Hispanic/Latino	167 (45.1)	160 (44.3)	31 (32.3)	35 (34.0)
Not Hispanic/Latino	200 (54.1)	201 (55.7)	65 (67.7)	68 (66.0)

Baseline Characteristic	MenQuadfi Group 1 N=370	Menveo Group 2 N=361	MenQuadfi Group 3 N=96	Menactra Group 4 N=103
Unknown	1 (0.3)	0	0	0
Not reported	2 (0.5)	0	0	0
Study site, n (%)				
Puerto Rico	10 (2.7)	8 (2.2)	1 (1.0)	2 (1.9)
United States	360 (97.3)	353 (97.8)	95 (99.0)	101 (98.1)

Source: Adapted from STN 125701/262, Study MET61 Clinical Study Report, Table 8.18; amendment 34. Data cutoff 08Jan2024.
Abbreviations: N=number of participants in Overall Safety Analysis Set for Any Dose; n=number of participants fulfilling the item listed in the first column.
Notes: Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age
Group 4: Menactra at 17-19 months of age and 20-23 months of age.
a. Age at enrollment

Reviewer Comment: Baseline characteristics were balanced across groups.

6.2.10.2 Participant Disposition

Disposition of the participants who contributed to the immunogenicity analyses are shown in Table . For Groups 1 and 2, approximately 26-47% of participants of the total randomized participants in each group contributed to each of the Per Protocol Analysis Sets. Approximately 63% of participants from Group 3 and 4 contributed to the Per Protocol Analysis Set. Across all three Per Protocol Analysis Sets, the most common reasons for exclusion were not having the relevant serology sample drawn or not providing the sample in the proper time window. For PPAS 2, participants were also commonly excluded for not completing the infant or second year of life vaccination schedule. Overall, the percentages of participants excluded from each of the Full Analysis and Per Protocol Analysis Sets and the reasons for exclusion were similar across the study groups.

Table 24. Participant Disposition, Immunogenicity Sets, Study MET61

Population	MenQuadfi Group 1 n (%)	Menveo Group 2 n (%)	MenQuadfi Group 3 n (%)	Menactra Group 4 n (%)
Randomized Set	N=380	N=370	N=96	N=104
Full Analysis Set 1	165 (43.4)	165 (44.6)	-	-
Excluded from Full Analysis Set 1	49 (12.9)	41 (11.1)	-	-
Did not receive study vaccine in infancy	5 (1.3)	3 (0.8)	-	-
Did not have a valid postvaccination serology result in infancy	49 (12.9)	41 (11.1)	-	-
Per Protocol Analysis Set 1	135 (35.5)	138 (37.3)	-	-
Excluded from Per Protocol Analysis Set 1	79 (20.8)	68 (18.4)	-	-
Did not meet all protocol-specified inclusion/exclusion criteria	10 (2.6)	6 (1.6)	-	-
Did not complete the vaccination schedule	9 (2.4)	9 (2.4)	-	-
Preparation/administration of vaccine was not done as per-protocol	2 (0.5)	3 (0.8)	-	-
Did not provide a post-dose serology sample in the proper time window at Visit 2	31 (8.2)	18 (4.9)	-	-
A post-dose serology sample was not drawn at Visit 2	39 (10.3)	35 (9.5)	-	-
Received a protocol-prohibited therapy/medication/vaccine	4 (1.1)	2 (0.5)	-	-
Did not provide a valid post-dose serology result	10 (2.6)	6 (1.6)	-	-
Other protocol deviations	0	2 (0.5)	-	-
Full Analysis Set 2	257 (67.6)	259 (70.0)	76 (79.2)	90 (86.5)
Excluded from Full Analysis Set 2	123 (32.4)	111 (30.0)	20 (20.8)	14 (13.5)
Did not receive study vaccine in the 2nd year of life	72 (18.9)	66 (17.8)	0	1 (1.0)
Did not have a valid postvaccination serology result in the 2nd year of life	123 (32.4)	111 (30.0)	20 (20.8)	14 (13.5)
Per Protocol Analysis Set 2	180 (47.4)	163 (44.1)	61 (63.5)	65 (62.5)
Excluded from Per Protocol Analysis Set 2	200 (52.6)	207 (55.9)	35 (36.5)	39 (37.5)
Did not meet all protocol-specified inclusion/exclusion criteria	12 (3.2)	8 (2.2)	5 (5.2)	5 (4.8)
Did not complete the vaccination schedule including the infant and the second year of the study	76 (20.0)	77 (20.8)	10 (10.4)	8 (7.7)
Received a vaccine other than the one that he/she was randomized to receive	0	1 (0.3)	0	0
Preparation/administration of vaccine was not done as per-protocol	8 (2.1)	11 (3.0)	3 (3.1)	0
Did not receive vaccine in the proper time window	57 (15.0)	64 (17.3)	9 (9.4)	12 (11.5)
Did not provide a post-dose serology sample in the proper time window	45 (11.8)	41 (11.1)	6 (6.3)	10 (9.6)
A post-dose serology sample was not drawn	111(29.2)	101 (27.3)	18 (18.8)	13 (12.5)
Received a protocol-prohibited therapy/medication/vaccine	2 (0.5)	5 (1.4)	2 (2.1)	11 (10.6)
Did not provide a valid post-dose serology result	12 (3.2)	10 (2.7)	2 (2.1)	1 (1.0)
Other protocol deviations	1 (0.3)	3 (0.8)	0	0

Population	MenQuadfi Group 1 n (%)	Menveo Group 2 n (%)	MenQuadfi Group 3 n (%)	Menactra Group 4 n (%)
Full Analysis Set 3	122 (32.1)	120 (32.4)	-	-
Excluded from Full Analysis Set 3	44 (11.6)	44 (11.9)	-	-
Not injected the study vaccine in the 2nd year of life	5 (1.3)	6 (1.6)	-	-
Did not have a valid postvaccination serology result in the 2nd year of life	44 (11.6)	44 (11.9)	-	-
Per Protocol Analysis Set 3	108 (28.4)	96 (25.9)	-	-
Excluded from Per Protocol Analysis Set 3	58 (15.3)	68 (18.4)	-	-
Did not meet all protocol-specified inclusion/exclusion criteria	2 (0.5)	2 (0.5)	-	-
Did not complete the infant series vaccination schedule	6 (1.6)	7 (1.9)	-	-
Preparation/administration of vaccine was not done as per-protocol	2 (0.5)	4 (1.1)	-	-
Did not provide a serology sample in the proper time window at Visit 3	12 (3.2)	19 (5.1)	-	-
Serology sample was not drawn at visit 3	43 (11.3)	39 (10.5)	-	-
Received a protocol-prohibited therapy / medication / vaccine	2 (0.5)	3 (0.8)	-	-
Did not provide a valid serology result at Visit 3	1 (0.3)	5 (1.4)	-	-
Other protocol deviations	1 (0.3)	0	-	-

Source: Adapted from STN 125701/262.2, Study MET61 Clinical Study Report, Tables 8.8,8.9,8.10 and from Additional Analysis submitted to Amendment 5. Data cutoff 08Jan2024.
Abbreviations: N=number of all participants in randomized set; n=number of study participants fulfilling the item listed; percentages based on N
Notes: Participants may have been excluded for more than 1 reason.
Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12- 13 months of age
Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age
Group 4: Menactra at 17-19 months of age and 20-23 months of age

Reviewer Comment: Because the study specified that only 50% of Groups 1 (MenQuadfi) and 2 (Menveo) participants would have blood draws at Visit 2 or Visit 3, the percentage of participants who contributed to relevant immunogenicity analyses sets (PPAS1 and PPAS3) were low. A high percentage of participants were excluded from the PPAS 2 for Groups 1 and 2 (52.6% and 55.9% of participants, respectively), most commonly due to not completing the vaccination schedule or missing post-serology blood sample. The study period overlapped with the beginning of the COVID-19 pandemic which may have contributed to difficulty for parents/guardians to adhere to multiple scheduled study visits. The reported exclusions from the immunogenicity analyses populations were balanced across vaccine groups and the available data was sufficient to assess the effectiveness of MenQuadfi for use as a 2-dose series after 6 months of age in infants/toddlers.

Disposition of participants in the Safety Analysis Sets is shown in Table 25. The percentage of participants who contributed to each of the safety analysis sets was balanced across Groups 1 and 2 and across Groups 3 and 4. Approximately 84% of participants who received a 2-dose series at 6-7 and 12-13 months of age (Group 1 and Group 2) completed at least 6 months of safety follow-up. For participants who received a 2-dose series at 17-19 and 20-23 months of age (Group 3 and Group 4), a slightly lower percentage of MenQuadfi recipients (86.5%) completed as least 6 months of follow-up compared with Menactra recipients (93.2%), which was also reflected in the slightly higher percentage of participants who withdrew from the study in the MenQuadfi group compared with the Menactra group (13.5% versus 9.7%, respectively).

Table 25. Participant Disposition, Safety Analysis Set by Vaccinations Group, Study MET61

Population	MenQuadfi Group 1 n (%) N=370	Menveo Group 2 n (%) N=361	MenQuadfi Group 3 n (%) N=96	Menactra Group 4 n (%) N=103
Overall safety analysis set for any dose	370 (100)	361 (100)	96 (100)	103 (100)
Safety analysis set for vaccinations at 6 months of age (SafAS1)	370 (100)	361 (100)	-	-
Safety analysis set for vaccinations at 12 months of age (SafAS2)	309 (83.5)	302 (83.7)	-	-
Safety analysis set for vaccinations at 17 months of age (SafAS3)	-	-	96 (100)	103 (100)
Safety analysis set for vaccinations at 20 months of age (SafAS4)	-	-	86 (89.6)	96 (93.2)
Participants withdrawn from study	72 (19.5)	71 (19.7)	13 (13.5)	9 (8.7)
Adverse event*	0	1 (0.3)	0	0
Lost to follow-up	19 (5.1)	11 (3.0)	5 (5.2)	2 (1.9)
Protocol deviation	10 (2.7)	5 (1.4)	1 (1.0)	1 (1.0)
Withdrawal by parent/guardian	43 (11.6)	54 (15.0)	7 (7.3)	6 (5.8)
Completed 6 months of safety follow-up	312 (84.3)	306 (84.8)	83 (86.5)	96 (93.2)

Source: Adapted from STN 125701/262.2, Study MET61 Clinical Study Report, 8.7 and Additional Analysis submitted to Amendment 5 . Data cutoff 08Jan2024.
Abbreviations: n=number of participants experiencing the endpoint listed in the first column; N=number of participants in overall safety analysis set for any dose; percentages based on N
Notes: Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age
Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age
Group 4: Menactra at 17-19 months of age and 20-23 months of age.
Participants may have been withdrawn for more than 1 reason. Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is < Grade 1 according to the Applicant.

Reviewer Comment: The percentages of participants who withdrew from the study were generally balanced across groups. Most study withdrawals were attributable to lost-to-follow-

up or parents/ guardian requests to be withdrawn. There were no study withdrawals due to adverse event in either of the MenQuadfi groups (Group 1 or Group 3).

6.2.11 Immunogenicity Analyses

The study design did not include clinical efficacy endpoints. Serologic samples were collected to assess immune endpoints (See section 6.2.1). Study endpoints considered integral to the assessment are presented below.

Analysis of the Primary Immunogenicity Objective

Primary Objective: Noninferiority of vaccine seroresponse following a 2-dose series (6-7 months, 12-13 months) of MenQuadfi compared with Menveo.

The primary objective evaluated the noninferiority of the hSBA vaccine seroresponse 30 days after second dose of MenQuadfi compared with Menveo when administered as a 2-dose series at 6-7 months and 12-13 months of age. The prespecified noninferiority success criterion of the LL of the 95% CI of the difference in percentage of participants with hSBA seroresponse (MenQuadfi- Menveo) >-10% was met for all four serogroups (Table 26).

Table 26. hSBA Vaccine Seroresponse Rate at 30 Days After the 2nd Dose of MenQuadfi or Menveo in 2-Dose Series (6-7 Months, 12-13 Months), PPAS 2, Study MET61

Serogroup	MenQuadfi Group 1 SRR % (95% CI)[a] N1=134-143	Menveo Group 2 SRR % (95% CI)[a] N1=123-128	Difference in Seroresponse Rate [MenQuadfi- Menveo] % (95% CI)[b]
A	89.4% (83.1, 93.9)	82.9% (75.1, 89.1)	6.4 (-1.9, 15.1)
C	99.3% (95.9, 100)	97.6% (93.2, 99.5)	1.6 (-2.1, 6.1)
Y	98.6% (94.9, 99.8)	97.7% (93.3, 99.5)	0.9 (-3.0, 5.4)
W	99.3% (96.2, 100)	92.9% (87.0, 96.7)	6.4 (1.8, 12.3)

Source: Adapted from STN 125701/262, Study MET61 Clinical Study Report, Tables 8.176. Data cutoff 08Jan2024.
Abbreviations: CI=confidence interval; N1=number of participants with available data for the relevant endpoint; hSBA=serum bactericidal activity using human complement; PPAS 2=Per Protocol Analysis Set 2
Notes: Seroresponse=postvaccination titer ≥ 1:16 for participants with prevaccination (pre-dose 1) hSBA titer <1:8, or a post-vaccination titer ≥4-fold increase from prevaccination for participant with prevaccination hSBA titer ≥1:8.
Group 1: MenQuadfi + recommended pediatric vaccines at 6- 7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
a 95% CI of the single proportion calculated from the exact binomial method;
b 95% CI of the difference calculated from the Wilson Score method without continuity correction. Noninferiority is demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

Analyses of Secondary Immunogenicity Objectives

Secondary Objective #1: Noninferiority of hSBA antibody response following a 2-dose series (6-7 months, 12-13 months) of MenQuadfi compared with Menveo

Secondary Objective #1 evaluated the noninferiority of the hSBA antibody response (titers ≥ 1:8) after the 2nd dose of MenQuadfi compared with Menveo when administered as a 2-dose series at 6-7 months of age and 12-13 months of age. The prespecified noninferiority criterion of the LL of the 95% CI of the difference in the percentage of participants who achieved hSBA titers ≥ 1:8 (MenQuadfi-Menveo) >-10% was met for all 4 serogroups (Table 27)

Table 27. Percentage of Participants With hSBA Titers ≥1:8 at 30 Days After the 2nd Dose of MenQuadfi or Menveo in 2-Dose Series (6-7 Months, 12-13 Months), PPAS 2, Study MET61

Serogroup	MenQuadfi Group 1 % with hSBA ≥1:8 (95% CI)[a] N1=162-171	Menveo Group 2 % with hSBA ≥1:8 (95% CI) [a] N1=158-160	Difference in % with hSBA ≥1:8 [MenQuadfi- Menveo] (95% CI)[b]
A	95.3% (90.9, 97.9)	93.0% (87.9, 96.5)	2.26% (-3.01, 7.83)
C	100% (97.7, 100)	98.1% (94.6, 99.6)	1.88 % (-0.75, 5.37)
Y	100% (97.9, 100)	97.5% (93.7, 99.3)	2.50% (-0.18, 6.25)
W	100% (97.9, 100)	95.6% (91.1, 98.2)	4.40% (1.25, 8.81)

Source: Adapted from STN 125701/262.2, Study MET61 Clinical Study Report, Tables 8.178. Data cutoff 08Jan2024.
Abbreviations: CI=confidence interval; hSBA=serum bactericidal activity using human complement; PPAS2: Per Protocol Analysis Set 2; N1=number of participants with available data for the relevant endpoint
Notes: Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
a.95% CI of the single proportion calculated from the exact binomial method
b.95% CI of the difference calculated from the Wilson Score method. Noninferiority is demonstrated if the lower limit of the 2-sided 95% CI is > -10% for all four serogroups.

Secondary Objective #2: Descriptive analyses of hSBA titers post-2nd dose in 2-dose series (6-7 months, 12-13 months)

hSBA GMTs at 30 days post-2nd dose of MenQuadfi or Menveo administered at 12-13 months of age, based on the PPAS2, are shown in Table 28. At 30 days after the second vaccination, hSBA GMTs were similar across the MenQuadfi and Menveo groups for serogroup A and higher in the MenQuadfi group compared with the Menveo group for all remaining serogroups, most notably for serogroup C.

Table 28. hSBA Geometric Mean Titers at 30 Days After the 2nd Dose of a 2-Dose Series (6-7 Months, 12-13 Months) of MenQuadfi or Menveo, PPAS2, Study MET61

Serogroup	MenQuadfi Group 1 GMT (95% CI)[a] N1=162-171	Menveo Group 2 GMT (95% CI)[a] N1=158-160
A	184 (143, 237)	119 (90.6, 157)
C	1473 (1236, 1756)	319 (263, 388)
Y	423 (358, 499)	133 (107, 166)
W	442 (367, 533)	106 (83.4, 135)

Source: Adapted from STN 125701/262, Study MET61 Clinical Study Report, Tables 8.188. Data cutoff 08Jan2024.
Abbreviations: CI=confidence interval; hSBA=serum bactericidal activity using human complement; PPAS2=Per Protocol Analysis, Set 2, GMT=geometric mean titer, N1=number of participants with available data for the relevant endpoint
Notes: Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
a 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation

Reviewer Comments:

1. Both the analyses of the primary and secondary hypothesis-tested endpoints met the protocol-specified noninferiority criteria for success, demonstrating the effectiveness of MenQuadfi compared with a currently licensed meningococcal vaccine when administered as a 2-dose series in infants/toddlers at 6-7 months and 12-13 months of age. Descriptive analyses of GMTs post-2nd dose supported the results observed in the noninferiority analyses.

2. The criterion for seroresponse used for the first primary endpoint of seroresponse rates after the 2nd dose was dependent on the participant's hSBA titers at pre-Dose 1 (at

approximately 6 months of age). Maternal antibodies should be waning by this age, and it is expected that the majority of participants would have low baseline hSBA titers. To assess for potential differences in seroresponse rates based on pre-dose 1 serostatus, descriptive subgroup analyses of SRR post-2nd dose were performed based on participants with baseline hSBA titers <1:8 versus those with titers ≥1:8 (see section 6.2.11.1). Overall, the percentages of participants achieving seroresponse were similar in the MenQuadfi group compared with the Menveo group, regardless of the pre-Dose 1 hSBA titer level.

Secondary Objective #3: hSBA titers and seroresponse rates post 1st dose in 2-dose series (6-7 months, 12-13 months)

In descriptive analyses of hSBA titers and seroresponse 30 days after first vaccination at 6-7 months, hSBA GMTs post-1st dose were higher among MenQuadfi recipients compared with Menveo recipients for serogroups C and Y, and similar across the two groups for serogroups A and W. The percentage of participants with seroresponse was low overall, but higher for all serogroups among those receiving MenQuadfi as compared with Menveo, with non-overlapping intervals for serogroup Y. A similar trend was also observed based on percentages of participants with a ≥ 4-fold rise of hSBA titer. Percentages of participants with post-1st dose hSBA titers ≥1:8 in the MenQuadfi and Menveo groups were 54.6% and 37.9%, respectively, for serogroup A, 96.9% and 90.2%, respectively, for serogroup C, 60.8% and 26.6%, respectively, for serogroup Y, and 38.1% and 28.4%, respectively, for serogroup W.

> Reviewer Comment: In both the MenQuadfi and Menveo groups, for all serogroups besides serogroup C, the percentages of participants achieving seroresponse or hSBA titers ≥1:8 were low, supporting the need for a second dose of the vaccine at 12-13 months of age to provide adequate protection. These data support the recommended dose and schedule of MenQuadfi in Section 2.2 of the USPI, which states that for infants initiating vaccination at 6 months through 11 months of age, the second dose should be administered in the second year of life and at least 3 months after the first dose.

Secondary Objective #4: hSBA titers and seroresponse pre-2nd dose in 2 dose (6-7 months, 12-13 months) *(results not shown)*

Descriptive analyses of hSBA GMTs 6 months after the first vaccination at 6-7 months (pre-2nd dose) are shown in Table 29. Pre-2nd dose hSBA titers were higher in the MenQuadfi group compared with the Menveo group for serogroups C, W, and Y and comparable across the two groups for serogroup A. Similarly, the percentage of participants with hSBA titers ≥ 1:8 at pre-2nd dose was higher in the MenQuadfi group compared with the Menveo group for serogroups C, W, and Y and comparable across the two groups for serogroup A. The percentages of participants with seroresponse from pre-2nd dose to 30 days after the 2nd dose, and the percentages of participants with at least a 4-fold rise in hSBA titers from pre- to post-2nd dose, were similar across the two groups for all serogroups (results not shown).

Table 29. hSBA GMTs and Percentage of Participants With hSBA titer ≥1:8 Pre- 2nd Dose of a 2-Dose Series (6-7 Months, 12-13 Months) of MenQuadfi or Menveo, PPAS3, MET42

Sero-group	Endpoint	MenQuadfi Group 1 N1=103-106	Menveo Group 2 N1=91-94
A	GMT (95% CI) [a]	20.1 (14.7, 27)	14.9 (11.0, 20.3)
C	GMT (95% CI) [a]	150 (117, 193)	12.7 (9.6, 16.8)
Y	GMT (95% CI) [a]	46.2 (36.3, 58.6)	6.7 (5.4, 8.4)
W	GMT (95% CI) [a]	46.8 (36.1, 60.5)	6.2 (4.9, 7.8)

Sero-group	Endpoint	MenQuadfi Group 1 N1=103-106	Menveo Group 2 N1=91-94
A	% with hSBA ≥1:8 (95% CI) [b]	77.7% (68.4, 85.3)	73.6% (63.3, 82.3)
C	% with hSBA ≥1:8 (95% CI) [b]	98.1% (93.2, 99.8)	69.1% (58.8, 78.3)
Y	% with hSBA ≥1:8 (95% CI) [b]	96.2% (90.6, 99.0)	54.8% (44.2, 65.2)
W	% with hSBA ≥1:8 (95% CI) [b]	96.2% (90.6, 99.0)	50.5% (40.0, 61.1)

Source: Adapted from STN 125701/262, Study MET61 Clinical Study Report, Tables 8.184, 8.190. Data cutoff 08Jan2024.
Abbreviations: N1=number of participants with valid serology results for the particular serogroup and time point, GMT=geometric mean titer; hSBA=serum bactericidal activity using human complement; PPAS3=per protocol analysis set 3
Notes: Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
a 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
b 95% CI of the single proportion calculated from the exact binomial method;

Reviewer Comment: Descriptive evaluation of hSBA GMTs and titers ≥1:8 at 6 months after first vaccination (prior to 2nd dose) demonstrate higher responses in MenQuadfi recipients compared with Menveo recipients. Although a high percentage of MenQuadfi recipients had hSBA titers ≥1:8 at pre-2nd dose for serogroups C, Y, and W, the hSBA GMTs at pre-2nd dose were much lower compared with those observed post-2nd dose (Table 28), supporting the need for a second dose.

Secondary Objective #5: hSBA titers and seroresponse post-2nd dose in 2-dose series (17-19 months, 20-23 months)

Descriptive analyses of hSBA GMTs, titers ≥1:8, and seroresponse rates in participants who received a 2-dose series of MenQuadfi or Menactra at 17-19 months and 20-23 months are shown in Table 30. After the 2nd dose at 20-23 months, GMTs were higher across all serogroups among MenQuadfi recipients compared with Menactra recipients. The percentages of participants with post-2nd dose hSBA titers ≥1:8 were higher in the MenQuadfi group compared with the Menactra group for serogroups A and W, and similar across the two groups for serogroups Y and W. The percentage of participants who achieved seroresponse was higher in the MenQuadfi group compared with the Menactra group for all serogroups, however the confidence intervals were overlapping except for serogroup W. A similar trend was observed for the percentage of participants with a ≥4-fold rise in hSBA titers from pre-1st dose to post-2nd dose (results not shown).

Table 30. hSBA GMTs, Percentage of Participants With hSBA Titer ≥1:8, and Seroresponse Rate 30 Days After 2nd Dose of a 2-Dose Series (17-19 Months, 20-23 Months) of MenQuadfi or Menactra, PPAS2, MET42

Sero-group	Endpoint	MenQuadfi Group 3 N1=59-61	Menactra Group 4 N1=58-65
A	GMT (95% CI)[a]	45.0 (29.8, 68.0)	13.2 (8.72, 19.9)
C	GMT (95% CI)[a]	1727 (1300, 2294)	59.4 (44.3, 79.6)
Y	GMT (95% CI)[a]	284 (218, 369)	45.5 (32.9, 62.8)
W	GMT (95% CI)[a]	202 (152, 267)	25.0 (17.6, 35.7)
A	% with hSBA ≥1:8 (95% CI)[b]	88.5% (77.8, 95.3)	62.5% (49.5, 74.3)
C	% with hSBA ≥1:8 (95% CI)[b]	100% (94.1, 100)	98.5% (91.7, 100)
Y	% with hSBA ≥1:8 (95% CI)[b]	100% (94.1, 100)	92.3% (83.0, 97.5)
W	% with hSBA ≥1:8 (95% CI)[b]	100% (94.1, 100)	84.6% (73.5, 92.4)
A	Seroresponse Rate, % (95% CI)[b]	72.9% (59.7, 83.6)	46.6% (33.3, 60.1)
C	Seroresponse Rate, % (95% CI)[b]	100% (93.9, 100)	93.2% (83.5, 98.1)
Y	Seroresponse Rate, % (95% CI)[b]	100% (93.9, 100)	88.1% (77.1, 95.1)

Sero-group	Endpoint	MenQuadfi Group 3 N1=59-61	Menactra Group 4 N1=58-65
W	Seroresponse Rate, % (95% CI)[b]	100% (93.9, 100)	76.3% (63.4, 86.4)

Source: Adapted from STN 125701/262, Study MET61 Clinical Study Report, Tables 8.208, 8.210, 8.216. Data cutoff 08Jan2024.
Abbreviations: N1=number of participants with valid serology results for the particular serogroup and time point, GMT=geometric mean titer; hSBA=serum bactericidal activity using human complement; PPAS2=per protocol analysis set 2
Notes: Seroresponse=post-vaccination titer ≥1:16 for participants with prevaccination hSBA titer <1:8, or a post-vaccination titer ≥4-fold increase from baseline for participant with prevaccination hSBA titer ≥1:8.
Group 3: MenQuadfi conjugate vaccine at 17-19 months of age and 20-23 months of age
Group 4: Menactra at 17-19 months of age and 20-23 months of age
a 95% CI calculated using calculation for normal distribution on log10(titer) following by antilog transformation
b 95% CI of the single proportion calculated from the exact binomial method

Reviewer Comments:

1. Descriptive analyses of hSBA responses after the 2nd dose for toddlers (2-dose series: 17-19 months, 20-23 months) following MenQuadfi were higher compared with Menactra, with greatest difference observed for serogroup C GMTs (MenQuadfi: 1727, Menveo: 59.4). Although formal noninferiority hypothesis testing was not performed, the immune responses described for the 2-dose series in the older toddler cohort align with the results of the noninferiority analyses in the younger infant/toddler cohort.

2. Together, the analyses in both age cohorts support the effectiveness of a 2-dose series over a flexible dosing interval and age range in children 6 months to <2 years, that includes both a minimum 3-month interval between the 1st and 2nd dose and the option to initiate the 2-dose series either during the first year of life (with the 2nd dose administered in the second year of life) or during the second year of life.

6.2.11.1 Subgroup Analyses

Immunogenicity results were comparable across groups for male and female participants and participants of different races.

Subgroup Analyses Based on Baseline Pre-Dose 1 hSBA Titers (< 1:8 and ≥1:8), when the 1st Dose is Administered at 6-7 months of age

The percentage of participants with pre-dose 1 hSBA titers <1:8 (baseline) at 6-7 months of age was comparable across both MenQuadfi and Menveo groups. The percentages of study participants in the PPAS2 with hSBA titers <1:8 at pre-dose 1 for each serogroup were as follows:

- Serogroup A: 70.8 %-75.6 %
- Serogroup C: 93.0 %-93.9%
- Serogroup Y: 91.3%-93.8%
- Serogroup W: 93.8%-95.3%

Reviewer Comment: The majority of participants across both groups had Pre-dose 1 titers <1:8 for all four serogroups. There was a higher percentage of participants with baseline hSBA titers ≥1:8 for serogroup A compared with other serogroups, which was not observed among participants at 2 months of age in MET42 (section 6.1.11.1).

Table 31 provides the percentage of participants achieving hSBA vaccine seroresponse based on pre-Dose 1 hSBA titers <1:8 or ≥1:8. For all serogroups, seroresponse rates were lower in participants with pre-Dose 1 titers ≥1:8 compared with those with pre-Dose 1 titers <1:8. For

participants with pre-Dose 1 hSBA titers <1:8, seroresponse rates were numerically higher in MenQuadfi recipients compared with Menveo recipients for all serogroups, although the confidence intervals overlap. Similarly, for participants with pre-Dose 1 hSBA titers ≥1:8, higher seroresponse rates were observed among MenQuadfi recipients compared with Menveo recipients; however, sample sizes were small resulting in wide confidence intervals that overlap.

Table 31. Descriptive Analyses of Vaccine Seroresponse Rate 30 Days After the 2nd Dose, by Pre-Dose 1 hSBA Titer (<1:8 and ≥1:8), PPAS2, MET 61

Sero-group	MenQuadfi Group 1 Pre-Dose 1 hSBA Titer <1:8 SRR % (95% CI) N=101-137	Menveo Group 2 Pre-Dose 1 hSBA Titer <1:8 SRR % (95% CI) N=95-121	MenQuadfi Group 1 Pre-Dose 1 hSBA Titer ≥1:8 SRR % (95% CI) N=5-40	Menveo Group 2 Pre-Dose 1 hSBA Titer ≥1:8 SRR % (95% CI) N =7-28
A	95.0 (88.8, 98.4)	88.4 (80.2, 94.1)	75.0 (58.8, 87.3)	64.3 (44.1, 81.4)
C	100 (97.2, 100)	98.3 (94.1, 99.8)	80.0 (28.4, 99.5)	85.7 (42.1, 99.6)
Y	100 (97.2, 100)	98.3 (94.2, 99.8)	80.0 (44.4, 97.5)	85.7 (42.1, 99.6)
W	100 (97.3, 100)	94.1 (88.3, 97.6)	83.3 (35.9, 99.6)	75.0 (34.9. 96.8)

Source: STN 125701/262, Amendment 41, Table 2.2, 2.3
Abbreviations: N =number of participants with valid serology results; PPAS2=per protocol analysis set2; hSBA=serum bactericidal activity using human complement; SRR=seroresponse rate
Notes: Seroresponse: if prevaccination (pre-1st dose) hSBA titer <1:8, then post-4th dose vaccinations titer must be ≥1:16; and if prevaccination hSBA titer ≥1:8, then post-4th dose vaccination titer ≥4-fold increase from prevaccination titer.
Subgroup 1a: MenQuadfi and recommended vaccines at 2, 4, 6, and 12-15 months of age. Immune responses assessed 30 days after the 4th dose of MenQuadfi administered concomitantly with recommended vaccines at 12-15 months.
Subgroup 2a: Menveo at 2, 4, 6, and 12 months of age and recommended vaccines at 2, 4, 6, 12, and 15-18 months of age. Immune responses assessed 30 days after the 4th dose of Menveo administered concomitantly with recommended vaccines at 12 months.

Reviewer Comment: As seen in the subgroup analysis for MET 42 (see section 6.1.11.1), the majority of participants contributing to this analysis had hSBA titer levels <1:8, suggesting the absence of maternal antibodies prior to receipt of study vaccines for these participants. As expected, across both the MenQuadfi and Menveo groups, infants with baseline hSBA titers <1:8 achieved seroresponse (post-2nd dose hSBA titers ≥1:16) at higher rates compared with infants with hSBA titers ≥1:8, which required at least 4-fold rise in hSBA titer levels post-2nd dose from pre-Dose 1, though these data are limited by small sample sizes.

Irrespective of baseline status, MenQuadfi vaccine effectiveness against each serogroup was demonstrated in the analyses of the secondary endpoint evaluating the noninferiority of percentage of participants who achieved hSBA titer ≥1:8 following the 2nd dose (Table 27) when compared with Menveo.

6.2.12 Safety Analyses

The Overall Safety Analysis Set for Any Dose (SafAS) for the 2-dose series administered at 6-7 months and 12-13 months included 370 participants who received MenQuadfi (Group 1) and 361 participants who received Menveo (Group 2), of whom 84.3% and 84.8% of participants, respectively, completed at least 6 months of safety follow-up post-last vaccination. In the study, 309 MenQuadfi recipients and 302 Menveo recipients completed both doses of the 2-dose series administered at 6-7 and 12-13 months. The SafAS for the 2-dose series administered at 17-19 months and 20-23 months included 96 participants who received MenQuadfi (Group 3) and 103 participants who received Menactra (Group 4), of whom 86.5% and 93.2% of participants, respectively, completed at least 6 months of safety follow-up post-last vaccination.

In the study, 86 MenQuadfi recipients and 96 Menveo recipients received both doses of the 2-dose series administered at 17-19 and 20-23 months of age.

6.2.12.1 Methods

See section 6.2.2 above.

6.2.12.2 Overview of Adverse Events

The table below provides an overview of solicited ARs and unsolicited AEs reported in the study for the MenQuadfi, Menveo, and Menactra groups. Rates of solicited ARs within 7 days and unsolicited AEs within 30 days were generally comparable between the MenQuadfi and Menveo groups and MenQuadfi and Menactra groups. Through the study duration (6 months after the last dose), the percentage of participants reporting any MAAEs were balanced across the groups. AESIs and SAEs were rare and were generally reported less frequently in the MenQuadfi group compared with the Menveo or Menactra groups. There were no deaths reported in the study.

Table 32. Percentages of Participants Reporting at Least One Adverse Event Following Vaccination, Overall Safety Analysis Set, Any Dose*, Study MET61

AE Type: Monitoring Period[a]	MenQuadfi Group 1 N=370 % (n/N1)	Menveo Group 2 N=361 % (n/N1)	MenQuadfi Group 3 N=96 % (n/N1)	Menactra Group 4 N=103 % (n/N1)
Immediate unsolicited AE* within 30 minutes	0 (0/370)	0.3 (1/361)	0 (0/96)	0 (0/103)
Solicited local AR[b] at injection site within 7 days	55.9 (199/356)	52.6 (180/342)	57.1 (52/91)	48.0 (48/100)
Grade 3 solicited local AR	2.8 (10/356)	2.9 (10/342)	0 (0/91)	1.0 (1/100)
Solicited systemic AR[c] within 7 days	66.0 (235/356)	62.9 (215/342)	60.4 (55/91)	62.0 (62/100)
Grade 3 solicited systemic AR	9.6 (34/356)	7.9 (27/342)	4.4 (4/91)	7.0 (7/100)
Unsolicited AEs*: within 30 days	49.2 (182/370)	42.7 (154/361)	37.5 (36/96)	35.9 (37/103)
Severe AEs	1.9 (7/370)	1.9 (7/361)	3.1 (3/96)	4.9 (5/103)
Related[d] AEs	3.0 (11/370)	2.5 (9/361)	3.1 (3/96)	3.9 (4/103)
MAAEs: Entire study period	68.1 (252/370)	69.0 (249/361)	63.5 (61/96)	62.1 (64/103)
Related[d] MAAEs	0.3 (1/370)	0 (0/361)	0 (0/96)	0 (0/103)
AESIs: Entire study period	0.3 (1/370)	0.6 (2/361)	0 (0/96)	1.9 (2/103)
Related[d] AESIs	0 (0/370)	0 (0/361)	0 (0/96)	1.0 (1/103)
SAEs: Entire study period	1.6 (6/370)	3.3 (12/361)	1.0 (1/96)	3.9 (4/103)
Related[d] SAEs	0 (0/370)	0 (0/361)	0 (0/96)	1.0 (1/103)
Deaths: Entire study period	0 (0/370)	0 (0/361)	0 (0/96)	0 (0/103)
AEs leading to withdrawal: Entire study period	0 (0/370)	0.3 (1/361)	0 (0/96)	0 (0/103)

Source: Adapted from STN 125701/262.2, Study MET61 Clinical Study Report, Tables 8.29, 8.34, 8.109, 8.124, 8.149, 8.161, 8.167, 8.172, 8.174, 8.175. Data cutoff 08Jan2024.
Abbreviations: AE=adverse event; AR=adverse reaction; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; N=number of participants in overall safety analysis set for any dose; N1=number of

participants with available data for the relevant endpoint; n=number of participants experiencing the endpoint listed in the first column; percentages based on N1.
Notes:
*AEs include all unsolicited events, including events classified as unsolicited AR
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local reactions included injection site tenderness, erythema and swelling.
c. Solicited systemic reactions included fever, vomiting, crying abnormal, drowsiness, appetite lost, irritability.
d. Relatedness to study vaccine as determined by principal investigator.
Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age.
Group 4: Menactra at 17-19 months of age and 20-23 months of age.

6.2.12.3 Solicited Adverse Reactions (ARs)

As described in section 6.2.7, solicited ARs were collected with diary cards by the parent/guardian and entered by study staff in the case report form (CRF) after review of the diary card with the parent/guardian at the subsequent study visit. In participants receiving at least one dose of the 2-dose series of MenQuadfi at 6-7 months and 12-13 months of age, 55.9% experienced one solicited local AR and 66.0% experienced at least one solicited systemic AR, which was comparable to the percentages of participants reporting one or more solicited local and systemic ARs in the Menveo group. In participants receiving at least one dose of the 2-dose series of MenQuadfi or Menactra at 17-19 months of age and 20-23 months of age, a slightly higher percentage of MenQuadfi recipients (57.1%) experienced at least one solicited local AR compared with Menactra recipients (48%). 62.9% of MenQuadfi recipients experienced at least one solicited systemic AR, with a comparable percentage in the Menactra group.

Solicited Local Adverse Reactions

Table 33 provides the reported rates of solicited local adverse reactions in the 7 days following each study dose. For all groups, tenderness was the most frequently reported solicited local AR. The majority were Grade 1 in severity. For participants receiving the 2-dose series at 6-7 months and 12-13 months, the rates and severity of solicited local ARs were generally comparable across the MenQuadfi and Menveo groups for both doses. For participants receiving the 2-dose series at 17-19 months and 20-23 months, the rates and severity of solicited local ARs were generally comparable across the MenQuadfi and Menactra groups for after the first dose, but higher in the MenQuadfi group compared with the Menactra dose after the 2nd dose.

Across all groups and for all doses, solicited local ARs had onset within the first 3 days after vaccination and resolved after 1-3 days.

Table 33. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction[#] Within 7 Days Following Vaccination in 2-Dose Series, by Maximum Severity, Relevant Safety Analysis Set*, Study MET61

Solicited Local Adverse Reaction	MenQuadfi Group 1 Dose 1 6-7 Months N1=350-351	Menveo Group 2 Dose 1 6-7 Months N1=337-338	MenQuadfi Group 1 Dose 2 12-13 Months N1=289	Menveo Group 2 Dose 2 12-13 Months N1=272	MenQuadfi Group 3 Dose 1 17-19 Months N1=90	Menactra Group 4 Dose 1 17-19 Months N1=99	MenQuadfi Group 3 Dose 2 20-23 Months N1=82	Menactra Group 4 Dose 2 20-23 Months N1=93
Any local reaction, %	47.3	42.6	37.7	40.1	42.2	42.4	48.8	34.4
Grade 1	35.9	30.8	27.3	31.3	33.3	34.3	40.2	30.1
Grade 2	9.1	9.8	9.3	6.6	8.9	7.1	8.5	3.2
Grade 3	2.3	2.1	1.0	2.2	0	91	0	1.1
Tenderness[a],%	--	--	--	--	--	--	--	--
Any	42.7	34.7	30.1	32.0	34.4	35.4	41.5	26.9
Grade 1	31.6	23.7	20.4	24.6	26.7	29.3	32.9	23.7
Grade 2	8.8	8.9	9.0	5.9	7.8	5.1	8.5	2.2
Grade 3	2.3	2.1	0.7	1.5	0	1	0	1.1
Erythema[b],%	--	--	--	--	--	--	--	--
Any	21.1	21.6	21.8	21.7	22.2	22.2	25.6	16.1
Grade 1	20.6	21	21.5	20.2	22.2	21.2	25.6	15.1
Grade 2	0.6	0.6	0.3	0.7	0	1.0	0	1.1
Grade 3	0	0	0	0.7	0	0	0	0
Swelling[b],%	--	--	--	--	--	--	--	--
Any	16.0	15.7	14.5	14.7	18.9	12.1	20.7	7.5
Grade 1	15.7	14.8	14.2	14.3	17.8	11.1	20.7	7.5
Grade 2	0.3	0.9	0	0	1.1	1.0	0	0
Grade 3	0	0	0.3	0.4	0	0	0	0

Source Adapted from STN 125701/260.2, Study MET61 Clinical Study Report, Tables 8.35, 8.36, 8.37, 8.38, 8.60, 8.61, 8.62, 8.63 and Additional Analysis submitted to Amendment 5. Data cutoff 08Jan2024.
Abbreviations: N1=number of participants with available data for the relevant endpoint.
Notes:
Solicited local adverse reaction at the injection site for MenQuadfi, Menveo, or Menactra
* Relevant SafAS for each dose were as follows: Dose 1 was defined as those participants who received the dose 1 study vaccine and have any safety data available; Dose 2 was defined as those participants who received the dose 2 study vaccine and have any safety data available.
Group 1: MenQuadfi + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6-7 months of age and 12-13 months of age.
Group 3: MenQuadfi at 17-19 months of age and 20-23 months of age.
Group 4: Menactra at 17-19 months of age and 20-23 months of age.
a. For tenderness, Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced.
b. For erythema and swelling, Grade 1: >0 to <25 mm; Grade 2: ≥25 to <50 mm; Grade 3: ≥50 mm

Reviewer Comment: After a 2nd dose of the 2-dose series administered at 20-23 months, solicited local ARs were reported in a greater percentage of participants in the MenQuadfi group compared with the Menactra group, most notably for swelling (MenQuadfi: 20.7%, Menactra 7.5%) and tenderness (MenQuadfi 41.5%, Menactra: 26.9%). However, interpretation of these findings is limited by small sample sizes. There were no severe (Grade 3) solicited local ARs reported by MenQuadfi recipients after the 2nd dose at 20-23 months.

Solicited Systemic Adverse Reactions

Table 34 provides the reported rates of solicited systemic adverse reactions within 7 days following vaccination. Irritability, abnormal crying, and drowsiness were the most frequently reported systemic reaction after any dose across the study groups. The majority of systemic ARs reported were Grade 1 or 2 in severity. In participants who received the 2-dose series at 6-7 months and 12-13 months of age, fever was reported by 16.7% of MenQuadfi recipients and 17.0% of Menveo recipients after any dose. In participants who received the 2-dose series at 17-19 months and 20-23 months of age, fever was reported by 14.4% of MenQuadfi recipients and 18.0% of Menactra recipients after any dose. Grade 3 (> 39.5°C) fever was rare and reported by a similar percentage (0.9%-1.2%) of participants across the study groups after any dose.

Overall, the rates and severity of reported solicited systemic ARs were comparable across Groups 1 and 2 and across Groups 3 and 4 after each dose, except for drowsiness, which was more frequently reported by MenQuadfi recipients (23.2%) compared with Menactra recipients (14.0%) after Dose 2 in participants who received a 2-dose series at 17-19 months and 20-23 months.

Across all groups and for both doses, most solicited systemic ARs had onset within 3 days after vaccination and resolved after 1-3 days.

Table 34. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days Following Vaccination in 2-Dose Series, by Maximum Severity, Relevant Safety Analysis Set*, Study MET61

Solicited Local Adverse Reaction	MenQuadfi Group 1 Dose 1 6-7 months N1=341-351	Menveo Group 2 Dose 1 6-7 months N1=325-339	MenQuadfi Group 1 Dose 2 12-13 months N1=279-290	Menveo Group 2 Dose 2 12-13 months N1=261-273	MenQuadfi Group 3 Dose 1 17-19 months N1=89-90	Menactra Group 4 Dose 1 17-19 months N1=98-99	MenQuadfi Group 3 Dose 2 20-23 months N1=82	Menactra Group 4 Dose 2 20-23 months N1=91-93
Any systemic reaction, %	59.5	56.9	47.2	47.3	54.4	51.5	50.0	46.2
Grade 1	27.1	29.2	25.9	26.4	31.1	27.3	28.0	30.1
Grade 2	25.4	22.7	17.2	17.2	18.9	20.2	20.7	12.9
Grade 3	7.1	5.0	4.1	3.7	4.4	4.0	1.2	3.2
Fever[a], %	--	--	--	--	--	--	--	--
Any	12.9	12.3	9.3	7.7	11.2	12.2	11.0	8.8
Grade 1	8.8	8.3	6.8	4.2	7.9	7.1	6.1	5.5
Grade 2	3.8	3.4	1.8	2.7	2.2	4.1	4.9	3.3
Grade 3	0.3	0.6	0.7	0.8	1.1	1.0	0	0
Vomiting[b], %	--	--	--	--	--	--	--	--
Any	8.5	8.0	5.5	3.7	4.4	6.1	3.7	3.2
Grade 1	5.7	4.4	4.8	2.9	4.4	5.1	1.2	1.1
Grade 2	2.6	3.5	0.3	0.4	0	1.0	2.4	1.1
Grade 3	0.3	0	0.3	0.4	0	0	0	1.1
Crying abnormal[c], %	--	--	--	--	--	--	--	--
Any	35.0	32.4	26.6	25.3	26.7	26.3	25.6	19.4
Grade 1	21.7	22.7	18.3	17.9	18.9	17.2	19.5	14.0
Grade 2	11.7	8.6	7.6	6.6	6.7	7.1	6.1	4.3
Grade 3	1.7	1.2	0.7	0.7	1.1	2.0	0	1.1
Drowsiness[d], %	--	--	--	--	--	--	--	--
Any	36.5	38.9	27.7	31.5	24.4	23.2	23.2	14.0
Grade 1	27.1	28.6	20.4	23.4	20.0	19.2	18.3	10.8
Grade 2	7.1	8.0	6.6	7.0	4.4	2.0	4.9	2.2
Grade 3	2.3	2.4	0.7	1.1	0	2.0	0	1.1
Appetite lost[e], %	--	--	--	--	--	--	--	--
Any	17.1	16.2	15.2	17.3	21.1	23.2	20.7	25.8
Grade 1	12.5	14.2	10.4	13.6	15.6	16.2	17.1	21.5
Grade 2	3.1	1.5	4.2	2.9	5.6	6.1	3.7	3.2
Grade 3	1.4	0.6	0.7	0.7	0	1.0	0	1.1

Solicited Local Adverse Reaction	MenQuadfi Group 1 Dose 1 6-7 months N1=341-351	Menveo Group 2 Dose 1 6-7 months N1=325-339	MenQuadfi Group 1 Dose 2 12-13 months N1=279-290	Menveo Group 2 Dose 2 12-13 months N1=261-273	MenQuadfi Group 3 Dose 1 17-19 months N1=89-90	Menactra Group 4 Dose 1 17-19 months N1=98-99	MenQuadfi Group 3 Dose 2 20-23 months N1=82	Menactra Group 4 Dose 2 20-23 months N1=91-93
Irritability[f], %	--	--	--	--	--	--	--	--
Any	49.0	45.1	40.0	40.4	40.0	43.4	35.4	33.3
Grade 1	24.2	24.5	22.8	27.2	22.2	24.2	22.0	24.7
Grade 2	19.9	17.1	14.1	11.4	14.4	16.2	12.2	5.4
Grade 3	4.8	3.5	3.1	1.8	3.3	3.0	1.2	3.2

Source Adapted from STN 125701/262.2, Study MET61 Clinical Study Report, Tables 8.35, 8.36, 8.37, 8.28, 8.90, 8.91, 8.92, 8.93 and from Additional Analysis submitted to Amendment 5. Data cutoff 08Jan2024.
Abbreviations: N1=number of participants with available data for the relevant endpoint.
Notes:
* Relevant SafAS for each dose were as follows: Dose 1 was defined as those participants who received the dose 1 study vaccine and have any safety data available; Dose 2 was defined as those participants who received the dose 2 study vaccine and have any safety data available.
Group 1: MenQuadfi + recommended pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age.
Group 2: Menveo + recommended pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age.
Group 3: MenQuadfi at 17 to 19 months of age and 20 to 23 months of age.
Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age.
a. For fever, Grade 1: ≥ 38.0°C to ≤ 38.5°C or ≥ 100.4°F to ≤ 101.3°F; Grade 2: > 38.5°C to ≤ 39.5°C or > 101.3°F to ≤ 103.1°F; Grade 3: > 39.5°C or > 103.1°F
b. For vomiting, Grade 1: 1 episode per 24 hours; Grade 2: 2– 5 episodes per 24 hours; Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration.
c. For crying abnormal, Grade 1: < 1 hour; Grade 2: 1 - 3 hours; Grade 3: > 3 hours
d. For drowsiness, Grade 1: Sleepier than usual or less interested in surroundings; Grade 2: Not interested in surroundings or did not wake up for a feed / meal; Grade 3: Sleeping most of the time or difficult to wake up
e. For appetite lost, Grade 1: Eating less than normal; Grade 2: Missed 1 or 2 feeds / meals completely; Grade 3: Refuses ≥ 3 feeds / meals or refuses most feeds / meals
f. For irritability, Grade 1: Easily consolable; Grade 2: Requiring increased attention; Grade 3: Inconsolable

Reviewer Comment**:** In general, the rate of any reported solicited systemic AR after each dose were similar in participants who received the 2-dose series of MenQuadfi at 6-7 months and 12-13 months of age compared with those who received the 2-dose series at 17-19 months and 20-23 months of age.

Rates of fever after any dose of a 2-dose series were generally similar to those seen after any dose of a 4-dose series of MenQuadfi (see the pooled data in the Fever section of the Integrated Safety Summary), with the exception of fever after the 2nd and 3rd doses of MenQuadfi in a 4-dose series which were slightly higher than those seen after any dose in the 2-dose series.

6.2.12.4 Unsolicited AEs

Immediate Unsolicited AEs

Only one participant in the study experienced an immediate AE within 30 minutes post-vaccination, which was an event of head injury after receipt of the 1st dose of Menveo.

Reviewer Comment: No participant in any group experienced anaphylaxis or other immediate AEs concerning for a severe systemic allergic reaction.

Unsolicited AEs Within 30 Days After Vaccination

Rates of unsolicited AEs within 30 days after any vaccination were generally comparable across the study groups. The percentage of participants with at least one unsolicited AE within 30 days after any dose of a 2-dose series administered at 6-7 and 12-13 months of age was 49.2% in the MenQuadfi group (Group 1) and 42.7% in the Menveo group (Group 2). The percentage of participants with at least 1 unsolicited AE within 30 days after any dose of a 2-dose series administered at 17-19 months and 20-23 months of age was 37.5% in the MenQuadfi group (Group 3) and 35.9% in the Menactra group (Group 4). The most frequently reported AEs across all groups were under the MedDRA SOC *Infections and infestations* (31.6% in Group 1, 27.1% in Group 2, 17.7% in Group 3, and 23.3% in Group 4). By MedDRA PT, the most frequently reported AEs across Groups 1 and 2 were upper respiratory tract infection (MenQuadfi: 11.1%, Menveo: 11.1%) and teething (MenQuadfi: 7.8%, Menveo 6.9%). By MedDRA PT, the most frequently reported AEs across Groups 3 and 4 were otitis media (MenQuadfi: 5.2%, Menactra: 4.9%) and diarrhea (MenQuadfi: 4.2%, Menactra: 3.9%).

Reviewer Comment: The reported rates and types of unsolicited adverse events were generally comparable between the study groups and represent medical conditions that are common in children.

Medically Attended Adverse Events (MAAEs)

Within 30 days after any vaccination, MAAEs were reported by 36.8% of MenQuadfi recipients in Group 1 compared with 32.4% of Menveo recipients in Group 2, and 29.2% of MenQuadfi recipients in Group 3 compared with 27.2% of Menactra recipients in Group 4. During the entire study duration of 6 months after the last vaccination, MAAEs were reported by a similar percentage of participants across all study groups (Group 1: 68.1%, Group 2: 69.0%, Group 3: 63.5%, Group 4: 62.1%). By MedDRA PT, across all groups, upper respiratory tract infection (Group 1: 30.0%, Group 2: 31.9%, Group 3: 19.8%, Group 4: 17.5%), and otitis media (Group 1: 16.5%, Group 2: 16.3%, Group 3: 13.5%, Group 4: 14.6%) were the most frequently reported MAAE. Of all the reported MAAEs during the study, only one event was assessed as related by

the study investigator, which was an event of injection site reaction reported by a MenQuadfi recipient in Group 1.

Reviewer Comment: The reported rates and types of MAAEs were generally balanced across the study groups and represent medical conditions that are common in children. The one MAAE assessed as related in the MenQuadfi group was an event representative of vaccine reactogenicity.

6.2.12.5 Deaths

No deaths were reported during the study in any group.

6.2.12.6 Nonfatal Serious Adverse Events

Within 7 days after any vaccination, SAEs were reported by no MenQuadfi recipients in Groups 1 or 3, by 0.3% of Menveo recipients in Group 2 (1 participant reporting 1 event), and by 1% of Menactra recipients (1 participant reporting 1 event) in Group 4.

Within 30 days after any vaccination, SAEs were reported by 0.3% (1 event in 1 participant) of MenQuadfi recipients in Group 1; 0.6% (2 events in 2 participants) of Menveo recipients in Group 2; no MenQuadfi recipients in Group 3; and 1.9% (2 events in 2 participants) of Menactra recipients in Group 4.

During the study (through 6 months after the last vaccination), SAEs were reported by 1.6% of MenQuadfi recipients in Group 1 (6 events in 6 participants); 3.3% of Menveo recipients in Group 2 (13 events in 12 participants); 1.0% of MenQuadfi recipients in Group 3 (1 event in 1 participant); and 3.9% of Menactra recipients in Group 4 (5 events in 4 participants). Most SAEs were under the MedDRA SOC *Infections and infestations*.

Across all study groups, only one SAE of febrile seizure in a Menactra recipient (also reported as AESI), was assessed as related to the study vaccine by the investigator. This event is described in 6.2.12.7.1.I

Reviewer Comment: The SAEs observed in the study generally reflected common childhood illnesses. A review of the narratives for all SAEs accrued in the study did not identify any events assessed by this clinical reviewer as causally related to MenQuadfi.

6.2.12.7 Adverse Events of Special Interest (AESIs)

Protocol specified AESIs included generalized seizures (febrile and non-febrile), Kawasaki disease, Guillain-Barré syndrome, and Idiopathic thrombocytopenic purpura (ITP).

During the first 7 days and 30 days after vaccination, there were no AESIs reported by participants in MenQuadfi Groups 1 and 3 or Menveo Group 2. AESIs were reported by 1% of Menactra recipients (1 participant reporting 1 event) in Group 4.

During the entire study period, AESIs were reported by 1 (0.3%) MenQuadfi recipient in Group 1; 2 (0.6%) Menveo recipients in Group 2; no MenQuadfi recipients in Group 3; and 2 (1.9%) Menactra recipients (reporting 3 events) in Group 4. All 6 AESIs reported in the study were events of febrile seizure, of which one febrile seizure in a Menactra participant was assessed as related to vaccination (see 6.2.12.7.1).

6.2.12.7.1 Febrile Seizures

See 6.2.12.7 for the percentage of participants reporting a febrile seizure in each study group within 7 and 30 days after vaccination and the entire study period (all AESIs were febrile seizures). The one febrile seizure in MenQuadfi Group 1 occurred in a 10-month-old participant 119 days post-Dose 1 and was assessed as unrelated to study vaccination by the investigator.

Of the febrile seizures reported in the study, only one event in a Menactra recipient (febrile seizure 1 day after first dose of Menactra in a 17-month-old) was assessed as related by the investigator to study vaccine. This participant was also reported to have a family history of febrile seizures. Two days after the febrile seizure event, the participant was diagnosed with an otitis media and tonsillitis. The participant went on to have another febrile seizure 53 days after the first dose of Menactra with no concomitant illnesses reported; this event was assessed as unrelated to the vaccine by the investigator. This participant then discontinued from the trial.

> Reviewer Comment: This clinical reviewer agrees with the investigator's assessment that the first febrile seizure event in the Menactra recipient described above was most likely related to study vaccination, due to close temporal relationship to vaccination, despite report of concomitant illness two days later. The clinical review team also agreed with the investigator's assessment of the second febrile seizure as likely not related to vaccination due to the lack of close temporal relationship.
>
> The remaining febrile seizure events across groups were not considered related to study vaccination after clinical team review of the case narratives, including the febrile seizure in a 10-month-old participant 119 days after MenQuadfi.

See section 8 Integrated Overview of Safety for additional assessment and discussion of febrile seizures across studies.

6.2.12.8 Discontinuation due to AE

One participant experienced an AE leading to study discontinuation. This was a participant in Group 2 (Menveo) who was diagnosed with acute myeloid leukemia 5 days after receipt of the 1st dose of Menveo. The event was assessed as unrelated to study vaccines by the investigator. In addition, the Menactra recipient in Group 4 who experienced the related SAE of febrile seizure also discontinued from the study due to withdrawal by parent/guardian.

6.2.12.9 Subgroup Analyses

Descriptive subgroup analyses of the safety data showed comparable a safety profile between male and female participants and participants of different races across the groups.

6.2.13 Study Summary and Conclusions

MET61 was designed to demonstrate the safety and immunogenicity (inferred effectiveness) of MenQuadfi, as compared with Menveo or Menactra, when administered as a 2-dose series in infants and toddlers 6 months to <2 years of age. The study met the noninferiority criteria for success based on hSBA seroresponse rates and hSBA titers ≥1:8 to each of the four serogroups following a 2-dose series of MenQuadfi administered at 6-7 months and 12-13 months of age when compared with Menveo, when both were given with recommended pediatric vaccines. In addition, descriptive immunogenicity analyses of MenQuadfi administered

in a 2-dose series in toddlers 17-19 and 20-23 months of age suggest sufficient and comparable immune responses to those seen in younger infants after a 2-dose series. The safety profile of MenQuadfi was generally similar to that of the comparator vaccines. There were no febrile seizures reported within 30 days of vaccination in MenQuadfi recipients. For clinical reviewer analysis of febrile seizures across all studies, see the Integrated Overview of Safety in section 8.4.3. The data generated from this study support the safety and effectiveness of a 2-dose series of MenQuadfi in infants and toddlers 6 months to <2 years of age.

6.3 Trial #3: MET41

NCT03673462: "Safety of a Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly With Routine Pediatric Vaccines in Healthy Infants and Toddler Conditions"

Study Overview: This was a Phase 3, modified double-blinded, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenQuadfi when administered concomitantly with recommended pediatric vaccines given to healthy infants and toddlers. The study enrolled 2,797 (2,099 MenQuadfi; 698 Menveo) participants and was conducted at 75 sites in the United States, including Puerto Rico. The study was conducted from September 17, 2018, to March 16, 2023, with a database lock date of June 21, 2023.

6.3.1 Objectives

Primary Objective

To describe the safety profile of MenQuadfi and Menveo when administered concomitantly with recommended pediatric vaccines in healthy infants and toddlers.

- Endpoints:
    - Any unsolicited systemic AEs reported in the 30 minutes after each vaccination
    - Solicited local (injection site) reactions occurring up to Day 7 after each vaccination
    - Solicited systemic reactions occurring up to Day 7 after each vaccination
    - Unsolicited AEs up to Day 30 after each vaccination
    - SAEs (including AESIs) throughout the trial from Visit 1 to the 6-month follow-up contact after the last vaccination
    - MAAEs throughout the trial, from Visit 1 to the 6-month follow-up contact after the last vaccination

6.3.2 Design Overview

Study MET41 was a modified double-blind, randomized, parallel-group, active-controlled, multi-center study in children 42 days through 89 days old at enrollment. A total of 1,620 children were enrolled and randomized in a 3:1 ratio to receive MenQuadfi concomitantly with recommended pediatric vaccines or Menveo concomitantly with recommended pediatric vaccines. The MenQuadfi and Menveo vaccines were administered at 2, 4, 6, and 12 months of age. The recommended pediatric vaccines administered were Pentacel (DTaP-IPV/Hib) at 2, 4, 6, and 15-18 months of age; Prevnar 13 (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age; RotaTeq (rotavirus vaccine) at 2, 4, and 6 months of age; Energix-B (hepatitis B vaccine) at 2 and 6 months of age (following first dose administered at least 28 days prior to enrollment); and M-M-R II (measles, mumps, and rubella vaccine) and Varivax (varicella vaccine) at 12 months of age. Participants were followed for safety through 6 months after the last study vaccination.

6.3.3 Population

The study population included healthy male and female participants 42 through 89 days old on the day of the first study visit. Participants had to have received the first dose of hepatitis B vaccine at least 28 days before the first study visit, and written informed consent had to be obtained from the participant's parent(s)/guardian.

Individuals were excluded from study enrollment if they planned participation in another clinical study investigating a vaccine, drug, medical device, or medical procedure in the 4 weeks before and/or following any study vaccination or if they received any vaccine in the 4 weeks preceding the first study vaccination (except for monovalent pandemic influenza vaccines and multivalent influenza vaccines, which could be received at least 2 weeks before or 2 weeks after any study vaccination). Participants could not have received more than 1 dose of hepatitis B vaccine prior to enrollment and could not have received previous vaccination against meningococcal disease, diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and /or rotavirus infection or disease. Individuals were excluded from enrollment if they had a history of any *Neisseria meningitidis*, diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, hepatitis A, measles, mumps, rubella, varicella, *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and/or rotavirus infection/disease.

6.3.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi: Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine (Sanofi Pasteur Inc.)

- Dose and route of administration: 0.5mL IM
- Schedule of administration: visits at 2, 4, 6, and 12 months
- Composition: sodium acetate buffered saline solution to contain 10 µg each of meningococcal capsular polysaccharides serogroups A, C, Y, and W and approximately 55 µg of tetanus toxoid protein carrier
- Presentation: solution for injection
- Lot #s: UD19645, UD20525, UD20584, UD21565, UD21952, UD22380, UD22548, UD7249AA

Menveo: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GSK Vaccines)

- Dose and route of administration: 0.5mL IM
- Schedule of administration: visits at 2, 4, 6, and 12 months
- Composition: 10 µg MenA oligosaccharide; 5 µg each of Men C, MenY, and MenW-135 oligosaccharide; 32.7 to 64.1 µg CRM_{197} protein; and ≤0.30 µg residual formaldehyde
- Presentation: lyophilized powder and liquid components combined to produce a solution
- Lot #s: M17035, AMVA035A, AMVA100A, AMVA196A, AMVA321A, AMVA414A, AMVA548A, AMVA655A

Pentacel: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Sanofi Pasteur Ltd.)

- Dose and route of administration: 0.5mL IM
- Schedule of administration: visits at 2, 4, 6, and 15-18 months
- Composition: diphtheria toxoid, tetanus toxoid, 5 component acellular pertussis antigens

(detoxified pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae types 2 and 3 (FIM)), inactivated polioviruses [Type 1 (Mahoney), Type 2 (MEF-1), Type 3 (Saukett)], and Hib antigen covalently bound to tetanus toxoid (PRP-T).
- Presentation: liquid DTaP-IPV used to reconstitute lyophilized ActHIB
- Lot #s: C5550AA, UJ065AAA, UJ390AAA, UJ601AAA

Prevnar 13: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein) (Wyeth Pharmaceuticals, Inc.)
- Dose and route of administration: 0.5mL IM
- Schedule of administration: visits at 2, 4, 6, and 12 months
- Composition: serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
- Presentation: suspension for injection
- Lot #s: X16197, DE8785, DR7167, EE7133, CM2357

RotaTeq: Rotavirus Vaccine, Live, Oral, Pentavalent) (Merck Sharp & Dohme Corp.)
- Dose and route of administration: 2 mL oral
- Schedule of administration: visits at 2, 4, and 6 months
- Composition: 5 live reassortant rotaviruses: serotypes G1, G2, G3, G4, and P1A (8)
- Presentation: Oral solution
- Lot #s: R002805, S005878, S017630, S013890, 1660685, S025595, 1661000, T026932, 1741377, T034512, S005874, S005876, T040208, 1658254

Engerix-B: Hepatitis B Vaccine [Recombinant] (GlaxoSmithKline Biologicals)
- Dose and route of administration: 0.5mL IM
- Schedule of administration: visits at 2 and 6 months
- Composition: Hepatitis B virus surface antigen (HBsAg) adsorbed on 0.25 mg aluminum as aluminum hydroxide
- Presentation: suspension for injection
- Lot #s: 5R52M, 97Y27, 3AM2M, P7294, K329E, 53YL7, F22EZ, FB9RH

M-M-R II: Measles, Mumps, and Rubella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Dose and route of administration: 0.5mL subcutaneous (SC)
- Schedule of administration: single dose at 12-month visit
- Composition:
    - Measles virus derived from Ender's Edmonston strain and propagated in chick embryo cell culture
    - Mumps virus, Jeryl Lynn (B level) strain propagated in chick embryo cell culture
    - Rubella virus, Wistar RA 27/3 strain propagated in WI-38 human diploid lung fibroblasts
- Presentation: lyophilized live virus vaccine
- Lot #s: S012944/S013898, S014431/S016519, S035354/S032591, T013003/T033839, T028935/U031355, U013035/T029521, T018892/T029529, R031679/S007963, R035701/S008566, R031679/S005076, S014431/S018821, T013003/T031063, R031679/S008566, S014431/S024969, S013683/S024969, R022423/R009955, S013683/S008566, S014431/S00856611

Varivax: Varicella Virus Vaccine Live (Merck Sharp & Dohme Corp.)
- Dose and route of administration: 0.5mL SC

- Schedule of administration: single dose at 12-month visit
- Composition: Oka/Merck varicella virus
- Presentation: suspension for injection
- Lot #s: S020159/S015238, S038175/S038151, T032315/T022571, T031381/S024969, T041501/U006135, S005084/S014277, R033660/S005076, R033660/S008566, S005084/S005076, S020159/S007963, T028306/T031063, S038175/S021106, R024144/S000978, S005084/S008566, S038175/S015238, T031381/T033839, T031381/T031063

6.3.5 Directions for Use

See section 6.1.4

6.3.6 Sites and Centers

Study MET41 was conducted at 75 sites in the United States, including Puerto Rico.

6.3.7 Surveillance/Monitoring

Safety Monitoring

Participants were followed for safety from Visit 1 (day of first study vaccination) to 6 months after the last vaccinations at 12 months of age. Refer to section 6.1.7 for adverse event monitoring. A physical examination was performed at Visits 1 and 4 prior to the first dose at 2 months of age and fourth dose at 12 months of age, respectively. Temperature measurement was obtained prior to administration of each dose, and reactogenicity and adverse events since the previous visit were reviewed.

> Reviewer Comment: See sections 3.2 and 6.1.7 and associated reviewer comments regarding the procedures for recording of safety data in the diary cards and the review process by the investigator before entry of the safety data into the CRF.

For any participant who prematurely withdrew from the study due to an AE, protocol deviation, or loss of eligibility, the site was to complete all scheduled safety follow-ups. If a participant was withdrawn by a parent/guardian or voluntarily withdrew, the site was to attempt to contact them for the 6-month follow-up unless the source document specified that they did not want to be contacted again.

An internal Safety Management Team (SMT) reviewed data from all ongoing studies with MenQuadfi at regular intervals for any new safety signals or safety concerns, with the authority to recommend a pause to investigate any potential signal or concern, if needed.

Immunogenicity Monitoring

There was no blood sampling and no immunogenicity monitoring for this safety-only study.

6.3.8 Endpoints

Refer to section 6.3.1 for study endpoints.

6.3.9 Statistical Considerations & Statistical Analysis Plan

This is a descriptive safety study with no hypothesis testing. There was no replacement for missing data.

Safety analysis included the following descriptive summaries for which exact (Clopper-Pearson) 2-sided 95% CIs were calculated for the percentages:

- Number and percentage of participants reporting any solicited local reactions and solicited systemic reactions occurring from Day 0 to Day 7 after each vaccination by study group for intensity, time of onset period, days of occurrence, and action taken
- Summary of immediate unsolicited systemic AEs and unsolicited AEs occurring up to Day 30 after each vaccination
- Number and percentage of participants reporting any unsolicited non-serious AEs by study group, intensity, time of onset period, duration, and by MedDRA PT and SOC, as well as by relationship to the study vaccine
- Number and percentage of participants reporting at least one MAAE throughout the study
- Number and percentage of participants reporting at least one SAE by study group, seriousness criterion, outcome, and by MedDRA SOC and PT, as well as by relationship to the study vaccine
- Number and percentage of participants reporting at least AESI throughout the study

No formal sample size calculation was performed. The sample size of this study was chosen to provide descriptive safety data. The overall planned study cohort of 3,080 participants provided a probability of approximately 95% of observing any AE with a true incidence of 0.15%. In the treatment arm with approximately 2,310 participants, there was a probability of approximately 95% of observing any AE with a true incidence of 0.2%.

Impact of COVID-19 pandemic was to be analyzed as follows:

- Participants impacted by COVID-19 pandemic defined as: at least one major/critical protocol deviation due to COVID-19 or did not complete the study due to COVID-19.
- If more than 10% of participants were impacted as per this definition, baseline and demographic characteristics and the main immunogenicity and safety endpoints were to be summarized in the subsets of impacted/non-impacted participants to assess the potential impact of the COVID-19 situation on study outcome.

Reviewer Comment: Less than 10% of study participants had at least one major/critical protocol deviation due to COVID-19 or did not complete the study due to COVID-19. Therefore, the additional sensitivity analyses specified above were not performed.

Protocol Amendments

Protocol version 3.0 (dated 9 May 2018) was the first version of the protocol to be submitted to FDA for review. Protocol version 4.0 (dated 29 May 2019) included updates to the inclusion criteria to allow a broader study population, including healthy participants born prematurely (<37 weeks) and with a birth weight <2.5 kg, to correspond with the population to be vaccinated under routine care, and added study sites in Puerto Rico to the study.

There were no changes in the conduct of the study and no changes in the planned analyses for the study prior to unblinding or database lock.

The following changes occurred after unblinding/database lock:

- The Applicant considered only Category 1 medications, those with potential impact on the evaluation of the safety of the study vaccines (e.g., antipyretics, analgesics, non-

steroidal anti-inflammatory drugs, systemic corticosteroids, and other immune modulators), to be relevant to MET41. Within Category 2, only non-study vaccines administered within the specified time were to be reported, as other Category 2 medications did not apply to MET41. However, all reportable and non-reportable medications were included.

- The database was initially locked on 2 Jun 2023; however, on 13 Jun 2023, the database was partially unlocked to allow correction of the following identified data errors: incorrect Menveo dose number, missing protocol deviation information, erroneous reporting of an AE symptom as an AE, and incorrect selection of the action taken for an AE.

6.3.10 Study Population and Disposition

A total of 2,797 participants were enrolled and randomized in the study between September 17, 2018, and September 30, 2021. Among these participants, 2,099 were randomized to the MenQuadfi group and 698 to the Menveo group.

6.3.10.1 Populations Enrolled/Analyzed

Safety data was analyzed for each dose according to the vaccine actually received at that dose. There was an Overall Safety Analysis Set (SafAS), comprised of participants who received at least 1 dose of study vaccine and had any safety data available, and five additional analysis sets as follows:

- SafAS1: participants who received study vaccine at Visit 1 (dose 1; ~2 months of age) and had any safety data available
- SafAS2: participants who received study vaccine at Visit 2 (dose 2; ~4 months of age) and had any safety data available
- SafAS3: participants who received study vaccine at Visit 3 (dose 3; ~6 months of age) and had any safety data available
- SafAS4: participants who received study vaccine at Visit 4 (dose 4; ~12 months of age) and had any safety data available
- SafAS5: participants who received all 4 doses of study vaccine and had any safety data available

6.3.10.2 Demographics

Among all vaccinated participants, there were more males (52.1%) than females (47.9%). The median chronological age at enrollment was 63 days (range: 61 days to 67 days). Infants born at less than 37 weeks gestational age accounted for 3.9% of study participants. Most participants (82.2%) identified as White and 27.2% of participants identified as Hispanic/Latino. The demographic characteristics of participants were similar across study groups and are shown in Table 35.

Table 35. Demographic and Baseline Characteristics, Overall SafAS, Study MET41

Baseline Characteristic	MenQuadfi N=2080	Menveo N=697
Sex, n (%)	--	--
Male	1087 (52.3)	361 (51.8)
Female	993 (47.7)	336 (48.2)
Age (days)[a]	--	--
Median age (min, max)	63.0 (42.0, 89.0)	63.0 (42.0, 89.0)
Race, n (%)	--	--
American Indian or Alaska Native	8 (0.4)	0

Baseline Characteristic	MenQuadfi N=2080	Menveo N=697
Asian	28 (1.3)	12 (1.7)
Black or African American	210 (10.1)	67 (9.6)
Native Hawaiian or Other Pacific Islander	9 (0.4)	5 (0.7)
White	1703 (81.9)	579 (83.1)
Mixed Origin	101 (4.9)	30 (4.3)
Unknown	12 (0.6)	0
Not Reported	9 (0.4)	4 (0.6)
Ethnicity, n (%)	--	--
Hispanic or Latino	558 (26.8)	198 (28.4)
Not Hispanic or Latino	1515 (72.8)	497 (71.3)
Unknown	0	0
Not reported	7 (0.3)	2 (0.3)
Study Site, n (%)	--	--
Puerto Rico	35 (1.7)	11 (1.6)
United States	2045 (98.3)	686 (98.4)
Born preterm[b]	--	--
Yes	89 (4.3)	20 (2.9)
No	1989 (95.6)	675 (96.8)
Unknown	2 (<0.1)	2 (0.3)

Source: Adapted from STN 125701/262, Study MET41 Clinical Study Report, Tables 8.14, 8.18, and from additional analyses submitted to Amendments 2 and 5. Data cutoff 21Jun2023.
Abbreviations: N=number of participants in overall safety analysis set for any dose; n=number of participants with the specified characteristic; SafAS=Safety Analysis Set
Note: Percentages based on N.
a. Age at study enrollment
b. Preterm is defined as infant born at gestational age <37 weeks.

Reviewer Comment: Demographics and baseline characteristics were balanced across study groups. The study included a total of 109 infants born preterm (32 to <37 weeks gestational age). Among the 89 infants born preterm in the MenQuadfi group, the large majority (83) were born at 34 to <37 weeks of gestation (late preterm). All 20 infants born preterm in the Menveo group were late preterm.

6.3.10.3 Participant Disposition

The disposition of study participants is shown in Table 36 below. A similar percentage of participants contributed to each of the safety analysis sets across the two groups. Through the end of the study, 86.4% of MenQuadfi recipients and 88.7% of Menveo recipients completed at least 6 months of safety follow-up. Study withdrawals due to adverse events were rare in both groups; however, there were more withdrawals due to AEs in the MenQuadfi group (0.5%) compared with the Menveo group (0.1%) (see section 6.3.12.7 for discussion of these events).

Table 36. Participant Disposition, Safety Analysis Sets, Study MET41

Population	MenQuadfi n (%) N=2080	Menveo n (%) N=697
Overall SafAS	2080 (100)	697 (100)
SafAS at 2 months of age	2080 (100)	697 (100)
SafAS at 4 months of age	2006 (96.4)	663 (95.1)
SafAS at 6 months of age	1951 (93.8)	648 (93.0)
SafAS at 12 months of age	1838 (88.4)	623 (89.4)
SafAS for all 4 doses received	1836 (88.3)	622 (89.2)

Population	MenQuadfi n (%) N=2080	Menveo n (%) N=697
Participants withdrawn from study	282 (13.6)	85 (12.2)
Reason for withdrawal	-	-
Adverse event*	11 (0.5)	1 (0.1)
Protocol deviation	19 (0.9)	10 (1.4)
Withdrawal by parent/guardian	150 (7.2)	55 (7.9)
Lost to follow-up	102 (4.9)	19 (2.7)
Completed 6 months safety follow-up	1797 (86.4)	618 (88.7)

Source: Adapted from STN 125701/262, Study MET41 Clinical Study Report, Table 8.7, 8.11 and from additional analyses submitted to Amendments 2, 5, and 41. Data cutoff 21Jun2023.
Abbreviations: N=number of participants in overall safety analysis set for any dose; n=number of participants with the specified characteristic; SafAS=Safety Analysis Set
Note: Percentages based on N.
*Discontinuations for adverse events may not be considered at the time of the safety analysis if intensity is <Grade 1 according to the Applicant.

Reviewer Comment: The proportion of participants who contributed to each analysis set and the proportion who withdrew from the study were balanced across the two groups.

6.3.11 Immunogenicity Analyses

There are no objectives for immunogenicity or efficacy in this study.

6.3.12 Safety Analyses

The Overall SafAS included 2,080 participants who received MenQuadfi and 697 participants who received Menveo, of whom 86.4% and 88.7%, respectively, completed at least 6 months of safety follow-up post-last vaccination. A total of 1,836 MenQuadfi recipients and 622 Menveo recipients received a full 4-dose series.

6.3.12.1 Methods

See section 6.1.7.

6.3.12.2 Overview of Adverse Events

Table 37 below provides an overview of AEs by type occurring for the MenQuadfi and Menveo groups. The reported rates of immediate AEs, solicited local and systemic ARs, unsolicited AEs, and MAAEs were generally comparable across study groups. Rates of AESIs and SAEs were low across groups with a slightly higher percentage of participants in the MenQuadfi group reporting events compared with the Menveo group. There were 3 deaths in the MenQuadfi group and none in the Menveo group. None of the deaths were considered related to MenQuadfi.

Table 37. Percentages of Participants Reporting at Least One Adverse Event Following Vaccination, Overall SafAS, Any Dose, Study MET41

AE Type: Monitoring Period[a]	MenQuadfi N=2080 % (n/N1)	Menveo N=697 % (n/N1)
Immediate AE*: within 30 minutes	0.3 (7/2080)	0.3 (2/697)
Solicited local AR[b] at the injection site of MenQuadfi or Menveo: within 7 days	79.0 (1596/2021)	77.7 (525/676)
Grade 3 solicited local AR	8.3 (168/2021)	8.0 (54/676)
Solicited systemic AR[c]: within 7 days	87.1 (1759/2019)	88.2 (596/676)

AE Type: Monitoring Period[a]	MenQuadfi N=2080 % (n/N1)	Menveo N=697 % (n/N1)
Grade 3 solicited systemic AR	18.8 (379/2019)	18.9 (128/676)
Unsolicited AEs*: within 30 days	65.0 (1352/2080)	62.7 (437/697)
Severe AEs	6.2 (128/2080)	4.6 (32/697)
Related[d] AEs	10.4 (216/2080)	10.6 (74/697)
MAAEs: Entire study period	76.0 (1581/2080)	75.5 (526/697)
Related[d] MAAEs	0.3 (7/2080)	0.7 (5/697)
AESIs: Entire study period	0.9 (19/2080)	0.1 (1/697)
Related[d] AESIs	0 (0/2080)	0 (0/697)
SAEs: Entire study period	5.2 (108/2080)	3.0 (21/697)
Related[d] SAEs	0 (0/2080)	0 (0/697)
Deaths: Entire study period	0.1 (3/2080)	0 (0/697)
Related[d] deaths	0 (0/2080)	0 (0/697)
AEs leading to withdrawal: Entire study period	0.5 (10/2080)	0.1 (1/697)

Source: Adapted from STN 125701/262, Study MET41 Clinical Study Report, Tables 8.20, 8.26, 8.88, 8.96, 8.104, 8.120, 8.131, 8.138, and 8.140 and from additional analyses submitted to Amendments 2, 5, and 32. Data cutoff 21Jun2023.
Abbreviations: AE=adverse event; AR=adverse reaction; MAAE=medically attended adverse event; AESI=adverse event of special interest; SAE=serious adverse event; SafAS=Safety Analysis Set; N=number of participants in overall safety analysis set for any dose; N1=number of participants with available data for the relevant safety set; n=number of participants who reported an event; %=percentage of participants with available data who reported an event
Notes: Participants were allocated to the vaccine groups as received at the first dose.
Severe corresponds to Grade 3.
*AEs include all unsolicited events, including events classified as unsolicited ARs
a. Monitoring Period: time interval that the relevant type of AE was monitored for post-vaccination.
b. Solicited local reactions included injection site tenderness, erythema and swelling.
c. Solicited systemic reactions included fever, vomiting, crying abnormal, drowsiness, appetite lost, irritability.
d. Relatedness to study vaccine as determined by principal investigator

6.3.12.3 Solicited Adverse Reactions

As described in section 6.3.7, solicited adverse reactions were recorded by parents/guardians in a diary card for 7 days after each vaccination. Within 7 days after any vaccination, a comparable percentage of participants in each group reported at least 1 solicited local or systemic adverse reaction after any dose (91.5% MenQuadfi and 92.9% Menveo).

Solicited Local Adverse Reactions

Table 38 below provides the reported rates, by severity grading, for solicited local adverse reactions (at the MenQuadfi or Menveo injection site) within 7 days following each study dose. The rates and severity of solicited local ARs were generally similar across the study groups. The majority of solicited ARs reported were mild (Grade 1). Tenderness was the most frequently reported solicited injection site reaction after any dose in both the MenQuadfi group (74.3%) and the Menveo group (73.8%). Solicited ARs were generally similar across the study doses, with the exception for erythema which showed a trend for increasing frequency following each subsequent dose.

The majority of solicited local reactions in both groups had onset within 3 days after vaccination and resolved after 1 to 3 days.

Table 38. Percentage of Participants Reporting at Least One Solicited Local Adverse Reaction# Within 7 Days Following Vaccination, by Maximum Severity, Relevant Safety Analysis Set*, Study MET41

Solicited Local Adverse Reaction	Dose 1 MenQuadfi N1=2007-2008	Dose 1 Menveo N1=673-674	Dose 2 MenQuadfi N1=1926-1927	Dose 2 Menveo N1=635-638	Dose 3 MenQuadfi N1=1795-1797	Dose 3 Menveo N1=598-599	Dose 4 MenQuadfi N1=1764-1767	Dose 4 Menveo N1=591-592
Any local reaction	54.4%	55.2%	54.1%	52.8%	54.2%	51.8%	53.7%	55.1%
Grade 1	37.6%	39.5%	40.4%	39.0%	42.8%	40.2%	39.8%	40.9%
Grade 2	13.1%	11.7%	10.7%	11.6%	9.2%	9.5%	11.3%	12.3%
Grade 3	3.7%	4.0%	3.0%	2.2%	2.1%	2.0%	2.5%	1.9%
Tender-ness[a]	49.7%	49.0%	47.9%	46.3%	46.9%	45.1%	49.2%	48.6%
Grade 1	33.5%	33.3%	34.3%	32.8%	35.7%	33.6%	35.8%	35.0%
Grade 2	12.5%	11.7%	10.7%	11.3%	9.1%	9.5%	11.1%	12.0%
Grade 3	3.6%	4.0%	2.9%	2.2%	2.1%	2%	2.3%	1.7%
Erythema[b]	15.9%	15.9%	21.1%	19.7%	24.6%	23.4%	25.5%	24.5%
Grade 1	15.0%	15.9%	21.0%	19.4%	24.3%	23.4%	25.0%	24.0%
Grade 2	0.8%	0%	0%	0.3%	0.2%	0%	0.3%	0.3%
Grade 3	<0.1%	0%	0.2%	0%	<0.1%	0%	0.2%	0.2%
Swelling[b]	10.3%	8.5%	12.0%	10.7%	12.9%	12.7%	14.8%	13.9%
Grade 1	9.8%	8.5%	11.7%	10.5%	12.8%	12.7%	14.5%	13.7%
Grade 2	0.4%	0%	0.2%	0.2%	<0.1%	0%	0.1%	0%
Grade 3	0.1%	0%	0.2%	0%	0%	0%	0.2%	0.2%

Source Adapted from STN 125701/262, Study MET41 Clinical Study Report, Tables 8.40,8.41,8.42,8.150,8.151 and from additional analyses submitted to Amendments 2 and 5. Data cutoff 21Jun2023.
Abbreviations: N1=number of participants with available data for the relevant AR; SafAS=Safety Analysis Set
Notes: For each dose, participants were allocated to the vaccine group as received at that visit. For 'Any Dose,' participants were allocated to the vaccine group as received for Dose 1.
Solicited local adverse reaction at the injection site for MenQuadfi or Menveo
* Relevant SafAS for each dose and for any dose were as follows: SafAS1 (Dose 1), SafAS2 (Dose 2), SafAS3 (Dose 3), SafAS4 (Dose 4)
a. For tenderness, Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is mobilized, or the movement of the injected limb is reduced.
b. For erythema and swelling, Grade 1: >0 to <25 mm; Grade 2: ≥25 to <50 mm; Grade 3: ≥50 mm

Solicited Systemic Adverse Reactions

Table 39 below provides the reported rates, by severity grading, for solicited systemic adverse reactions within 7 days following each study dose. The percentage of participants who reported a solicited systemic AR after any dose was similar across groups (87.1% MenQuadfi and 88.2% Menveo). Most systemic ARs were mild to moderate in severity. Irritability, crying abnormal, and drowsiness were the most common systemic ARs after any dose in both groups.

Reports of fever were less frequent following Dose 1 of MenQuadfi (7.6%) compared with subsequent doses (16.2%-18.5%), while reports of vomiting were more frequent following dose 1 of MenQuadfi (14.8%) compared with subsequent doses (6.4%-10.8%). Grade 3 fever (>39.5°C) was rare, reported by 2.4% and 1.8% of MenQuadfi and Menveo recipients, respectively, after any dose.

The majority of solicited systemic reactions in both groups had onset within 3 days after vaccination and resolved after 1 to 3 days.

Table 39. Percentage of Participants Reporting at Least One Solicited Systemic Adverse Reaction Within 7 Days Following Vaccination, by Maximum Severity, Relevant Safety Analysis Set*, Study MET41

Solicited Systemic Adverse Reaction	Dose 1 MenQuadfi N1=1972-2005	Dose 1 Menveo N1=663-674	Dose 2 MenQuadfi N1=1899-1927	Dose 2 Menveo N1=629-638	Dose 3 MenQuadfi N1=1742-1796	Dose 3 Menveo N1=583-600	Dose 4 MenQuadfi N1=1733-1767	Dose 4 Menveo N1=583-593
Any systemic reaction	75.3%	74.3%	71.5%	74.5%	65.6%	64.8%	65.6%	64.2%
Grade 1	34.9%	33.1%	31.1%	35.4%	33.9%	35.8%	30.7%	32.5%
Grade 2	33.5%	34.1%	32.9%	31.3%	26.4%	23.8%	27.8%	26%
Grade 3	6.9%	7.1%	7.5%	7.7%	5.3%	5.2%	7.1%	5.7%
Fever[a]	7.6%	8.0%	18.5%	18.0%	16.8%	13.4%	16.2%	10.5%
Grade 1	6.2%	6.5%	11.5%	11.3%	11.1%	8.6%	9.1%	6.7%
Grade 2	1.3%	1.4%	6.3%	6.2%	4.8%	3.8%	5.9%	3.1%
Grade 3	0.2%	0.2%	0.6%	0.5%	0.8%	1.0%	1.2%	0.7%
Vomiting[b]	14.8%	12.6%	10.8%	10.0%	7.9%	10.0%	6.4%	4.6%
Grade 1	9.7%	7.6%	6.3%	6.4%	5.2%	7.0%	4.3%	3.0%
Grade 2	4.6%	4.7%	4.0%	3.6%	2.6%	2.7%	1.8%	1.4%
Grade 3	0.4%	0.3%	0.5%	0%	<0.1%	0.3%	0.3%	0.2%
Crying abnormal [c]	48.7%	48.4%	47.0%	49.2%	39.3%	39.9%	41.9%	40.8%
Grade 1	31.8%	30.9%	28.0%	31.2%	25.4%	26.7%	25.8%	25.9%
Grade 2	14.1%	14.5%	15.9%	15.2%	11.9%	10.9%	13.3%	12.7%
Grade 3	2.8%	3.0%	3.0%	2.8%	1.9%	2.3%	2.8%	2.2%
Drowsi-ness[d]	53.6%	51.3%	48.2%	48.6%	41.7%	41.6%	40.4%	36.9%
Grade 1	39.0%	35.9%	35.6%	37.1%	31.0%	31.6%	30.6%	28.1%
Grade 2	12.3%	12.6%	10.6%	8.5%	9.5%	9.0%	7.6%	7.1%
Grade 3	2.3%	2.8%	1.9%	3.0%	1.2%	1.0%	2.2%	1.7%
Appetite lost[e]	25.4%	25.2%	24.5%	23.4%	22.8%	22.5%	26.1%	25.9%
Grade 1	18.7%	18.8%	17.9%	18.0%	16.7%	17.2%	18.5%	19.1%
Grade 2	6.2%	5.5%	5.8%	4.5%	5.5%	4.0%	5.9%	5.8%
Grade 3	0.6%	0.9%	0.8%	0.8%	0.6%	1.3%	1.7%	1.0%
Irritability[f]	60.7%	60.7%	58.6%	61.1%	53.7%	55.2%	56.3%	56.1%
Grade 1	30.7%	31.8%	29.2%	32.9%	30.5%	32.2%	29.5%	29.1%
Grade 2	26.0%	24.9%	25.2%	24.1%	20.0%	20.0%	22.4%	23.3%
Grade 3	4.0%	4.0%	4.1%	4.1%	3.2%	3.0%	4.4%	3.7%

Source Adapted from STN 125701/262, Study MET41 Clinical Study Report, Tables 8.64, 8.65, 8.66, 8.162, and 8.163 and from additional analyses submitted to Amendments 2 and 5. Data cutoff 21Jun2023.
Abbreviations: AR=adverse reaction; N1=number of participants with available data for the relevant AR; SafAS=Safety Analysis Set
Notes: For each dose, participants were allocated to the vaccine group as received at that visit. For 'Any Dose,' participants were allocated to the vaccine group as received for Dose 1.
* Relevant SafAS for each dose and for any dose were as follows: SafAS1 (Dose 1), SafAS2 (Dose 2), SafAS3 (Dose 3), SafAS4 (Dose 4)
a. For fever, Grade 1: ≥38.0°C to ≤38.5°C or ≥100.4°F to ≤ 101.3°F; Grade 2: >38.5°C to ≤39.5°C or >101.3°F to ≤103.1°F; Grade 3: >39.5°C or >103.1°F
b. For vomiting, Grade 1: 1 episode per 24 hours; Grade 2: 2–5 episodes per 24 hours; Grade 3: ≥6 episodes per 24 hours or requiring parenteral hydration.
c. For crying abnormal, Grade 1: <1 hour; Grade 2: 1-3 hours; Grade 3: >3 hours
d. For drowsiness, Grade 1: Sleepier than usual or less interested in surroundings; Grade 2: Not interested in surroundings or did not wake up for a feed / meal; Grade 3: Sleeping most of the time or difficult to wake up
e. For appetite lost, Grade 1: Eating less than normal; Grade 2: Missed 1 or 2 feeds / meals completely; Grade 3: Refuses ≥3 feeds / meals or refuses most feeds / meals
f. For irritability, Grade 1: Easily consolable; Grade 2: Requiring increased attention; Grade 3: Inconsolable

Compared with earlier doses, the rates of late onset fever (fever starting Day 5 postvaccination) after Dose 4 were slightly higher across both the MenQuadfi and Menveo groups, though generally still low. This included fever that was reported during the 7-day reporting period and was ongoing at 8 days postvaccination (2.3% MenQuadfi group versus 1.4% Menveo group), was late onset starting Day 5 postvaccination (4.0% MenQuadfi group versus 2.2% Menveo group), and was late onset starting Day 5 postvaccination that was still ongoing 8 days postvaccination (1.7% MenQuadfi group versus 0.9% Menveo group).

Reviewer Comment: Overall, the solicited safety results from MET41 were similar to those observed in MET42. The reported rates of solicited local and systemic ARs were comparable across the MenQuadfi and Menveo groups. While the majority of fevers postvaccination started within 3 days of study vaccination, the higher rates of delayed onset fever (starting Day 5) after the 4th dose of MenQuadfi or Menveo (at 12 months) may be due to the concomitant administration of MMR vaccine, which is known to cause delayed onset of fever 7-12 days after vaccination, during the 4th dose visit.

6.3.12.4 Unsolicited Adverse Reactions

Immediate Unsolicited AEs

Within 30 minutes of vaccination, 0.3% of MenQuadfi recipients (7 participants) and 0.3% of Menveo recipients (2 participants) reported an immediate unsolicited AE. In the MenQuadfi group, by MedDRA PT, there were 2 participants with erythema, 1 with rash macular, 2 with flushing, 1 with ocular hyperemia, and 1 with otitis media acute. In the Menveo group, there was 1 participant with dermatitis and 1 with peripheral swelling. None of the immediate unsolicited AEs were assessed as severe (Grade 3).

Reviewer Comment: No participant experienced anaphylaxis or any other immediate AE concerning for a severe systemic allergic reaction.

Unsolicited Adverse Events

Rates of unsolicited AEs within 30 days after vaccination were generally comparable across study groups (MenQuadfi: 65.0%, Menveo: 62.7%). The most frequently reported events, by MedDRA SOC, were *Infections and infestations* (MenQuadfi 41.2% versus Menveo 36.6%) and *General disorders and administration site conditions* (MenQuadfi 25.6% versus Menveo 21.5%). The most frequently reported events, by MedDRA PT, were injection site bruising (MenQuadfi 17.0% versus Menveo 15.4%) and upper respiratory tract infection (MenQuadfi 14.3% versus Menveo 12.8%).

Rates of unsolicited AEs assessed by the investigator as related to study vaccine were similar across groups (MenQuadfi 10.4% versus Menveo 10.6%) and most had onset within 3 days post-vaccination. The majority of events were from the MedDRA SOC *General disorders and administration site conditions* and were mild to moderate in severity.

Reviewer Comment: The reported rates and types of unsolicited adverse events were generally comparable across study groups and represented medical conditions that are common in children; however, there was an observed imbalance across study groups in the rate of COVID-19 within 30 days of any vaccination (MenQuadfi 1.0% versus Menveo 0.1%). In response to a request from FDA for further information regarding this imbalance, the Applicant confirmed that there were no identified differences across vaccine groups based

on collected baseline characteristics such as sex, race, and ethnicity. Data on other demographic factors that might increase the risk of COVID-19 exposure (e.g., social settings such as daycare attendance) were not collected. The Applicant provided other possible explanations for the observed imbalance, including the study's 3:1 randomization scheme, differences in COVID-19 activity by geography and time period, and chance. In the absence of additional data on study population demographics and baseline characteristics, the cause(s) of the imbalance is uncertain. Based on the available information, including the small number of COVID-19 cases overall (21 in the MenQuadfi group and 1 in the Menveo group), the variability in COVID-19 activity over time and place, and the likely contribution of chance, the clinical review team does not consider the imbalance in COVID-19 cases to represent a safety signal.

Medically Attended Adverse Events

Within 30 days after vaccination, MAAEs were reported by 51.0% of MenQuadfi recipients and 48.6% of Menveo recipients. The most commonly reported MAAEs occurring in the MenQuadfi group were upper respiratory tract infection, otitis media, and otitis media acute. There were 7 MAAEs in the MenQuadfi group (0.3% of participants) and 3 in the Menveo group (0.4% of participants) assessed as related to vaccine by the investigator. The 7 related MAAEs in the MenQuadfi group were rash (2 events), gastroenteritis viral, rash macular, pyrexia, vaccination complication, and periorbital swelling.

Throughout the entire study duration of 6 months after the last vaccination, MAAES were reported in 76.0% of MenQuadfi recipients and 75.5% of Menveo recipients. The most commonly reported MAAEs occurring in the MenQuadfi group were the same events most commonly reported within 30 days of vaccination. There were no additional MAAES assessed as related in the MenQuadfi group beyond 30 days after vaccination.

Reviewer Comment: Rates and types of MAAEs were balanced across the study groups and represent illnesses that are common in infants and toddlers.

6.3.12.5 Deaths

During the study, there were three participant deaths in the MenQuadfi group and no deaths in the Menveo group. In the MenQuadfi group:

- A 12-week-old male with no medical history died with the primary cause of death reported as "non-accidental injury of the head" and secondary cause of death as "skull fracture and brain bleed due to shaking of baby" (b) (6) days after Dose 1.
- A 12-week-old male with no medical history was reportedly found prone and unresponsive in an adult bed with a comforter. His primary cause of death was reported as "sudden unexplained infant death" and secondary cause of death as "pulmonary edema" (b) (6) days after Dose 1.
- A 6-month-old female with a medical history of large for gestational age with neonatal hypoglycemia and in utero tobacco exposure was found unresponsive in bed (b) (6) days after Dose 3 with the cause and manner of death reported by the pathologist as "undetermined." Postmortem results included a toxicology report notable for a low level of diphenhydramine and a metabolic screen reported as normal. At autopsy, the pathologist reported findings of unclear significance that were potentially consistent with asphyxiation. The autopsy report also noted that there was no evidence for an acute inflammatory state. No fevers were reported from the time of Dose 3 vaccination through 3 days postvaccination. The only solicited adverse reactions reported following Dose 3

were Grade 1 crying (<1 hour) and Grade 2 irritability (requiring increased attention) on the day of vaccination.

All events were assessed by the investigator as unrelated to study vaccination.

Reviewer Comment: Based on review of the information provided for the reported study deaths, the clinical review team agrees with the investigator assessments that the reported deaths due to “non-accidental injury of the head” and “sudden unexplained infant death” in two 12-week-old infants were not related to study vaccine due to the delayed time to onset after vaccination and findings consistent with an alternative etiology.

The Applicant provided additional information in response to two FDA information requests, including autopsy results, regarding the 6-month-old infant with an “undetermined” cause of death 4 days following vaccination. Based on the report of tobacco and diphenhydramine exposure, evidence of asphyxia, and absence of evidence of an acute inflammatory state following vaccination (including no reported fevers and mild to moderate solicited ARs reported on day of vaccination only), findings that indicate a cause of death other than vaccination, the clinical review team agrees with the investigator assessment that the reported death was unlikely to be related to study vaccine.

6.3.12.6 Nonfatal Serious Adverse Events

Within 7 days after vaccination, SAEs were reported in 0.6% of MenQuadfi recipients (13 participants reporting 13 events), and no Menveo recipients. Most events belonged to the SOC *Infections and infestations*. None of these SAEs were considered related to study vaccine by the investigator. Within 30 days after vaccination, SAEs were reported in 2.1% of MenQuadfi recipients (44 participants reporting 51 events) and 1.3% of Menveo recipients (9 participants reporting 9 events). The most commonly reported SAEs occurring in the MenQuadfi group were RSV infection (8 cases), bronchiolitis (5 cases), RSV bronchiolitis (3 cases), and febrile seizure (3 cases). None of these SAEs were considered related to study vaccine by the investigator.

Overall, in the study with a randomization ratio of 3:1, SAEs were reported in 5.2% of the MenQuadfi recipients (108 participants reporting 133 events) and 3.0% of Menveo recipients (21 participants reporting 26 events). Most SAEs belonged to the SOC *Infections and infestations* (2.4% of the MenQuadfi group and 2.2% of the Menveo group). The three most frequently reported SAEs (by PT) occurring in the MenQuadfi group during the study were febrile seizure, RSV infection, and bronchiolitis occurring in 0.7%, 0.5%, and 0.4% of participants, respectively. The most frequently reported SAEs in the Menveo group were dehydration, croup infectious, and rhinovirus infection, occurring in 0.4%, 0.3%, and 0.3% of participants, respectively. None of the SAEs were considered related to the study vaccine by the investigator.

Reviewer Comment: Most SAEs were illnesses commonly reported in the infant/toddler general population. The clinical review team agrees with the investigator conclusions that the reported SAEs were not related to the study intervention, except for two events of febrile seizure (see section 6.3.2.7.1 for additional discussion of these two events).

6.3.12.7 Adverse Events of Special Interest

AESIs for MET41 included generalized seizures (febrile and non-febrile), Kawasaki disease, Guillain-Barré syndrome, and ITP. All AESIs reported during the study belonged to the SOC *Nervous system disorders*.

Within 7 days after vaccination, a total of 2 AESIs (febrile seizure and seizure) were reported in 2 participants in the MenQuadfi group, and none were reported in the Menveo group. Neither event was considered related to study vaccine by the investigator.

Within 30 days after vaccination, a total of 6 AESIs were reported in 5 participants in the MenQuadfi group, and none were reported in the Menveo group. The most frequently reported AESI was febrile seizure (3 cases), followed by seizure (2 cases), and seizure-like phenomena (1 case). None of these AESIs were considered related to study vaccine by the investigator. The 3 events of febrile seizure are discussed below in section 6.3.12.7.1. The 2 events of seizure and 1 event of seizure-like phenomena reported in the MenQuadfi group were as follows:

- A 10-week-old male experienced an AESI of seizure 7 days after receiving Dose 1 of MenQuadfi concomitantly administered with DTaP-IPV/Hib, hepatitis B, PCV 13, and rotavirus vaccines. He was hospitalized for intractable epilepsy 62 days later. Evaluation identified pathogenic variant KCNTI, a gene mutation-related epilepsy.
- An 11-week-old female experienced an AESI of seizure 13 days after receiving Dose 1 of MenQuadfi concomitantly administered with DTaP-IPV/Hib, hepatitis B, PCV 13, and rotavirus vaccines. At the time of the event, a history of possible ongoing seizures over the past month was reported. She was treated with an anticonvulsant. Twenty-one days after receiving Dose 3 of MenQuadfi concomitantly administered with hepatitis B, DTaP-IP/-Hib, PCV 13, and rotavirus vaccines, an AESI of seizure-like phenomena was reported and the participant was scheduled to see a neurologist.

Throughout the study, AESIs were reported by 0.9% of MenQuadfi recipients (19 participants reporting 22 events) and 0.1% of Menveo recipients (1 participant reporting 2 events) during the study. The most commonly reported AESI was febrile seizure (15 MenQuadfi recipients reporting 16 events and 1 Menveo recipient reporting 1 event). The other events included seizure in 3 MenQuadfi recipients and 1 Menveo recipient, epilepsy in 2 MenQuadfi recipients, and seizure like phenomena in 1 MenQuadfi recipient. None of the AESIs were considered related to study vaccine by the investigator.

> Reviewer Comment: The majority of AESIs were events of febrile seizure, with most occurring beyond 30 days after vaccination. The clinical review team agrees with the investigator conclusions that the reported AESIs were not related to the study intervention based on review of the information provided, including delayed time to onset postvaccination, concurrent illness, identified biologically plausible etiologies, and concomitant vaccine administration, except for two events of febrile seizure that occurred within 30 days postvaccination. See section 6.2.12.7.1. for further details regarding these events of febrile seizure.

6.3.12.7.1 Febrile Seizures

Within 7 days after vaccination, one event of febrile seizure occurred in the MenQuadfi group and none in the Menveo group (<0.1% versus 0%, respectively). Within 30 days after vaccination, 3 events were reported in 3 participants in the MenQuadfi group and none in the

Menveo group (0.1% versus 0%, respectively). Throughout the study, with a randomization ratio of 3:1, a total of 16 febrile seizures were reported by 15 participants in the MenQuadfi group compared with 1 febrile seizure in one participant in the Menveo group (0.7% versus 0.1%, respectively). All events of febrile seizure were considered by the investigator as unrelated to the study vaccine. The three febrile seizures occurring within 30 days after vaccination were as follows:

- A 12-month-old female experienced a febrile seizure 8 days after receiving Dose 4 of MenQuadfi concomitantly administered with MMR, varicella, and PCV13 vaccines. The participant was afebrile until 6 days after vaccination, when maximum daily temperatures of 101.4°F (Day 6) and 103.9°F (Day 7) were reported in the diary card. No other solicited systemic AR was reported around the same time. On Day 8 postvaccination, the participant experienced a febrile seizure at home and was taken to the emergency department (ED) where she was diagnosed with bilateral otitis media. She was treated in the ED with an antibiotic and received antipyretics until 11 days postvaccination.
- A 12-month-old female experienced a febrile seizure 1 day after receiving Dose 4 of MenQuadfi concomitantly administered with MMR, varicella, and PCV13 vaccines for which she was seen in the ED and hospitalized but discharged home on the same day. There were no documented findings on physical exam and no laboratory evaluations indicative of an infectious source for the fever. Although urinary tract infection was initially suspected, there was no urine culture collected, and no antibiotic treatment was initiated. The fever was limited to the first day after vaccination (maximum temperature 103.7°F), along with solicited systemic ARs of crying abnormal, drowsiness, appetite lost, irritability, and vomiting. There were no fevers reported from Day 2 through Day 7 after vaccination based on the daily temperature recorded in the diary card.
- A 12-month-old male experienced a febrile seizure 9 days after receiving Dose 4 of MenQuadfi concomitantly administered with MMR, varicella, and PCV13 vaccines. He was seen in the ED and there were no documented physical exam findings indicative of an infectious source for the fever. Fever to 101.4°F had previously been reported for this participant on the day of vaccination, and he then remained afebrile from Day 1 through Day 6. On Day 7, he was reported to have a fever of 101.7°F and reported daily fevers through Day 12, with a maximum reported temperature of 104.6°F. Based on the diary card, the participant experienced other solicited systemic adverse reactions after vaccination including crying abnormal (through Day 6), irritability (through Day 5), drowsiness (Day 1 through Day 5), vomiting (Day 1, Day 4, and Day 5), and appetite lost (through Day 1), which were mostly mild to moderate in severity.

Reviewer Comment:

- For the febrile seizure with onset 8 days after vaccination, the clinical review team agrees with the investigator assessment that this event was unlikely to be related to study vaccine based on the delayed onset of fever relative to study vaccination, with no other solicited systemic ARs indicative of vaccine reactogenicity reported around the same time, and the presence of alternative etiology for the fever (bilateral otitis media).
- For the febrile seizure with onset one day after vaccination, the clinical review team considers this event to be possibly related to MenQuadfi due to close temporal relationship to study vaccination (1 day postvaccination, consistent with timing of fever onset most frequently reported by study participants based on analyses of solicited safety) and lack of clear alternative etiology, although the assessment is confounded by receipt of concomitant vaccines.

- For the febrile seizure with onset 9 days after vaccination, the clinical review team considers this event to be possibly related to MenQuadfi due to lack of clear alternative etiology, although similar to the previous case, assessment is confounded by receipt of concomitant vaccines, including M-M-R II (for which febrile seizure is a labeled warning). The fever most proximal to the event of febrile seizure occurred starting on Day 7 after vaccination, which is later than the most commonly reported time frame of fever onset observed in the solicited safety analyses. However, delayed onset of fever after Dose 4 was reported among a small percentage of study participants, and this participant's history of fever on day of vaccination and report of multiple solicited systemic ARs through 5 days after vaccination raises the possibility that the fever on Day 7 may be part of continued vaccine reactogenicity.

Based on the available information at the time of this review, the clinical review team assessed the two events of febrile seizure occurring 1 day and 9 days postvaccination as possibly related to study vaccine. These cases will be included in the prescribing information for MenQuadfi. For further discussion regarding febrile seizures observed in clinical studies of MenQuadfi, see the Integrated Overview of Safety in section 8.4.3.

6.3.12.8 Discontinuations Due to Adverse Events

Of the 2,080 participants in the MenQuadfi group, 7 (0.3%) had at least one AE leading to study discontinuation after any dose compared with 1 participant out of 697 (0.1%) in the Menveo group. A total of 11 AEs leading to study discontinuation were reported among the 7 participants in the MenQuadfi group, with 5 of these events (pyrexia, crying, injection site erythema, injection site pain, and injection site rash) considered related to study vaccines by the investigator.

Reviewer Comment: The events leading to study discontinuation that were assessed by the investigator as related to study vaccine in the MenQuadfi group were events representative of vaccine reactogenicity.

Subpopulation Safety Analyses

Overall, safety results were comparable across subpopulations, and to those of the overall study population, by sex and race.

Subgroup analysis of preterm infants

A total of 89 preterm infants who received MenQuadfi were included in the descriptive subgroup analysis by preterm and full-term birth status. Of the 89 preterm infants, 93.3% were late preterm (defined as born at 34 to <37 weeks of gestation), with the majority born at 36 to <37 weeks gestation. Overall, the rates of solicited local and systemic adverse reactions among preterm participants were similar to those in participants born at term. See the section 8 Integrated Overview of Safety for additional safety data in infants born preterm across the clinical studies.

6.3.13 Study Summary and Conclusions

Study MET41 was included in the MenQuadfi Phase 3 clinical development plans to increase the overall safety database and support licensure of MenQuadfi in infants and toddlers. The primary objective of the study was to describe the safety profile of MenQuadfi compared with Menveo when administered concomitantly with recommended pediatric vaccines in healthy infants and toddlers. Overall, the study demonstrated that MenQuadfi has a comparable safety profile to Menveo when administered as a 4-dose series when administered with concomitant recommended pediatric vaccines in healthy infants and

toddlers. The percentage of participants who experienced a febrile seizure within 30 days after vaccination was 0.1% in the MenQuadfi group and 0% in the Menveo group. Two related SAEs of febrile seizure which occurred 1 day and 9 days after the 4th dose of MenQuadfi administered with concomitant vaccines will be included in the prescribing information. For clinical reviewer analysis of febrile seizures across all studies, see the Integrated Overview of Safety in section 8.4.3.

6.4 Trial #4: MET39

NCT01049035: "A Study of a Quadrivalent Meningococcal Tetanus Protein Conjugate Vaccine in Infants and Toddlers"

Study Overview: MET39 was a Phase 2 randomized, open-label, multi-center study to evaluate the safety and immunogenicity of five different schedules of MenQuadfi administered concomitantly with recommended pediatric vaccines compared with two control groups receiving only recommended childhood vaccines. The study enrolled infants and toddlers 2 months through 12 months of age and was conducted at 21 sites in the U.S. from December 16, 2009 to February 13, 2012, with a database lock date of April 13, 2012.

6.4.1 Objectives (No Formal Hypothesis Testing)

- To describe the safety profile of MenQuadfi administered at 5 different schedules and concomitantly with recommended pediatric vaccinations

- To describe the immunogenicity profile of MenQuadfi administered at 5 different schedules (Group 1: 4-dose series at 2, 4, 6, and 12 months; Group 2: 4-dose series at 2, 4, 6, and 15 months; Group 3: 3-dose series at 2, 4, and 12 months; Group 4: 2-dose series at 6 and 12 months; and Group 5: 1 dose at 12 months of age) and concomitantly with recommended pediatric vaccinations

- To describe the immunogenicity profiles of selected licensed pediatric vaccines (Pentacel, Prevnar or Prevnar 13, M-M-R II, and Varivax) when administered either concomitantly with or without MenQuadfi.

6.4.2 Design Overview

The purpose of this Phase 2 randomized, open-label, multi-center study was to evaluate the safety and immunogenicity of 5 different schedules of MenQuadfi administered to infants/toddlers concomitantly with recommended childhood vaccines compared with 2 control groups receiving only recommended childhood vaccines. Participants were randomized to one of seven groups as follows:

MenQuadfi groups with concomitant U.S. licensed recommended childhood vaccines:
- Group 1 (N = 100): 4-dose schedule at 2, 4, 6, and 12 months
- Group 2 (N = 100): 4-dose schedule at 2, 4, 6, and 15 months
- Group 3 (N = 100): 3-dose schedule at 2, 4, and 12 months
- Group 4 (N = 75): 2-dose schedule at 6 and 12 months
- Group 5 (N = 75): 1-dose schedule at 12 months

Control Groups with recommended childhood vaccines only:
- Group 6 (N = 50): No MenQuadfi; recommended vaccines only at 2, 4, 6, and 12 months
- Group 7 (N = 50): No MenQuadfi; recommended vaccines only at 2, 4, 6, and 15 months

Concomitantly administered recommended childhood vaccines were as follows:

- Pentacel at 2, 4, 6 months
- RotaTeq or Rotarix at 2, 4, 6 months or 2, 4 months, respectively
- Engerix-B or Recombivax HB at 2 months and 6 months if 1 dose given previously, or only at 6 months if 2 doses given previously
- Prevnar or Prevnar 13 at 2, 4, 6 months and either 12 months or 15 months, depending on study group
- M-M-R II and Varivax at 12 months

Safety Monitoring

Participants were monitored for immediate reactions occurring within 30 minutes after each vaccination.

Solicited local reactions[11] (tenderness, redness, and swelling at the injection site) and solicited systemic reactions[12] (temperature, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability) occurring up to 7 days after each vaccination were recorded by parents/guardians in a safety diary card, including solicited local reactions for the concomitant vaccines.

Unsolicited AEs[13] were also recorded by parents/guardians in the diary card up to 30 days following each vaccination. At specified intervals, parents/guardians were interviewed to collect the information recorded in the diary card and to clarify information as needed. Beyond 30 days and up to 180 days after the last vaccination, parents/guardians were provided a memory aid in which to record information about any SAE that occurred. Information in the memory aid was collected by telephone call.

Immunogenicity Monitoring

Serum samples were obtained 30 days after completion of all doses administered before 12 months of age in the series; immediately before the second year of life dose (at 12 months or 15 months); and 30 days after the second year of life dose (at 13 months or 16 months) according to the assigned group. Samples from all groups were tested for antibodies elicited by the meningococcal antigens contained in MenQuadfi as well as for antibodies elicited by selected recommended pediatric vaccines.

11 Grading scale for solicited local reactions:
- For tenderness, Grade 1: Minor reaction when injection site is touched; Grade 2: Cries or protests when injection site is touched; Grade 3: Cries when injected limb is moved, or the movement of the injected limb is reduced
- For redness and swelling, Grade 1: > 0.0 to < 2.5 cm; Grade 2: ≥ 2.5 to < 5 cm; Grade 3: ≥ 5 cm

12 Grading scale for solicited systemic adverse reactions: .
- For fever, Grade 1: ≥ 38.0°C to ≤ 38.5°C or ≥ 100.4°F to ≤ 101.3°F; Grade 2: > 38.5°C to ≤ 39.5°C or > 101.3°F to ≤ 103.1°F; Grade 3: > 39.5°C or > 103.1°F
- For vomiting, Grade 1: 1 episode per 24 hours; Grade 2: 2– 5 episodes per 24 hours; Grade 3: ≥ 6 episodes per 24 hours or requiring parenteral hydration
- For crying abnormal, Grade 1: < 1 hour; Grade 2: 1 - 3 hours; Grade 3: > 3 hours
- For drowsiness, Grade 1: Sleepier than usual or less interested in surroundings; Grade 2: Not interested in surroundings or did not wake up for a feed/meal; Grade 3: Sleeping most of the time or difficult to wake up
- For appetite lost, Grade 1: Eating less than normal; Grade 2: Refused 1 or 2 feeds/meals; Grade 3: Refused ≥3 feeds/meals or refused most feeds/meals
- For irritability, Grade 1: Easily consolable; Grade 2: Requiring increased attention; Grade 3: Inconsolable

13 Grading scale for unsolicited AEs:
- Grade 1: No interference with activity
- Grade 2: Some interference with activity
- Grade 3: Significant; prevents daily activity

6.4.3 Study Population and Disposition

The study enrolled a total of 580 healthy participants born at full term. Individuals were excluded from participation if they had previously received a meningococcal vaccine, had a history of meningococcal infection, or were at high risk for meningococcal infection during the trial.

Of the 580 enrolled participants, 69.2%-94.7% of participants in each group completed the study. The most frequently reported reasons for discontinuation included non-compliance with the protocol in 9.3% of all participants, voluntary withdrawal not due to an AE in 7.6% of all participants, and lost to follow-up in 3.4% of all participants. Four participants (0.7%) did not complete the study due to an SAE (two of which resulted in death) and one participant (0.2%) did not complete the study due to a non-serious AE (see section 6.4.5.5 below). None of these events were considered related to the study vaccine by the investigator.

> Reviewer Comment: Due to failure to monitor and document refrigerator temperatures for some of the licensed products at one study site, 28 participants were withdrawn early from the study, with continued follow-up for 6 months after their last vaccination. The discontinuations were reported under “non-compliance with the protocol.” Revaccination was recommended for participants who received these vaccines.

Approximately 95% of the enrolled population (450 in MenQuadfi groups and 101 in control groups) were included in the safety population, the study population in which safety analyses were conducted. By group, the safety population included 104 participants in Group 1, 102 in Group 2, 100 in Group 3, 74 in Group 4, 70 in Group 5, 52 in Group 6, and 49 in Group 7.

Approximately 57.6% of the enrolled population (278 in MenQuadfi groups and 56 in control groups) were included in the per protocol (PP) population, the study population in which immunogenicity analyses were conducted. By group, the PP population included 59 participants in Group 1, 59 in Group 2, 52 in Group 3, 46 in Group 4, 62 in Group 5, 30 in Group 6, and 26 in Group 7.

> Reviewer Comment: Based on sensitivity analyses in the intent-to-treat (ITT) population with generally similar results to analyses in the PP population, the proportion of participants excluded from the PP population does not appear to have impacted the immunogenicity conclusions.

Males represented 52.6% of the total safety population. Most participants were Caucasian (75.3%), followed by Black (11.1%), other (9.1%), Hispanic (3.4%), American Indian or Alaska Native (0.5%), Asian (0.4%), and Native Hawaiian or other Pacific Islander (0.2%). The demographic characteristics of the PP and ITT populations were similar to those of the safety population.

6.4.4 Immunogenicity Analyses

Immunogenicity testing for meningococcal antigens A, C, Y, and W in MenQuadfi included functional antibodies measured by hSBA. Immunogenicity testing for antigens in U.S. licensed childhood vaccines included antibodies to the antigens contained in Pentacel, Prevnar or Prevnar13, M-M-R II, and Varivax.

Groups 1 through 4: 4-dose, 3-dose, and 2-dose series groups

3 doses in the first year (at 2, 4, and 6 months of age):

- One month following 3 doses administered at 2, 4, and 6 months (Groups 1 and 2 pooled), the percentage of participants who achieved an hSBA titer of ≥1:8 based on serogroup were as follows:
    - A: 69.0%
    - C: 92.5%
    - Y: 90.6%
    - W: 95.6%

2 doses in the first year (at 2 and 4 months of age):

- One month following 2 doses administered at 2 and 4 months (Group 3), the percentage of participants who achieved an hSBA titer of ≥1:8 based on serogroup were as follows:
    - A: 77.6%
    - C: 95.9%
    - Y: 73.5%
    - W: 83.7%

1 dose in the first year (at 6 months of age):

- One month following a single dose at 6 months (Group 4), the percentage of participants who achieved an hSBA titer of ≥1:8 based on serogroup were as follows:
    - A: 59.5%
    - C: 88.4%
    - Y: 27.9%
    - W: 27.9%

Prior to an additional dose in the second year (at 12 or 15 months of age):

- For 4-dose series at 2, 4, 6, and 12 months (Group 1), 4-dose series at 2, 4, 6, and 15 months (Group 2), 3-dose series at 2, 4, and 12 months (Group 3), and 2-dose series at 6 and 12 months (Group 4), the percentage of participants who achieved an hSBA titer of ≥1:8 based on serogroup were as follows:
    - A: 26.2% to 39.3%
    - C: 51.0% to 90.7%
    - Y: 81.6% to 93.1%
    - W: 85.7% to 95.3%

Following an additional dose in the second year (at 12 or 15 months of age):

- For 4-dose series at 2, 4, 6, and 12 months (Group 1), 4-dose series at 2, 4, 6, and 15 months (Group 2), 3-dose series at 2, 4, and 12 months (Group 3), and 2-dose series at 6 and 12 months (Group 4), greater than 91% of participants achieved an hSBA titer of ≥1:8, irrespective of the prior number of doses received in the first year of life.
- Across Groups 1 – 4, the range of the percentage of participants who achieved an hSBA titer of ≥1:8 based on serogroup were as follows:
    - A: 92.9% to 100.0%
    - C: 91.8% to 100.0%
    - Y: 100.0%
    - W: 100.0%

Group 5: single dose group
Single dose (at 12 months of age):

- For participants in Group 5 who received only a single dose at 12 months of age, the percentages who achieved an hSBA titer of ≥1:8 were as follows:
    - A: 74.6%
    - C: 90.2%
    - Y: 47.5%
    - W: 54.2%

For serogroups A and C, the immune responses generated following the 12-month dose were generally similar irrespective of whether participants received 1, 2, or 3 doses in the first year of life. For serogroups Y and W, a greater number of doses in the first year of life resulted in a higher percentage of participants achieving an hSBA titer of ≥1:8 one month following completion of the first-year doses. The additional dose administered in the second year of life resulted in a higher percentage of participants achieving an hSBA titer of ≥1:8 for all serogroups. A single dose at 12 months of age elicited lower responses for serogroups Y and W compared with serogroups A and C.

The immune responses to concomitantly administered recommended childhood vaccines were similar to those observed in the control groups.

Reviewer Comment: Immunogenicity data from this Phase 2 study support the Applicant's selection of the 4-dose and 2-dose schedules selected for advancement to Phase 3 evaluation based on the schedules determined to provide the best protection through the second year of life.

6.4.5 Safety Analyses

6.4.5.1 Solicited Adverse Reactions

Solicited Local Adverse Reactions

Overall, the percentage of participants who experienced at least one solicited adverse reaction after any dose was similar across the MenQuadfi groups (83.8% to 97.0%) and when compared with the control groups (90.0% to 91.8%).

The rate of participants who reported at least one solicited local reaction at the MenQuadfi injection site was generally higher in those who received more doses compared with those who received fewer doses:

- Groups 1 and 2 (4-dose schedules): 80.0% and 80.8%, respectively
- Group 3 (3-dose schedule): 74.0%
- Group 4 (2-dose schedule): 75.3%
- Group 5 (1-dose schedule): 57.4%

Solicited Systemic Adverse Reactions

After any dose of MenQuadfi, 73.5% to 96.0% of participants reported at least one solicited systemic adverse reaction, compared with 88.0% to 89.8% of control vaccine recipients.

Fever was reported at higher rates, but not higher severity grade, in those participants who received more doses of MenQuadfi compared with those who received only 1 dose:

- MenQuadfi Groups 1 and 2 (4-dose schedules): 32.3% and 42.0%, respectively

- MenQuadfi Group 3 (3-dose schedule): 42.0%
- MenQuadfi Group 4 (2-dose schedule): 38.9%
- MenQuadfi Group 5 (1-dose schedule): 16.2%
- Control Groups 6 and 7 (recommended childhood vaccines only): 38.0% and 45.8%, respectively

The rates of Grade 3 fever in the MenQuadfi groups ranged from 1.5% in Group 5 (single dose at 12 months) to 4.0% in Group 1 (4 doses at 2, 4, 6, and 12 months) compared with 2.0% to 10.4% in the control groups.

6.4.5.2 Unsolicited Adverse Events

The rates of participants who reported at least one unsolicited AE were similar across the 4-dose MenQuadfi groups (79.4% to 79.8%) and their respective control groups who received only recommended childhood vaccines (77.6% to 84.6%).

Compared with the 4-dose MenQuadfi groups, the unsolicited AE rates were lower in the groups receiving fewer doses:

- MenQuadfi Group 3 (3-dose schedule): 71.0%
- MenQuadfi Group 4 (2-dose schedule): 63.5%
- MenQuadfi Group 5 (1-dose schedule): 50.0%

Reviewer Comment: Overall, the unsolicited adverse events reported in the study represented medical conditions that are common in children.

6.4.5.3 Deaths

Two deaths were reported in the 2-dose MenQuadfi group (Group 4). The cause of death and age of participant were as follows:

- Hypoxic ischemic encephalopathy in a 9-month-old female which started (b) (6) days after vaccination and was associated with findings suspicious for possible child abuse.
- Non-accidental head trauma in a 13-month-old male which occurred (b) (6) days after vaccination.

Both deaths were assessed by the investigator and Applicant as not related to study vaccine.

Reviewer Comment: Following independent review of the available clinical information, including death event narratives, the clinical reviewer agrees with the investigator assessments that the reported deaths were likely not related to study vaccine.

6.4.5.4 Nonfatal Serious Adverse Events

SAEs within 30 days after vaccination ranged from 1.0% to 2.7% among MenQuadfi recipients compared with 3.8% to 4.1% among control vaccine recipients. SAEs through study completion ranged from 1.4% to 7.0% across the MenQuadfi groups compared with 7.7% to 8.2% in the control groups. None of the SAEs were assessed as related to study vaccine by the investigator.

Reviewer Comment: Most SAEs were illnesses common in infants and toddlers. Following independent review of the available clinical information, including SAE event narratives, the clinical reviewer agrees with the investigator assessments that the reported SAEs were likely not related to study vaccine.

6.4.5.4.1 Febrile Seizures

Throughout the study, a total of 5 SAEs of febrile seizures (4 MenQuadfi, 1 control) were reported in 5 participants as follows: in the MenQuadfi groups, 2 participants (2.0%) in Group 2 (4-dose group), 1 participant (1.0%) in Group 3 (3-dose group), and 1 participant (1.4%) in Group 5 (single dose at 12 months); in the control groups, 1 participant (2.0%) in Group 7 (recommended childhood vaccines only). The rates of participants who experienced a febrile seizure across the 4-dose MenQuadfi groups and their respective control groups who received only recommended childhood vaccines were the same: 0% in MenQuadfi Group 1 and Control Group 6 with a 2, 4, 6, and 12 month vaccination schedule and 2.0% in MenQuadfi Group 2 and Control Group 7 with a 2, 4, 6, and 15 month vaccination schedule.

No events of febrile seizure within 7 days after vaccination were reported. One event *within 30 days* after vaccination was reported in one MenQuadfi recipient:

- A 12-month-old male MenQuadfi recipient (Group 5, 1-dose group) experienced an event of febrile seizure 9 days after receipt of MenQuadfi concomitantly with PCV13, MMR, Varicella vaccines. He experienced diarrhea on the day of vaccination lasting for 4 days, followed by fever starting 7 days after vaccination, and herpangina starting 8 days after vaccination. Maximum temperature recorded on the day of the febrile seizure was 103.4°F, at 9 days after vaccination. The fever resolved the same day, and the herpangina resolved 2 days later.

The other febrile seizure events in the MenQuadfi groups were reported *greater than 30 days after vaccination* and included the following:

- A 16-month-old female in Group 2 (4-dose group) 34 days post-Dose 4 with a concomitant viral syndrome
- A 12-month-old female in Group 2 (4-dose group) 203 days post-Dose 3
- A 12-month-old female in Group 3 (3-dose group) 257 days post-Dose 2

In Group 7 (a comparator group that received only recommended pediatric vaccines), one event of complex febrile seizure with concomitant influenza A infection was reported in an 11-month-old male 164 days postvaccination with Pentacel, Prevnar, Recombivax HB, and Rotateq.

None of the SAEs of febrile seizures were assessed by the investigator as related to study vaccine.

> Reviewer Comment: Based on the delayed time to onset relative to study vaccination and/or the presence of concurrent illness, the clinical review team agrees with the investigator assessments that the reported cases of febrile seizure were likely not related to study vaccine. For further discussion regarding febrile seizures observed in clinical studies of MenQuadfi, see section 8.4.3 in the Integrated Overview of Safety.

6.4.5.4.2 Kawasaki disease

There were 2 SAEs of Kawasaki disease (KD) (one each in Group 2 [4-dose MenQuadfi group] and Group 3 [3-dose MenQuadfi group]), in a 9-month-old male with onset 106 days after vaccination and in a 7-month-old male with onset 52 days after vaccination who was diagnosed with right middle lobe pneumonia 2 days prior, respectively. Both participants were discontinued from the study due to the SAE of KD and receipt of IVIG treatment. Neither SAE of KD was considered related to the study vaccine by the investigator.

Reviewer Comment: Based on the delayed time to onset relative to study vaccination and the participants' ages being consistent with the peak age of occurrence of KD in the U.S. (6 to 24 months) (American Academy of Pediatrics, Committee on Infectious Diseases 2024), the clinical review team agrees with the investigator assessments that the reported cases of KD were not related to study vaccine.

6.4.5.5 Discontinuations Due to Adverse Events

A total of 5 participants were discontinued from the study due to an AE, four of whom discontinued due to an SAE (as discussed above) which include the following: Kawasaki disease, pneumonia and Kawasaki disease, hypoxic ischemic encephalopathy, and head trauma. In addition, a 6-month-old male participant in Group 4 (2-dose MenQuadfi group) discontinued the study following a nonserious AE of viral rash in the setting of an ongoing cough, acute otitis media, and clear rhinorrhea. The rash occurred 1 day after receipt of the 6-month study vaccinations and lasted 3 days. None of these events were considered related to study vaccine by the investigator.

Reviewer Comment: The clinical review team agrees with the investigator assessments that the AEs leading to study discontinuation were likely not related to study vaccine.

6.4.6 Study Summary and Conclusions

MenQuadfi was immunogenic for serogroups A and C, irrespective of the number of doses received in the first year of life; however, 2 to 3 doses in the first year of life were required to generate an adequate response for serogroups Y and W. For all dosing regimens limited to the first year of life, a subsequent dose in the second year of life resulted in a greater percentage of participants achieving hSBA titers of ≥1:8 for all serogroups. Additionally, no immune interference was noted in the response to recommended pediatric vaccines evaluated in this study.

Based on the results of MET39, reactogenicity rates appear similar in the MenQuadfi groups receiving a 4-dose series compared with their respective control groups; however, higher rates of reactogenicity occurred with more doses of MenQuadfi compared with fewer doses. No safety signals were identified. There were 4 febrile seizure events that occurred in MenQuadfi recipients, none of which the clinical review team assessed as related to MenQuadfi. For clinical reviewer analysis of febrile seizures across the three Phase 3 studies (MET 42, MET61, and MET41), see the Integrated Overview of Safety in section 8.4.3.

Immunogenicity and safety data from Study MET39 evaluating five different dosing regimens of MenQuadfi administered concomitantly with recommended pediatric vaccines compared with two control groups receiving only recommended pediatric vaccines supported further clinical development of MenQuadfi for use in infants and toddlers and informed selection of the 4-dose and 2-dose vaccination schedules assessed in Phase 3 studies.

7. INTEGRATED OVERVIEW OF IMMUNOGENICITY

In the studies submitted to this sBLA, the immunogenicity of a 4-dose series was only evaluated in Study MET42, and immunogenicity of a 2-dose series was only evaluated in Study MET61. Therefore, an integrated overview of immunogenicity is not applicable to this review.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data included in this application and reviewed to characterize the safety profile of MenQuadfi in infants 6 weeks to <2 years of age were from the following Phase 3 studies: MET41, MET42, and MET61.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were three studies (listed above) included in this application to describe the safety profile of MenQuadfi. The age of study participants at time of enrollment and the dosing regimens evaluated were as follows:

- Infants 2 months of age (42 through 89 days): 4-dose series at 2, 4, 6, 12-18 months of age
- Infants 6 to 7 months of age: 2-dose series at 6-7 months and 12-13 months of age
- Infants 17 to 19 months of age: 2-dose series at 17-19 months and 20-23 months of age

The two objectives of the Integrated Analysis of Safety were as follows:

- To present a descriptive comparison of the safety profile of MenQuadfi with the safety profile of comparator vaccine (Menveo) when administered in a 4-dose schedule concomitantly with routine pediatric vaccines
- To describe the safety profile of the MenQuadfi and comparators (Menveo and Menactra) after any dose (at least one dose administered from 6 weeks to 23 months either in 2-doses or 4-doses)

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The Integrated Summary of Safety (ISS) database across the pooled studies included the following participants:

- Pooled MET41 and MET42:
  - 4-dose series with 3,807 MenQuadfi recipients and 1,564 Menveo recipients
  - Sex, age, racial origin, ethnicity, and gestational age at birth (preterm versus full term) were overall balanced between the groups.
- Pooled MET41, MET42, and MET61: 4,273 MenQuadfi recipients,1,925 Menveo recipients, 103 Menactra participants
  - 4-dose series with 3,807 MenQuadfi recipients and 1,564 Menveo recipients
  - 2-dose series with 466 MenQuadfi recipients, 361 Menveo Recipients, and 103 Menactra recipients
  - Sex, racial origin, and ethnicity were overall balanced between the groups.

8.2.3 Categorization of Adverse Events

See sections 6.1.7, 6.2.7, and 6.3.7 for safety assessments in each study.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The Applicant integrated safety data for these studies because of comparable study design (randomized, double-blind, active-controlled). The integrated safety data for MET41 and MET42 also enrolled the same study populations (healthy infants 42 through 89 days of age at enrollment), and similar dosing regimens (4-dose series at 2, 4, 6, and 12 months or 12-18 months of age). The integrated analysis of MET41, MET42, and MET61 includes three age groups at enrollment (42 through 89 days, 6 through 7 months, or 17 through 19 months of age at enrollment) and two dosing regimens (4-dose and 2-dose series).

Safety data accrued from study visits that included study meningococcal vaccinations were included in the integrated analysis. Therefore, unsolicited AEs reported following the administration only of recommended vaccines (e.g. in MET42, after Visit 5 at 12 months and prior to Visit 6 at 15 months for Group 1b) were not included.

> Reviewer Comment**:** Although the age of participants at enrollment across studies differed, all study participants were infants/toddlers <2 years of age with dosing regimens that overlapped across age intervals. Therefore, the total safety database of MenQuadfi recipients in this application to support an indication in individuals <2 years is robust.
>
> In each study, unsolicited AEs were collected through 6 months after the last vaccination, and these are reported for each individual study. Because the integrated safety analysis does not include unsolicited AEs occurring after visits in which MenQuadfi was not administered, there are fewer unsolicited AEs, SAEs, AESIs, and MAAEs reported in the integrated analysis compared to those reported across the individual studies. Therefore, the ISS primarily focuses on adverse events temporally associated with MenQuadfi vaccination.

8.4 Integrated Safety Results

Summary of Safety After Any Dose of a 4-Dose Series (Pooled MET41 and MET42)

The reported rates of solicited adverse reactions in the first week after vaccination with any dose of MenQuadfi or Menveo were similar for solicited local ARs (75.7% and 74.0%, respectively) and solicited systemic ARs (83.6% and 84.1%, respectively). The reported rates of unsolicited AEs within 30 days after any vaccine dose were also similar across groups (59.5% MenQuadfi and 57.1% Menveo). Rates of SAEs for MenQuadfi and Menveo groups were, respectively, 0.6% versus 0.3% within 7 days, 2.2% versus 1.2% within 30 days, and 5.3% versus 3.6% over the full study period.

Summary of Safety After any Dose of a 4-Dose or 2-Dose Series (Pooled MET41, MET42, and MET61)

The reported rates of solicited adverse reactions including solicited local adverse reactions in the first week after vaccination with any dose of MenQuadfi, Menveo, or Menactra were generally similar across MenQuadfi and Menveo recipients (73.6% and 70.0%, respectively) but lower among Menactra recipients (48.0%). A similar trend was observed for solicited systemic adverse reactions after any dose, which were similar across MenQuadfi and Menveo recipients (81.5% and 80.2%, respectively), but lower among Menactra recipients (62.0%).

Unsolicited AEs within 30 days after any dose were reported by 58.0% of MenQuadfi recipients and 54.4% of Menveo recipients, compared with 35.9% of Menactra recipients. SAEs within 30 days after any dose were reported by 1.9%, 1%, and 1.9% of MenQuadfi, Menveo, and

Menactra recipients, respectively, and by 4.9%, 3.6%, and 3.9% of participants, respectively, during the entire study period.

Reviewer Comment**:** As seen in the individual studies MET41, MET42, and MET61, and in the pooled analyses, reported rates of solicited ARs and unsolicited AEs after any dose were generally similar across MenQuadfi and Menveo recipients. Reported rates of solicited ARs and unsolicited AEs were generally lower in the Menactra group compared with the MenQuadfi and Menveo group; however, interpretation of data from Menactra recipients is limited by the much smaller sample size in the Menactra groups compared with the MenQuadfi groups (N=103 for Menactra, N=4,273 for MenQuadfi, and N=1,925 for Menveo). In addition, Menactra participants did not receive concomitant vaccines as per the prespecified study protocol, whereas the majority of MenQuadfi participants and all of the Menveo participants did receive concomitant vaccines.

8.4.1 Fever

MenQuadfi compared with Menveo (Pooled MET41 and MET42):
Rates of fever were similar across the MenQuadfi and Menveo groups after each dose of the 4-dose series (2, 4, 6, and 12-18 months). Rates of fever were lowest after dose 1 (7.7% MenQuadfi and 7.2% Menveo) and highest after dose 2 (18.1% MenQuadfi and 17.9% Menveo). Rates of delayed onset fever (onset 4 -7 days after vaccination) were slightly higher in participants receiving the 4th dose of MenQuadfi or Menveo at 12 months of age (4.3% and 3.1%, respectively) compared with the rates of fever following Doses 1, 2, or 3 (range of 0.5%-0.9% for MenQuadfi and 0.5%-1.6% for Menveo) and compared with participants who received the 4th dose of MenQuadfi at 15-18 months of age (1.8%).

Reviewer Comment***:*** When evaluating the 4-dose series safety data, the slightly higher rates of delayed onset of fever (Day 4- Day 7) in both study groups following Dose 4 when concomitantly administered with MMR vaccine at 12 months of age likely reflects the known safety profile of MMR vaccine that includes delayed onset of fever 7-12 days after vaccination. The rate, severity, time of onset, and duration of fever after MenQuadfi were similar to those reported following Menveo after any dose of a 4-dose series.

8.4.2 AESIs (All Seizure Events)

MenQuadfi compared with Menveo and Menactra:
AESIs evaluating for all seizure events collected in the study included the following system organ class and preferred terms: febrile seizure, seizure, epilepsy, seizure like phenomena, and infantile spasms. AESIs were reported by a greater percentage of MenQuadfi recipients compared with Menveo recipients within 7 days, 30 days, and during the entire study period after any dose, though Menactra recipients experienced the highest percentage in the context of a small sample size. The rates of all seizure events by time from vaccination and study group reported across all three studies include the following:

- 7 days after any dose:
  - <0.1% of MenQuadfi recipients (3 participants reporting 3 events, of which 2 participants reported febrile seizures and 1 reported other seizure event)
  - 0% of Menveo recipients
  - 1% of Menactra recipients (1 participant reporting 1 event which was a febrile seizure)
- 30 days after any dose:
  - 0.2% of MenQuadfi recipients (8 participants reporting 9 events, of which 5 participants reported febrile seizures and 4 reported other seizure events)

  - 0% of Menveo participants
  - 1% of Menactra recipients (1 participant reporting 1 event which was a febrile seizure)
- Entire study duration after any dose:
  - 0.7% of MenQuadfi recipients (31 participants reporting 38 events, of which 22 participants reported 26 febrile seizures and 11 participants reported 12 other seizure events)
  - 0.4% of Menveo recipients (8 participants reporting 10 events, of which 6 participants reported 7 febrile seizures and 3 participants reported 3 other seizure events)
  - 1.9% of Menactra recipients (2 participants reporting 3 events, of which 2 participants reported 3 febrile seizures).

Reviewer Comment: The majority of the AESIs reported in all three study groups were 1) febrile seizures and 2) had occurred 30 days or more after any dose of the study vaccine. Although there is an imbalance in the seizure events across the study groups with a nominally higher rate seen in the MenQuadfi group compared with the Menveo group, interpretation of these rates is limited by the sample size differences across the groups, with the MenQuadfi group having over twice as many participants as the Menveo and Menactra groups combined due to the planned randomization ratios in each study. Although the reason for the imbalance in seizure events across the study groups is unclear, it is unlikely that febrile seizure events occurring >30 days after vaccination could have a biologically plausible relationship to vaccination. Because the majority of the seizure events were reported as febrile seizures, a detailed discussion of the febrile seizures reported in the studies is included below.

8.4.3 Febrile Seizures

MenQuadfi compared with Menveo and Menactra:
Similar to the trend seen for all AESIs, febrile seizure events that occurred in participants enrolled in studies MET41, MET42, and MET61 were reported by the largest proportion of Menactra recipients, followed by MenQuadfi recipients, and then Menveo recipients. As previously mentioned, the protocol specified randomization ratio resulted in a greater proportion of MenQuadfi recipients compared with either Menveo or Menactra recipients. In addition, the sample size of Menactra recipients was small (n = 103). The rates of febrile seizure events by time from vaccination and study group reported across all three studies include the following:

- 7 days after any dose:
  - <0.1% of MenQuadfi recipients (2 participants reporting 2 events)
  - 0% of Menveo recipients
  - 1% of Menactra recipients (1 participant reporting 1 event)
- 30 days after any dose:
  - 0.1% of MenQuadfi recipients (5 participants reporting 5 events)
  - 0% of Menveo recipients
  - 1% of Menactra recipients (1 participant reporting 1 event)
- Entire study duration after any dose:
  - 0.5% of MenQuadfi recipients (22 participants reporting 26 events)
  - 0.3% of Menveo recipients (6 participants reporting 7 events)
  - 1.9% of Menactra recipients (2 participants reporting 3 events)

Of the febrile seizures reported in MenQuadfi recipients, the clinical review team considered two events as possibly related to study vaccination, both of which occurred after Dose 4 administered at 12 months of age in study MET41. One event occurred 1 day postvaccination and the other 9 days postvaccination (see narratives in section 6.3.12.7.1). A Menactra recipient reported a febrile seizure 1 day after Dose 1 (administered at 17 months of age) of the two-dose series, that was also assessed as possibly related by the clinical review team.

Table 40. Rates of Febrile Seizures Reported After Any Dose of MenQuadfi, Menveo, or Menactra in Studies MET41, MET42, and MET61

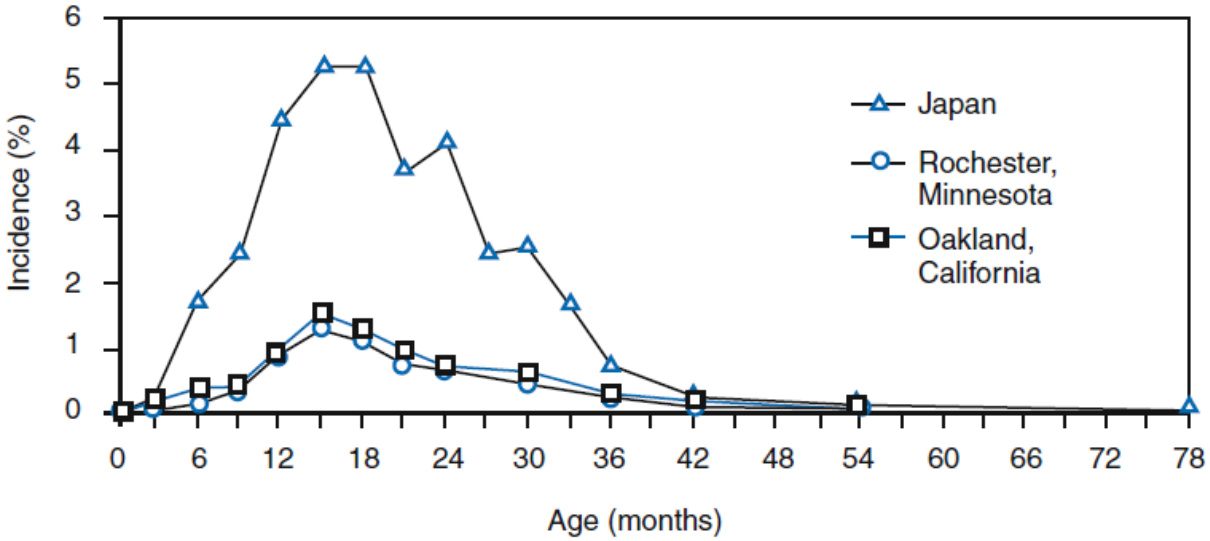
Time to Onset After Most Recent Vaccination	MenQuadfi N= 4273 % (95% CI) n	Menveo N= 1925 % (95% CI) n	Menactra N= 103 % (95% CI) n
Within 7 days after any dose	<0.1% (0; 0.2) 2	0% (0; 0.3) 0	1 % (0; 5.3) 1
Within 30 days after any dose	0.1% (0; 0.3) 5	0% (0; 0.2) 0	1 % (0; 5.3) 1
During the entire study period	0.5% (0.3; 0.8) 22	0.3% (0.1; 0.7) 6	1.9 % (0.2; 6.8) 2

Source; CSR MET41, MET42, and MET61 (Overall Safety Analysis Set after any Dose), ISS
Abbreviations: N=number of participants in the corresponding safety analysis set; n=number of participants experiencing the endpoint listed in the first column; ISS=Integrated Analysis of Safety

Clinical Reviewer Assessment of Febrile Seizures:
A febrile seizure is a seizure occurring with fever (temperature ≥38.0°C) and without central nervous system infection in children 6 months through 60 months of age. Simple febrile seizures, which are primary generalized seizures lasting for <15 minutes and not recurring within 24 hours, are considered benign and have an excellent prognosis. The risk of epilepsy after a simple febrile seizure has been shown to be only slightly higher than that of the general population, although one-third of children will experience a recurrence of febrile seizure. In general, a simple febrile seizure does not require further evaluation (Subcommittee on Febrile Seizures 2011).

The cumulative lifetime prevalence of febrile seizures is between 2%-5% in children 6 months through 5 years of age, with the peak incidence occurring between 14 through 18 months of age. Figure 1 below (Hauser 1994) illustrates that incidence of febrile seizures is highest in the second year of life (CDC 2024d).

Figure 1. Age-Specific Incidence of Febrile Seizures Among Infants and Toddlers in the General Populations of Japan, Rochester, MN and Oakland, CA



Source: Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia. 1994 Apr;35:S1-6

In addition to age, the most common risk factors for febrile seizures include high fever, viral infection, recent immunization, and family history of febrile seizures. Viral infections have been commonly identified in association with febrile seizures, with those associated with high fever (e.g., human herpesvirus 6 [HHV-6] and influenza) having the highest risk. In one study, HHV-6 infections were associated with one third of all first-time febrile seizures in children up to 2 years of age. Administration of certain vaccines, including diphtheria, tetanus toxoid, and whole-cell pertussis (DTwP) and MMR vaccines, can also increase the risk of febrile seizures (Millichap 2025). In general, febrile seizures occurring after vaccination do not appear to be different from febrile seizures due to other causes in terms of outcome and prognosis (Cendes 2011).

Given the expectation of a background rate of febrile seizures in the study populations and multiple other risk factors for febrile seizures, assessment of a causal relationship for the febrile seizure events with MenQuadfi vaccination is complicated by multiple confounding factors. For instance, concomitant administration of recommended pediatric vaccines precludes assignment of causality directly to MenQuadfi vaccination, as it is not possible to conclusively determine which of the administered vaccines resulted in fever with subsequent onset of seizure activity. However, MenQuadfi contribution to the participant's febrile experience, whether alone or synergistically with the other pediatric vaccines, cannot be excluded.

MenQuadfi and Menveo were both administered concomitantly with MMR (M-M-R II) vaccinations at the 12 months of age vaccination visit in the clinical studies. The M-M-R II USPI Section 5.1 Warnings and Precautions states that there is a risk of fever and associated febrile seizure in the first 2 weeks following vaccination, and that for children who have experienced a previous febrile seizure (from any cause) and those with a family history of febrile seizures, there is a small increase in risk of febrile seizure following receipt of the vaccine. Additionally, when M-M-R II was concomitantly administered with Varivax, ~66% of study participants 12 through 18 months of age reported any fever (temperature ≥38.0°C) within 42 days of vaccination. Fever following M-M-R II vaccination is often characterized by delayed onset, occurring ~7 to 12 days after vaccination.

Finally, fever due to viral illness, otitis media, and other common childhood illnesses are common in this age group and often co-exist during and after administration of recommended vaccines, further confounding the relationship between vaccination and a febrile seizure.

Among the cases of febrile seizure which occurred across the studies, two were considered possibly related to MenQuadfi following CBER review of available clinical data. Both cases occurred in MenQuadfi recipients in MET41, 1 day and 9 days after receipt of the 4th dose when administered at 12 months of age of the four-dose series (section 6.3.12.7.1). In both cases, participants were administered MenQuadfi concomitantly with other pediatric vaccines (including MMR), and there was a plausible temporal relationship to vaccination as well as a lack of a definitive alternative cause, including the absence of concurrent illness. Neither febrile seizure event was prolonged or recurred during the study period. While administration of concomitant pediatric vaccines, including those with known associations with febrile seizures, may obfuscate determination of causality, MenQuadfi contribution to the onset of these two febrile seizure events cannot be excluded.

As shown in Table 40 above, the overall rates of febrile seizure in the ISS were 0.5% in MenQuadfi recipients, 0.3% in Menveo recipients, and 1% in Menactra recipients. The clinical review in the context of available study safety data, the Phase 3 study design, and known information about the risks associated with febrile seizure, considered the following factors to assess the overall febrile seizure risk after MenQuadfi vaccination:

1. As specified with the study-specific randomization ratios, numerically there were over twice as many MenQuadfi recipients with safety data included in the ISS compared with Menveo and Menactra recipients.[14] The reported lower number of febrile seizure events in the Menveo group may be due to variability from the smaller sample size, which may not be large enough to detect differences in less frequently reported events. The higher rate of febrile seizures (1%) in the Menactra group based on one participant with a febrile seizure in a small sample size further suggests how differences in sample size impact comparisons across groups.
2. The rate of febrile seizures in these clinical studies cannot be directly compared with the background rate of febrile seizures in this age group (2%- 5% lifetime prevalence in children 6 months to 5 years of age, with peak incidence 14-18 months of age). However, the rate of febrile seizures in the Menveo group (no events within 30 days after any dose) is not representative of the expected background rates for febrile seizure for young pediatric populations, since at least one case would have been expected to occur in this group. Therefore, an imbalance between the groups may be more reflective of the lower-than-expected rates in the Menveo group.
3. All febrile seizures reported within 30 days after vaccination occurred in participants 12 to <24 months of age, which aligns with the peak incidence of febrile seizures in this age group.
4. An association between MenQuadfi and febrile seizures is expected to be limited to the immediate time period after vaccination when fever peaks. Analyses of solicited safety data from MET42, MET41, and MET61 indicate fever onset occurred most commonly within 3 days after vaccination. Furthermore, based on literature reviewed by Deng et al., 2019, timing of fever onset after vaccination varied by vaccine type (inactivated 0-2 days, live-attenuated 5-14 days, combination of inactivated and live-attenuated 0-14 days). Because the majority of febrile seizure events reported in the infant/toddler clinical trials of MenQuadfi occurred > 30 days after vaccination, these events were unlikely to be vaccine related.

14 Safety database: 4,273 MenQuadfi recipients, 1,925 Menveo recipients, and 103 Menactra recipients.

5. Assessment of causality is confounded by concomitant administration of recommended pediatric vaccines, including those with a known association with febrile seizures (e.g., MMR, which was administered in both febrile seizures cases which were considered possibly related to MenQuadfi vaccination). Furthermore, many participants who reported febrile seizure events also reported concurrent illnesses, including bronchiolitis, upper respiratory tract infections, acute otitis media, and pyelonephritis, which are common childhood illnesses.

In summary, of the reported febrile seizures in MenQuadfi recipients across the studies, two events were assessed as possibly related to the vaccine by the clinical review team. Based on the totality of data from the pediatric clinical trials of MenQuadfi, as well as the epidemiology of febrile seizures in the U.S. infant/toddler population, an increased risk for febrile seizures following MenQuadfi cannot be definitively concluded. However, because an association with MenQuadfi also cannot be excluded, collection of additional postmarketing safety data may address potential uncertainties identified with the clinical trial safety database. The Applicant has agreed to conduct enhanced postmarketing surveillance for febrile seizure events in vaccinated young pediatric populations. Furthermore, MenQuadfi prescribing information (USPI Section 6) includes descriptions of the two febrile seizure events considered to be possibly related to MenQuadfi vaccination in two MET41 study participants.

8.4.4 Deaths (MenQuadfi vs. Menveo vs. Menactra)

Across studies MET41, MET42, and MET61, a total of 4 deaths were reported among MenQuadfi recipients (<0.1%), all within 30 days after vaccination, and no deaths were reported among Menveo and Menactra recipients. None of these deaths were assessed as related to study vaccination by the investigator or the clinical review team. See sections 6.1.12.5 and 6.3.12.4 for narratives and assessments of these events.

Reviewer Comment: The overall number of deaths across the studies is small and the sample size varies across study groups due to prespecified randomization ratios. A review of U.S. general population expected infant mortality rate is provided to support the assessment of the observed rates of deaths across the three studies. Infant post-natal[15] mortality rates in the United States are ~2 infant deaths per 1,000 births[16] as described by 2022 final and 2023 provisional data, which is approximately 0.2% for the infant population. Based on this data, the finding of 0 deaths in the Menveo and Menactra groups may not be representative of the expected background U.S. post-natal infant mortality rate, which limits the comparison of the observed rate MenQuadfi recipients (<0.1%) with that of Menveo and Menactra recipients. Furthermore, the available clinical information for the reported deaths in MenQuadfi recipients did not suggest causality with the study vaccination.

8.4.5 Infants Born Preterm

In a descriptive comparison of the safety of a 4-dose MenQuadfi series in the infants born preterm (31 to <37 weeks gestational age) to that in term infants (≥37 weeks gestational age) for participants in studies MET41 and MET42, similar rates of solicited ARs and unsolicited AEs were reported across the two groups. These analyses included a total of 222 MenQuadfi

15 Post-natal mortality rate for the number of deaths reported in infants (28 to 364 days of age) per 1,000 live births
16 National Vital Statistics System. National Center for Health Statistics Infant Mortality in the United States: Provisional Data From the 2023 Period Linked Birth/Infant Death File Danielle M. Ely, Ph.D., and Anne K. Driscoll, Ph.D. Report 37, November 2024

recipients who were born preterm and 3,582 MenQuadfi recipients who were born at term. Within 7 days after any vaccination of a 4-dose series of MenQuadfi, solicited local ARs were reported by 69.5% of preterm participants compared with 76.1% of term participants. Solicited systemic ARs were reported by 77.9% of preterm participants compared with 84% of term participants. Fever within 7 days after vaccination was reported by a similar percentage of participants in both groups (preterm: 35.5%, term: 34.4%).

Unsolicited AE within 30 days after any dose were reported by 52.7% of preterm participants compared with 59.9% of term participants. The percentages of participants reporting any SAE were also similar between the preterm participants and term participants (2.3% versus 2.1%, respectively, within 30 days, and 5.4% versus 5.3%, respectively, for the entire study period).

> Reviewer Comment: These subgroup analyses generally suggest similar safety profiles of MenQuadfi across infants born preterm or at term. Interpretation of these descriptive data is limited by the difference in overall size of each safety population (preterm versus term infants).

8.6 Safety Conclusions

In three randomized clinical studies conducted in U.S. including Puerto Rico, 4,273 infants and toddlers 6 weeks through 23 months of age received at least one dose of a 4-dose or 2-dose series of MenQuadfi. Reported rates of local and systemic adverse reactions were generally comparable between MenQuadfi and Menveo recipients, but higher in MenQuadfi recipients than Menactra recipients when administered as a 2-dose series in toddlers 17-19 months and 20-23 months of age.

Within 30 days of vaccination, 0.1% of MenQuadfi recipients (5 participants) reported a febrile seizure, compared with 0% of Menveo recipients. However, the absence of febrile seizures in the Menveo group within 30 days of vaccination was not representative of the expected background rate in the general population in the same age group, limiting the comparability of Menveo with MenQuadfi recipients. Furthermore, the majority of the febrile seizure events observed in the studies were seen outside of the expected time frame after vaccination when a biologically plausible temporal relationship between vaccination and the febrile seizure is likely to exist. However, because of the noted imbalances in febrile seizures and the challenges in excluding an association with MenQuadfi due to multiple confounding factors, enhanced postmarketing surveillance for febrile seizure events in young pediatric populations vaccinated with MenQuadfi will be conducted. No other safety concerns were identified.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Pediatric Use and PREA Considerations

Studies MET41, MET42, and MET61, included in this sBLA submission, fulfill the 3 post-marketing requirements (PMRs) identified under PREA in the initial BLA approval (April 23, 2020) for the deferred evaluation of MenQuadfi in children 6 weeks through 23 months of age. These 3 studies were presented to the FDA's Pediatric Review Committee on April 1, 2025. The committee agreed that the Applicant's PMRs for children 6 weeks through 23 months of age were fulfilled by the included studies.

9.1.2 Immunocompromised Patients

Immunocompromised participants were not included in the studies.

10. CONCLUSIONS

In study MET42, effectiveness of a 4-dose series of MenQuadfi administered at 2, 4, 6, and 12-15 months of age was demonstrated based on noninferiority of hSBA seroresponse rate after the 4th dose and percentage of participants with hSBA titers ≥ 1:8 after the 3rd dose, when compared with a 4-dose series of Menveo. Furthermore, robust hSBA GMTs were observed following completion of the 4-dose series, with comparable hSBA responses in participants who received the 4th dose of MenQuadfi at 15-18 months of age and at 12-15 months of age. Noninferiority of immune responses to recommended pediatric vaccines administered concomitantly with MenQuadfi compared with Menveo was also demonstrated

In study MET61, effectiveness of a 2-dose series of MenQuadfi administered at 6-7 months and 12-13 months of age was demonstrated based on noninferiority of hSBA seroresponse rate and hSBA titers ≥1:8 following the second dose of MenQuadfi compared with Menveo. The study also evaluated a 2-dose series of MenQuadfi compared with Menactra when administered at 17-19 months and 20-23 months of age. In descriptive analyses, hSBA responses were similar across the MenQuadfi and Menactra groups.

The safety of a 4-dose series of MenQuadfi was evaluated in studies MET41 and MET42, and the safety of a 2-dose series was evaluated in MET61. Across all three studies, the safety profile of MenQuadfi was generally similar to that of the comparator vaccine. Across the three studies, there were 2 SAEs (also classified as AESIs) of febrile seizure considered possibly related to MenQuadfi. In the integrated safety analysis across all three studies, the rate of febrile seizure in MenQuadfi recipients was 0.1% within 30 days postvaccination, compared with 0% of Menveo recipients and 1% of Menactra recipients. The comparability of MenQuadfi and comparator vaccine groups is limited by differences in sample size and the lack of any reported febrile seizure cases within 30 days in the Menveo group, which is not representative of the estimated background rate of febrile seizures for this age group. Enhanced postmarketing surveillance for febrile seizures is planned to further assess for the risk of febrile seizures after vaccination with MenQuadfi.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 41. Risk-Benefit Considerations for MenQuadfi

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Invasive meningococcal disease (IMD) usually presents as bacteremia with or without meningitis or sepsis. Even with prompt antimicrobial therapy, up to 15% of infected individuals will have a fatal outcome (CDC 2024a). Up to 20% of survivors will have substantial morbidity including neurologic disability, deafness, and loss of limbs.	IMD due to serogroups A, C, W and Y is a serious and potentially life-threatening condition that can result in significant morbidity and mortality in any age group. In the U.S., children <1 year of age are at highest risk to develop IMD.
Unmet Medical Need	Other than a prophylactic vaccine, measures for preventing IMD include targeted antibiotic use in close contacts of individuals with meningococcal disease; however, this approach depends on a	Market availability of another meningococcal vaccine for use in infants and toddlers would reduce risk of possible vaccines

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	timely diagnosis of the index case, timely identification of close contacts, rapid communication of risk to close contacts, and access to medical care or medications for those contacts, and compliance with the prescribed regimen. Two meningococcal A, C, W, Y vaccines are licensed and available in the U.S.: Menveo and MenQuadfi. Menveo is approved for individuals 2 months through 55 years of age. In children <2 years, for those initiating vaccination at 2 months of age, Menveo is administered as a 4-dose series at 2, 4, 6, and 12 months of age. In children <2 years initiating vaccination at 7 months through 23 months of age, Menveo is administered as a 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose. MenQuadfi is currently approved for individuals 2 years of age and older as a single dose. In addition, there are two U.S.-licensed meningococcal A, B, C, W, Y vaccines: Penbraya and Penmenvy, both approved for use in individuals 10 through 25 years of age (CDC 2024b).	supply shortage in the U.S., as Menveo is currently the only available meningococcal vaccine licensed for use in children 2 months through 23 months of age. The proposed dosing regimen for MenQuadfi in children initiating vaccination at 2 months is a 4-dose series administered at 2, 4, 6, and 12-18 months of age. This longer time window (12-18 months of age for MenQuadfi versus 12 months of age for Menveo) for the 4th dose of the series allows health care providers additional flexibility in administering this final dose.
Clinical Benefit	Vaccine effectiveness against IMD can be inferred through the evaluation of serum bactericidal activity using human complement (hSBA). The effectiveness of MenQuadfi as a 4-dose series and as a 2-dose series were evaluated in ~4,000 study participants 6 weeks through 23 months of age. In clinical studies, MenQuadfi elicited noninferior hSBA responses when compared with Menveo. There was no evidence of immunological interference when MenQuadfi was administered concomitantly with recommended pediatric vaccines recommended by the ACIP.	The data submitted to the sBLA support the effectiveness of MenQuadfi for use as a 4-dose and 2-dose series in children 6 weeks through 23 months of age when administered concomitantly with recommended pediatric vaccines recommended by the ACIP and meet the evidentiary standards for approval.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	For the 4-dose series of MenQuadfi administered at 2, 4, 6, and 12-18 months of age, the rates of solicited adverse reactions as a range after any dose were: injection site tenderness (38.5% - 45.6%), injection site erythema (12.5%- 19.5%), injection site swelling (9.6%-12.7%), fever (7.8%-17.6%), vomiting (3.5%- 13.2%), crying abnormal (27.3% - 42.1%), drowsiness (25.1%- 43.4%), appetite lost (17.3%-21.8%), and irritability (40.1%-51.9%) For the 2-dose series of MenQuadfi administered at 6-7 months and 12-13 months of age, the rates of solicited adverse reactions as a range after either dose were: injection site tenderness (30.1%-42.7%), injection site erythema (21.1%- 21.8%), injection site swelling (14.5%-16.0%), fever (9.3% - 12.9%), vomiting (5.5%- 8.5%), crying abnormal (26.6%- 35.0%), drowsiness (27.7%- 36.5%), appetite lost (15.2%- 17.1%), and irritability (40.0%-49.0%). In the clinical studies, there was an imbalance in the percentage of participants reporting febrile seizures within 30 days postvaccination in the MenQuadfi groups (0.1%) compared with Menveo groups (0%). Two serious adverse events (SAEs) of febrile seizures reported after Dose 4 of MenQuadfi at 12 months were considered possibly related to MenQuadfi.	The data from clinical studies of MenQuadfi in infants and toddlers adequately characterize the safety of MenQuadfi. The safety profile of MenQuadfi is comparable to another U.S.-licensed MenACWY vaccine. The majority of the febrile seizure events observed in the studies were seen outside of the expected time frame after vaccination when a biologically plausible temporal relationship between vaccination and the febrile seizure is likely to exist. The absence of febrile seizures in the Menveo group within 30 days of vaccination was not representative of the expected background rate in the general population in the same age group, limiting the comparability of Menveo with MenQuadfi recipients. The two SAEs of febrile seizures assessed as possibly related to MenQuadfi will be described in Section 6 of the USPI. Enhanced postmarketing surveillance for febrile seizures will allow for further elucidation of the risk of febrile seizures following receipt of MenQuadfi.
Risk Management	The most common risks of vaccination with MenQuadfi in infants and toddlers 6 weeks through 23 months are described in “Risk” section above. The proposed USPI (following labeling negotiations) has adequately captured these risks. MenQuadfi does not prevent *N. meningitidis* serogroup B disease.	The reactogenicity and safety profile of MenQuadfi is adequately characterized in the USPI. Enhanced postmarketing surveillance for febrile seizures and routine pharmacovigilance to monitor for other adverse events adequately mitigate the risks. USPI Indications & Usage Section states that MenQuadfi does not prevent serogroup B disease.

11.2 Risk-Benefit Summary and Assessment

The overall clinical benefit of MenQuadfi in individuals 2 months through 23 months of age in preventing invasive meningococcal disease is favorable compared with potential risks associated with vaccination. Data submitted to this supplemental BLA establish the safety and effectiveness of a 4-dose series of MenQuadfi in infants initiating vaccination at 2 months of age, and a 2-dose series in infants initiating vaccination from 6 months to <2 years of age. There was no evidence of immune interference when recommended pediatric vaccines were administered concomitantly with MenQuadfi at 2, 4, 6, and 12-18 months, as compared with Menveo. The safety of MenQuadfi is adequately described in the prescribing information, and the Applicant's routine pharmacovigilance, in addition to enhanced postmarketing surveillance for febrile seizures, is adequate for monitoring of AEs postmarketing.

11.3 Discussion of Regulatory Options

Because invasive meningococcal disease is rare, clinical endpoint studies evaluating reduction in disease incidence are not feasible. Use of hSBA to infer effectiveness of meningococcal conjugate vaccines was discussed and endorsed by a VRBPAC (April 2011). Immunologic noninferiority to U.S.-licensed vaccines based on hSBA response rates has been used to establish effectiveness of other meningococcal conjugate vaccines. The safety data and analyses provided in the BLA do not raise concerns that would preclude approval.

11.4 Recommendations on Regulatory Actions

The clinical reviewers recommend approval of this efficacy supplement application because the submitted and reviewed clinical data support the safety and effectiveness of MenQuadfi for use in individuals 6 weeks through 23 months of age in preventing invasive meningococcal disease.

11.5 Labeling Review and Recommendations

The proprietary name MenQuadfi was previously reviewed by the Advertising and Promotional Labeling Branch at CBER as a part of the initial BLA and found to be acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the Applicant. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

The Applicant will conduct enhanced surveillance for febrile seizures, through submission of periodic safety reports with aggregate safety assessments for the risk of febrile seizures (based on interval and cumulative postmarketing safety data) at 6-month intervals, effective during the 2025-2026 reporting period, and to continue for 3 years.