BLA Clinical Review Memorandum

Application Type	Original Efficacy
STN	125701.0
CBER Received Date	26 April 2019
PDUFA Goal Date	25 April 2020
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Anuja Rastogi, MD, MHS Clinical Reviewer, CRB1, DVRPA, OVRR, CBER
Review Completion Date / Stamped Date	22 April 2020
Supervisory Concurrence	Lucia Lee, MD Team Leader, CRB1, DVRPA, OVRR, CBER Douglas Pratt, MD, MPH Associate Director, Medical Affairs DVRPA, OVRR, CBER
Applicant	Sanofi Pasteur, Inc.
Established Name	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine
(Proposed) Trade Name	MenQuadfi ™
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Meningococcal Serogroup A Polysaccharide: 10ug Meningococcal Serogroup C Polysaccharide: 10ug Meningococcal Serogroup Y Polysaccharide: 10ug Meningococcal Serogroup W Polysaccharide: 10ug Tetanus Toxoid Protein (TT): ~55ug* *TT is approximate and dependent on (b) (4) lots used in formulation
Dosage Form(s) and Route(s) of Administration	Solution Intramuscular route of administration
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	- Active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. - Individuals 2 years of age and older - Use: Primary and booster immunization (single dose)
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

ABCs	Active Bacterial Core surveillance (ABCs) program
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BIMO	FDA's Bioresearch Monitoring Program
BLA	Biologics License Application
CDC	Centers for Disease Control and Preventions
CFR	Code of Federal Regulations
CMC	Chemistry, Manufacturing, and Controls
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
hSBA	Serum Bactericidal Activity using human complement
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
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
PerC	Pediatric Review Committee
PPS	Per Protocol Analyses Set
PT	Preferred Term
PREA	Pediatric Research Equity Act
SAE	Serious Adverse Event
SOC	System Organ Class
USPI	United States Package Insert
VRBPAC	Vaccines and Related Biological Products Advisory

1. EXECUTIVE SUMMARY

An original Biologics License Application (BLA) for candidate Meningococcal (Groups A, C, Y, W) Polysaccharide Tetanus Toxoid Conjugate Vaccine has been submitted by Sanofi Pasteur Inc. with a proposed indication for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y for use in individuals 2 years and older.

The applicant has submitted data from 8 clinical studies as part of this BLA, including 5 trials (four Phase 3 trials, one Phase 2 trial) which provided the principal data to support the safety and immunogenicity of MenQuadfi for the intended indication in individuals 2 years of age and older, as well as data to support clinical lot consistency. These 5 trials (MET43, MET35, MET49, MET56, MET50) were conducted at 232 sites in the United States (US), including Puerto Rico. Three supportive studies were included in the application, including a Phase 2 study (MET44) conducted in the US that provided additional safety and immunogenicity data in older adults ≥56 years of age. Two early phase non-US trials (MET28, MET32) were also included that evaluated different vaccine formulations that varied based on the (b) (4) . Data generated from these two studies helped determine the final MenQuadfi formulation.

Immunogenicity Analyses:

For the 5 main studies, immunogenicity endpoints were used to infer effectiveness of MenQuadfi in participants 2 years of age and older who received a primary vaccination dose and in participants 15 years of age and older who received a booster vaccination dose at least 4 years following a previous dose of a meningococcal (Groups A, C, W, Y) conjugate vaccine. The antibody responses to the antigens present in MenQuadfi vaccine were evaluated based on the proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA at 30 days post-vaccination compared to baseline (pre-vaccination). Seroresponse was defined as post-vaccination titer ≥ 1:16 for participants with pre-vaccination hSBA titer < 1:8, or post-vaccination titer at least 4-fold greater than the pre-vaccination titer for participants with pre-vaccination titer ≥1:8. For each of the 5 main studies, the primary objective evaluated the non-inferiority of serogroup-specific hSBA seroresponse rates following the administration of MenQuadfi compared to a US licensed meningococcal A,C,W,Y vaccine[1], as defined by a lower bound of the 95% CI of the difference in seroresponse rates between treatment groups > -10. Non-inferiority of MenQuadfi seroresponse rates versus those for the comparator vaccines was demonstrated across all 5 main studies for primary dose and booster dose vaccinations. By serogroup, the lower bound of the 95% CI of the difference in seroresponse rates in the 4 studies evaluating primary dose vaccination in participants 2 years of age through 97 years of age were as follows:

- serogroup A: 1.1% to 14.8%
- serogroup C: 21% to 42.2%
- serogroup Y: 7.7% to 24.6%
- serogroup W: 8.9% to 22.5%

The lower bounds of the 95% CI of the difference in seroresponse rates evaluating booster dose vaccination in participants 15 years of age through 58 years of age were as follows by serogroup: A: 0.74%, C: 2.16%, Y: -0.91%, and W: 4.3%. Secondary immunogenicity

1 Meningococcal A, C, Y, W vaccines licensed in the US for the prevention of vaccine serogroup meningococcal disease served as the active comparators in the 5 main studies that provided the principal data to support the safety and effectiveness of MenQuadfi

objectives evaluating Geometric Mean Titers (GMTs) 30 days post-vaccination supported the findings of the primary analyses with GMT responses that followed serogroup-specific seroresponse rate trends. The immunogenicity data based on hSBA endpoints demonstrate that MenQuadfi is effective in generating serogroup specific bactericidal activity after primary dose and booster dose vaccination. The reviewer recommends that the hSBA data for primary dose and booster dose vaccinations be included in the US package insert (USPI) to support the effectiveness of MenQuadfi for use as primary and booster meningococcal A, C, Y and W conjugate vaccinations.

Safety Analyses:
Safety data were reviewed on 5118 participants enrolled in 6 randomized clinical trials (MET43, MET35, MET49, MET56, MET50, MET44) conducted in the US. These study participants received at least one dose of MenQuadfi and provided post-vaccination safety data.
The most frequently reported adverse (solicited) reactions included injection site pain, myalgia, headache, and malaise. The rates observed were comparable to those observed following Menveo and Menactra in the respective studies. In adults ≥56 years of age, the solicited reaction rates were higher in MenQuadfi (conjugate vaccine) group compared to Menomune (polysaccharide vaccine) group. Conjugate vaccines are often more reactogenic and immunogenic than polysaccharide vaccines. No deaths were reported in the clinical studies and no vaccine related SAEs were reported.

Lot Consistency
The applicant satisfactorily demonstrated consistency of lot performance based on comparisons of hSBA GMTs of three different lots of MenQuadfi. Safety profiles across lots were consistent.

Concomitant Vaccination
Safety and effectiveness of MenQuadfi when administered concomitantly with Tdap vaccine (Adacel®) and HPV Quadrivalent (Types 6, 11, 16, & 18) vaccine (GARDASIL®) in adolescents 10 years through 17 years of age were evaluated in Study MET50. No evidence of interference in hSBA seroresponse rates was observed when MenQuadfi was co-administered with Tdap vaccine and HPV vaccine. Antibody responses to HPV vaccine, and to the tetanus and diphtheria antigens in Tdap vaccine were similar when Tdap and HPV were administered with and without MenQuadfi. Anti-pertussis GMC responses were non-inferior for the pertussis toxoid (PT) antigen when Tdap and HPV were administered with MenQuadfi compared to when Tdap and HPV were only co-administered. However, anti-pertussis GMC responses did not meet pre-specified non-inferiority criteria for the other 3 pertussis antigens, FHA, PRN, and FIM. Because a serologic correlate of protection for pertussis antigens has not been established, it is unclear if these findings suggest that concomitant administration will result in increased susceptibility to pertussis infection. However, additional analyses evaluated whether protocol specified post-vaccination titers were achieved for each pertussis antigen based on the baseline titer for the respective pertussis antigen. These analyses demonstrated comparable post-vaccination response rates for each pertussis antigen when Tdap and HPV were administered with MenQuadfi compared to when Tdap and HPV were only co-administered. These additional analyses provide some assurance of adequate pertussis immune responses when MenQuadfi and Tdap vaccines are co-administered.

Pediatric Assessment and Pediatric Research Equity Act
The Pediatric Study Plan was presented to FDA's Pediatric Review Committee (PerC) on March 10, 2020. Safety and effectiveness of MenQuadfi have not been established in individuals younger than 2 years of age in the US. The applicant's plan for an assessment of MenQuadfi in pediatric individuals 0 to <6 weeks was waived because the candidate vaccine did not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used. The applicant's assessment in children 6 weeks to 23 months of age (<2 years) was deferred because the candidate vaccine was ready for approval for use in individuals 2 years of age and older before all pediatric studies are complete. The applicant's deferred studies include Study MET41 to be conducted in infants/toddlers 6 weeks through 12 months of age evaluating a 4-dose series; Study MET42 to be conducted in infants/toddlers 6 weeks through 18 months of age evaluating a 4-dose series; and Study MET61 to be conducted in infants/toddlers 6 months through 23 months of age evaluating a 2-dose series. The committee agreed with the Pediatric Study Plan, including the partial waiver, partial deferral, and the proposed timelines for each study's completion and submission.

Clinical Reviewer Recommendation:
The totality of clinical data presented in this application supports approval of MenQuadfi candidate vaccine for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y for use in individuals 2 years of age and older as a primary vaccination dose, and in individuals 15 years of age and older as a booster dose vaccination, if at least 4 years have elapsed since a prior meningococcal A, C, Y, W conjugate vaccine was administered.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

For each study, the demographic characteristics were reviewed individually.

Immunogenicity:
Age: For all serogroups, there was an age-dependent increase in MenQuadfi hSBA seroresponse rates from early childhood (2 through 5 years) (A 52%, C 94%, Y 88%, W 74%) to adolescents (10 through 17 years) (A 74%, C 96%, Y 96%, W 85%), and age-dependent decrease thereafter to age 56 years of age or older (A 58%, C 77% Y 74%, W 63%). Similarly, the magnitude of the serogroup C hSBA hSBA GMTs following MenQuadfi vaccination were numerically highest in adolescents (10 through 17 years) and lowest in adults ≥75 years. Of the overall incidence of meningococcal disease in the US, the incidence of meningococcal serogroup C disease is second highest after meningococcal serogroup B disease.

Sex and Race/Ethnicity: In two studies, MET 43 and MET49, there were greater proportions of females enrolled than males (55-60% females; 40-45% males). There were no substantial differences in hSBA responses to each serogroup, based on analyses categorized by sex. Subgroup analyses of serogroup-specific hSBA responses based on race were not meaningful because the number of Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin participants were small.

Safety:
The adverse event (AE) rates in MenQuadfi recipients when stratified by age or sex followed similar trends as those observed in all participants for the corresponding AE rate for that study. However, no conclusions could be made about racial/ethnic differences in AE rates due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application:

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

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Conditions Studied[2,3,4,5,6]

Invasive meningococcal disease, including meningococcemia, meningitis, and/or bacterial pneumonia is associated with significant morbidity and mortality. *Neisseria meningitidis*, a gram-negative endotoxin-producing diplococcal bacterium exclusively infects humans. Transmission occurs by aerosolized droplet or contact with nasopharyngeal secretions from colonized individuals. Subsequent spread to the blood in colonized individuals can occur in up to 1% of individuals, of whom 50% may develop meningitis.

Clinical Presentation:
Common clinical symptoms include fever, neck stiffness, headache, altered mental status, myalgia, and vomiting. Petechial rash is seen initially in 50% of patients upon presentation and can coalesce into the pathognomonic meningococcal purpuric and ecchymotic rash. Purpura fulminans is a severe complication, seen in 15-25% of bacteremic individuals, resulting in cutaneous hemorrhage and necrosis due to vascular thrombosis and disseminated intravascular coagulopathy.

Prognosis:
The course of meningococcal disease is wide-ranging, from an initial nonspecific febrile illness to a rapidly progressive fulminant infection with multi-organ involvement, sepsis, and possibly death within hours. Early diagnosis and intervention are an important prognostic factor, as classic meningococcal symptoms appear late. Early features suggesting sepsis include leg pain, cold extremities, and abnormal skin color (pallor/mottling). Long term sequelae occur in 11-19% of those who survive and include hearing loss, neurologic disability, loss of limbs, and/or other serious conditions. Overall case fatality rate is 10-15%, though among adults ≥65yo the rate is ~24%. For those individuals with meningococcal bacteremia, the fatality rate is ~40%.

Epidemiology:
The incidence of invasive meningococcal disease in North America has ranged from 0.5 to 1.5 cases per 100,000 over the past several decades with a steady decline in the past one decade, partially due to the introduction of a meningococcal conjugate vaccine in 2005. During 2005-2011, there were an estimated 800-1200 cases of meningococcal disease in the U.S., with an incidence rate of 0.3/100,000 population. In 2018, the Centers for Disease Controls (CDC's)

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2 Pace D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. *Vaccine*. 2012 May 30;30 Suppl 2: B3-9.
3 CDC. Meningococcal Disease Chapter. *Pink Book*, 12th Ed. May 2012.
4 CDC. Active Bacterial Core Surveillance (ABCs) Report: *Neisseria meningitidis*, 2012.
5 Cohn AC, MacNeil JR, Harrison LH, et al. changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998-2007: implication for prevention of meningococcal diseases. *Clin Infec Dis.* 2010;50:184-91.
6 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.

Active Bacterial Core Surveillance (ABCs) Report[7] estimated 330 cases of meningococcal disease (confirmed and probable) that were reported to the National Notifiable Disease Surveillance System, resulting in incidence of 0.10/100,000 population, which was a historic low.

The 2018 Enhanced Meningococcal Surveillance Report[8] provides the number of meningococcal disease cases (incidence rate/100,000 population) by serogroup and includes the following:

- B: 119 cases (0.04)
- C: 90 cases (0.03)
- W: 17 cases (0.01)
- Y: 48 cases (0.01)
- Non-groupable: 27 cases (0.01)
- Other/Unknown: 28 cases (0.01)
- Overall: 329 cases (0.10)

The number of cases (incidence rate per 100,000 population) by age includes the following:

- <1years: 32 cases (0.83)
- 1-4 years: 29 cases (0.18)
- 5-10 years: 9 cases (0.04)
- 11-15 years: 7 cases (0.03)
- 16-23 years: 34 cases (0.10)
- 24-44 years: 65 cases (0.07)
- 45-64 years: 79 cases (0.09)
- ≥65 years: 74 cases (0.14)

The number of cases (incidence rate/100,000 population) in 18 to 24 years of age individuals attending college was 18 cases (0.16) and those not attending college was 16 (0.08). The overall case fatality rate in 2018 was 12.0 per 100 cases (39 deaths) with known outcomes, the majority of which were due to serogroup C (13 deaths) and serogroup B (9 deaths), followed by serogroup Y (7 deaths), serogroup W (4 deaths), unknown serogroup (4 deaths), and non-groupable (2 deaths)

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

Due to the variable clinical presentation of invasive meningococcal disease, a high index of suspicion is required by the clinician early in the disease process to reduce both morbidity and mortality. After a diagnosis of meningococcal disease is confirmed, empiric treatment with a broad-spectrum antibiotic (e.g., third-generation cephalosporin), followed by switch to penicillin, if penicillin susceptibility has been confirmed. Chemoprophylaxis with antibiotics is recommended by the American Academy of Pediatrics for close contacts of infected individuals[9].

7https://www.cdc.gov/meningococcal/surveillance/surveillance-data html#figure01 accessed 3/23/2020

8 https://www.cdc.gov/meningococcal/downloads/NCIRD-EMS-Report-2018.pdf accessed 3/23/2020.

9 American Academy of Pediatrics. Meningococcal Infections. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book®: 2015 REPORT OF THE COMMITTEE ON INFECTIOUS DISEASES.* American Academy of Pediatrics; 2015; 547-558

2.3 Safety and Efficacy of Pharmacologically Related Products

Two meningococcal ACWY conjugate vaccines, are licensed and available for use in the US. Menveo (MenACWY-CRM conjugate) is approved for use in individuals 2 years through 55 years of age as a single dose, 7 months through 23 months of age as a 2-dose series, and 2 months of age as a 4-dose series. Menactra (MenACWY-D conjugate) is approved for use in individuals 2 years to 55 years of age as a single dose, 9 months through 23 months of age as a 2-dose series, and 15 years through 55 years of age as a booster dose. In addition, Menomune is a meningococcal ACWY polysaccharide vaccine licensed for use in individuals ≥2 years of age as a single dose. Information about the safety and immunogenicity (inferred effectiveness) of each vaccine is described in the package insert.

Advisory Committee on Immunization Practices (ACIP): Meningococcal Conjugate Vaccinations

The U.S. Centers for Disease Control and Prevention (CDC)'s Advisory Committee on Immunization Practices (ACIP) recommended meningococcal ACWY conjugate vaccine for routine use as a primary vaccination (single dose) in healthy (e.g., individuals without complement deficiency, HIV, or asplenia; travelers to endemic areas) children 11-12 year of age in May 2005. This recommendation was expanded in June 2007 to include all healthy adolescents 11-18 years of age.

Subsequently, the ACIP recommended in October 2010 a booster vaccination with a meningococcal ACWY conjugate vaccine at 16 years of age, approximately 5 years following a primary dose vaccination at 11 to 12 years of age. The recommendations for meningococcal conjugate vaccination in adolescence include[10]:

1. Routine vaccination of adolescents, preferably at age 11 or 12 years, with a revaccination (booster) dose at age 16 years, and
2. For those vaccinated at 13-15 years of age, a one-time revaccination dose was recommended at 16-18 years of age.

For children 6 weeks through 10 years of age meningococcal ACWY conjugate vaccination is recommended for individuals at ongoing risk for meningococcal disease.

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

At the time of this review, MenQuadfi is not approved/authorized for use in any country. The following regulatory agencies have received marketing applications for Menquadfi:

(b) (4)

[redacted]

10 CDC. Prevention and Control of Meningococcal Disease: Recommendations of the ACIP. MMWR 2013; 62 (2): 1-22.

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 original BLA:

- September 15, 2009: Pre-IND Meeting
  - Following the completion of the applicant's Phase 1 program in 2008, a Pre-IND meeting was held to discuss initiation of US studies under IND.
- July 11, 2013: End of Phase 2 Meeting
  - The meeting discussions included the following: review of the Phase 2 study infant/toddler data, Phase 3 manufacturing plans, and clinical development plans in all age cohorts to support licensure of MenQuadfi.
- April 11, 2016: Type C Meeting
  - The major discussions pertained to the Phase 3 clinical development plan, including the required safety database, concomitant vaccinations, booster dose evaluations, lot-to-lot consistency general study design, and infant/toddler study primary endpoint assessments.
- October 20, 2017: Type C Meeting-Written Response Only
  - The applicant's approach to integration and analysis of the data from the 5 main clinical trials were reviewed, in addition to their Study Data Standardization Plan (SDSP) for the electronic data submission.
- December 7, 2018: Pre-BLA Meeting
  - The meeting discussions focused on data to be included in the BLA.

2.6 Other Relevant Background Information

Immunologic Marker of Protection: Serum Bactericidal Activity[11]

The use of immunogenicity data to support the effectiveness of meningococcal vaccines was discussed at two Vaccines and Related Biological Products Advisory Committee (VRBPAC) meetings. In September 1999, the committee concurred that a serological marker could be used to infer effectiveness of new meningococcal conjugate vaccines in children 2 years of age and older. In a second meeting 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 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 post-vaccination were protective against systemic infection. During MenQuadfi clinical development, CBER advised the applicant (Type C Meeting, April 2016) that the Phase 3 primary immunogenicity (inferred effectiveness) objectives incorporate a 4-fold response[12] from baseline in the definition of seroresponse. This seroresponse definition was based on the increasing recognition of pre-existing titers at baseline in adolescents and adults. The applicant agreed with CBER's request and included the 4-fold vaccine hSBA seroresponse definition in all studies included in the Phase 3 program.

11 FDA. Vaccines and Related Biological Products Advisory Committee. Rockville, Maryland. April 6-7 2011.
12 Based on assay validation information that supported Lower Limit of Quantitation (LLOQ) 1:4.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission of this efficacy 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 five main studies were provided in this application (MET43, MET35, MET49, MET50, MET56) to support licensure of Menquadfi, and were conducted in accordance with Good Clinical Practice (GCP) and International Committee on Harmonization guidelines. The informed consent form for each study contained all the essential elements as stated in 21CFR 50.25. In accordance with 21 CFR 312.120, the applicant provided the required elements to ensure that each study confirmed with GCP.

CBER's Division of Inspections and Surveillance (DIS) issued Bioresearch Monitoring (BIMO) inspections for 4 clinical study sites that recruited and enrolled individuals in MET35, MET43 and MET49, all of which were conducted in the US or Puerto Rico. Sites were selected based upon inspection history, numbers of subjects enrolled, and types of protocol studies conducted at each site. The inspections at 4 sites located in South Carolina, California, Arkansas, Kansas did not reveal any issues that impacted the data submitted in this BLA.

3.3 Financial Disclosures

Covered clinical study (name and/or number): MET 43, MET35, MET49, MET50, MET56, MET44		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 245 investigators		
Number of investigators who are applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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

4.1 Chemistry, Manufacturing, and Controls

Manufacturing process development, in-process testing, release and stability testing were reviewed and support licensure. The data supports 36-month expiry dating for Drug Product (DP) unit dose vials[13] stored at 2-8°C. Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

4.2 Assay Validation

The *in vivo* potency test for the final drug product (immunogenicity test) and clinical serologic assays were adequate to support licensure as determined by CBER assay review.

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

Vaccination with MenQuadfi leads to the production of bactericidal antibodies directed against the capsular polysaccharides of serogroups A, C, Y, and W. Bactericidal anti-capsular antibodies have been associated with protection from invasive meningococcal disease due to serogroups A, C, Y, and W.

4.4.2 Human Pharmacodynamics (PD)

Not applicable

4.4.3 Human Pharmacokinetics (PK)

Not applicable

4.5 Statistical

CBER statistical reviewers concluded that the datasets and analyses provided in this application were adequate to assess the safety and effectiveness of the candidate vaccine.

4.6 Pharmacovigilance

The CBER Epidemiology/Pharmacovigilance (Epi/PV) reviewer did not identify any safety concerns that would require a post-marketing study (PMR) or a Risk Evaluation and Mitigation Strategy (REMS). Based on the safety profile of similar quadrivalent meningococcal vaccines

13 Vial information: 2 mL, USP Type I borosilicate clear glass vials with 13 mm butyl (latex free) stopper and a flip off seal

licensed in the US, the important potential risks are: anaphylaxis, Guillain-Barré syndrome (GBS), and Bell's palsy. There were no cases of any of these three adverse reactions in the completed MenQuadfi clinical trials, except one case of Bell's palsy, that the Epi/PV reviewer and the clinical reviewer did not consider related to study vaccination. The Epi/PV reviewer recommended routine pharmacovigilance to monitor adverse events in accordance with 21 CFR 600.80 and agreed with the applicant's proposed Pharmacovigilance Plan (PVP). The Epi/PV reviewer also agreed to the applicant's proposal of a US based pregnancy registry to monitor safety in women exposed to the candidate vaccine during pregnancy.

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

5.1 Review Strategy

This BLA was submitted electronically and included clinical data from 5 main trials (MET43, MET35, MET49, MET56, MET50) to support immunogenicity (inferred effectiveness) and safety of a primary dose of MenQuadfi in individuals 2 years of age and older (no upper age limit), and a booster dose administered to individuals 15 years of age and older at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of meningococcal (Groups A, C, W, Y) conjugate vaccine. The submission also included 3 supportive trials, including an additional primary dose study (Phase 2) in adults 56 years of age and older, and two early phase trials (MET28, MET32) which provided data to support vaccine formulation/dosage selection. The clinical, labeling, and financial disclosure information section of the application were reviewed with detailed analyses of the main trials' study reports, pertinent line listing, case report forms, and datasets. ACIP vaccine recommendation for the prevention of meningococcal disease and current meningococcal U.S. surveillance data were also reviewed.

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

The following STN#125701/0 Amendments (Am) were reviewed (listed by modules)

- Am 0: 1.1, 1.2, 1.3, 1.6, 1.9, 1.12, 1.14, 1.16, 2.5, 2.7, 5.2, 5.3.5.1, 5.3.5.3
- Am 2: 1.1, 5.3.5.3.
- Am 3: 1.11, 5.3.5.1
- Am 5: 1.2
- Am 7: 1.9.4
- Am 9: 1.11, 5.3.5.1
- Am 10: 1.11.3, 5.3.5.1
- Am 11: 5.3.5.1
- Am 17: 5.3.5.1
- Am 22: 1.11
- Am 28: 1.11, 1.14
- Am 30: 1.11
- Am 34: 1.11, 1.14
- Am 35: 1.11
- Am 36: 1.11, 5.3.5.1
- Am 37: 1.14
- Am 38: 1.14
- Am 39: 1.14

5.3 Table of Studies/Clinical Trials

Study Number	Country	Description (relevance to US licensure)	Population	Study Groups: # Enrolled (#Exposed)
MET43	US	Phase 3 Controlled, DB, Multicenter, Imm/Safety, Lot-to-Lot Consistency, Primary Dose, Vaccine-naïve Adol./Adults: 10 to 55 years, Noninferiority to Menactra	10 through 17 years 18 through 55 years	MenQuadfi Lot 1: 902 (895) MenQuadfi Lot 2: 895 (886) MenQuadfi Lot 3: 906 (900) Menactra: 641 (636)
MET35	US#	Phase 3 Controlled, DB, Multicenter, Imm./Safety, Primary Dose, Vaccine-naïve Children: 2 years to 9 years, Noninferiority to Menveo	2 through 5 years 6 through 9 years	MenQuadfi: 499 (497) Menveo: 501 (495)
MET49	US#	Phase 3 Controlled, DB, Multicenter Imm/Safety, Primary Dose, Vaccine-naïve Adults ≥56 years, Noninferiority to Menomune	56 through 64 years 65 through 74 years ≥75 years	MenQuadfi: 451 (448) Menomune: 455 (453)
MET56	US#	Phase 3 Controlled, DB, Imm./Safety, Multicenter, Booster Dose, History of Primary MCV4 (4y to 10y prior), Noninferiority to Menactra	≥15 years	MenQuadfi: 403 (402) Menactra: 407 (407)
MET50	US	Phase 2 Controlled, DB, Imm/Safety, Multicenter, Primary Dose, Noninferiority to Menveo. Concomitant Tdap + HPV4	10 through 17 years	MenQuadfi: 505 (499) Menveo: 507 (504) MenQ.+Tdap+HPV: 403 (377*) Tdap+HPV: 300 (273*)
MET44	US	Phase 2, Open-label, Controlled, Imm/Safety, Multicenter Primary dose, Vaccine-naïve Adults ≥56 years Comparator: Menomune	56 through 64 years ≥65 years	MenQuadfi 56-64y: 101 (101) MenQuadfi ≥65y: 100 (100) Menomune 56-64y: 50 (50) Menomune ≥65y: 50 (50)
MET28	Canada	Phase 1, Single-blind, Partially-controlled, Safety/Imm, Formulation Selection (b) (4)), Multicenter, Step-down (Adults, Toddlers, Infants) Infant controlled only-Menjugate	18y - <40y 12mo -<19mo 2mo old	Adult Grp 1-(b) (4): 15 (15) Adult Grp 2-(b) (4): 15 (15) Toddler. Grp 3-(b) (4): 21 (21) Tod. Grp 4-(b) (4): 20 (19) Infant Grp 5-(b) (4): 45 (46) Infant Grp 6-(b) (4): 45 (44) Infant Grp 7-(b) (4): 45 (43) Infant Grp 8- Menjugate: 44(44)
MET32	Australia	Phase 1/Phase 2, Controlled, Observer Blind, Multicenter Antigenic Dose and Protein Conjugate Selection Comparator: Neis-Vac-C	12 months	5 different dose groups: 310 (306) Neis-Vac-C group: 63 (62)

Source: STN 125701, Section 5.2-Tabular Listing of all Clinical Studies, adapted from Table 1. DB: double blind;
Imm.: immunogenicity, Adol.: adolescents, MCV4: meningococcal conjugate ACWY vaccine; MenQ: MenQuadfi;
#: Includes sites in Puerto Rico. *exposure to all study vaccine doses, (b) (4) . Tod.: Toddler
Menjugate (Meningococcal serogroup C CRM197conjugate vaccine, GSK) not licensed in US
NeisVax-C (Meningococcal serogroup C tetanus toxoid conjugate vaccine, Baxter International) not licensed in US

5.4 Consultations

During the review of this original BLA, external input was not sought.

5.4.1 Advisory Committee Meeting

An Advisory Committee meeting was not convened during the review of this BLA.

5.4.2 External Consults/Collaborations

External consults were not obtained during the review of this BLA

5.5 Literature Reviewed (if applicable)

During the review of this BLA, the following references were used to discuss U.S. meningococcal disease epidemiology, current ACIP recommendations for prevention of infection against serogroups A, C, W, Y, and FDA Advisory Committee findings. These references include the following:

1. Pace, D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. *Vaccine*. 2012 May 30;30 Suppl 2: B3-9.
2. CDC. Meningococcal Disease Chapter 14. *Pink Book*, 13th Ed. May 2015.
3. CDC. Active Bacterial Core Surveillance (ABCs) Report: *Neisseria meningitidis*, 2017.
4. CDC. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(RR02);1-22.
5. CDC. 2017 Enhanced Meningococcal Surveillance Report. Website accessed June 28, 2019.
6. FDA. Vaccines and Related Biological Products Advisory Committee. Rockville, Maryland. April 6 - 7 2011.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Study MET43)

NCT#02842853
A Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Menactra®, and describe the safety and additional immunogenicity of these study vaccines in adolescents and adults aged 10 to 55 years in the United States (US)[14]

Study Overview: Study MET43 was designed to demonstrate lot consistency of 3 MenQuadfi lots, immunological non-inferiority of MenQuadfi (pooled lots) and safety compared Menactra. MenQuadfi and Menactra were administered as a single intramuscular dose to meningococcal vaccine-naïve adolescents 10 years through 17 years of age and adults 18 years through 55 years of age. The study was conducted between July 2016 and February 2017 and enrolled over a total of 3000 healthy meningococcal vaccine-naïve individuals at 90 sites in the United States.

6.1.1 Objectives

The study objectives, endpoints and statistical success criteria, if applicable are described below.

Primary Immunogenicity:

1. To demonstrate the immune lot consistency as determined by antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi vaccine with respect to hSBA GMTs.
   - *Primary Endpoint:* Geometric mean titer ratios (GMTRs) of antibodies against meningococcal serogroups A, C, Y, and W, measured by hSBA at 30 days (+14 days) after vaccination.
   - *Primary Hypothesis:* Thirty days after the administration of MenQuadfi vaccine, GMTs of antibodies against serogroups A, C, Y and W in Groups 1, 2, and 3 are equivalent.
     - *Criteria for Success:* If the 2-sided 95% CI of the ratio of the GMTs was >0.5 and <2.0 for each pair of lots and each antigen, then equivalence was demonstrated for each pair of lots.

2. To demonstrate the non-inferiority of hSBA responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi vaccine (pooled Lots 1+2+3) compared to those observed following the administration of a single dose of Menactra®
   - *Primary Endpoint:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y and W, measured by hSBA at 30 days after vaccination.
     Seroresponse was defined as:
     - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
     - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.*
   - *Primary Hypothesis:* Thirty days after the administration of MenQuadfi or Menactra, the percentages of subjects who achieve an hSBA vaccine seroresponse for serogroups A,

14 Study population included individuals between 10 years and 55 years of age, beginning on the day of the 10th birthday and ending on the day before the 56th birthday.

C, Y and W in Groups 1, 2, and 3 combined are non-inferior to the corresponding percentages in Group 4.

- *Criteria for Success* If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions ($p_{MenQuadfi}$-$p_{Menactra}$) achieving seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup.

Reviewer Comment*:*
The study objectives were discussed during a Type C Meeting on 11 April 2016 under IND 14171 in the context of the overall clinical development plan. During the meeting, the applicant clarified that lot-to-lot consistency would be demonstrated first, as a condition for pooling MenQuadfi immunogenicity data (3 lots combined) to then demonstrate non-inferiority of MenQuadfi to Menactra. In addition, the seroresponse definition used in phase 2 studies was revised for the phase 3 studies, based on CBER's review of hSBA assay validation information.

Secondary Immunogenicity:

1. To demonstrate non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi vaccine (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra in the adult population (18 through 55 years old).
   - *Secondary Endpoint #1:* Seroresponse, as measured by hSBA

   Secondary Hypothesis #1: Thirty days after the administration of MenQuadfi or Menactra percentages of subjects who achieved an hSBA vaccine seroresponse for serogroups A, C, Y and W in Groups 1b, 2b, and 3b combined were non-inferior to the corresponding percentages in Group 4b.
   - *Criteria for Success:* If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions achieving seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup.

2. To demonstrate the non-inferiority of the hSBA antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi vaccine (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra in the adolescent population (10 to 17 years old)
   - *Secondary Endpoint #2*: Seroresponse, as measured by hSBA, for each serogroup
   - *Secondary Hypothesis #2*: Thirty days after the administration of MenQuadfi vaccine or Menactra, the percentages of subjects who achieved an hSBA vaccine seroresponse for serogroups A, C, Y, and W in Group 1a, 2a, and 3a combined were noninferior to the corresponding percentages in Group 4a
     - *Criteria for Success*: If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions achieving seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup

3. To compare the hSBA vaccine seroresponse rates of meningococcal serogroups A, C, Y, and W for each of 3 lots of MenQuadfi vaccine 30 days after vaccination
   - *Secondary Endpoint:* Seroresponse, as measured by hSBA, for each serogroup
   - *Descriptive Analyses*

4. To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi vaccine (pooled Lots 1 to 3) to those observed following the administration of Menactra

- *Secondary Endpoint*: Geometric Mean Titer Rise, as measured by hSBA, for each serogroup
- *Descriptive Analyses*

Observational Immunogenicity: Descriptive analyses
To describe the antibody responses to the meningococcal serogroups A, C, Y, and W before vaccination and 30 days (+14 days) after vaccination with MenQuadfi vaccine or Menactra.

- *Immunogenicity Endpoints:*
  - hSBA GMTs and 95% CI at each time point for each group
  - hSBA titer distribution and RCDC
  - % of subjects with hSBA titer ≥ 1:4 & ≥ 1:8, 95% CI at D0 & D30 for each group
  - % of subjects with hSBA titer ≥ 4-fold rise from pre- to post- vaccination, 95% CI

Observational Safety: Descriptive analyses
To describe the safety profile of MenQuadfi vaccine and that of licensed Menactra.

- *Safety Endpoints:*
  - Proportion of subjects with unsolicited systemic AEs reported in the 30 minutes after vaccination
  - Proportion of subjects with solicited injection site and systemic reactions reported up to 7 days after vaccination
  - Proportion of subjects with unsolicited systemic reported up to 30 days after vaccination and if event led to early termination
  - Proportion of subjects with SAEs reported during the 180 days after vaccination (study duration) and if event led to early termination
  - Proportion of subjects with MAAEs reported from Visit 2 (Day 30 +14days) through the 6-month follow-up contact. MAAEs occurring during the 30 days following vaccination were reported as unsolicited AEs.

6.1.2 Design Overview

Study MET43 was a modified double-blind, randomized, parallel-group, active-controlled, multi-center study in the US. Planned enrollment included approximately 3300 healthy, meningococcal-vaccine naïve adolescents and adults ages 10 years through 55 years randomized to one of 3 MenQuadfi lot groups or Menactra group (randomization ratio 3:3:3:2, respectively). The study groups included:

- Group 1: MenQuadfi vaccine (Lot 1)
  - Group 1a: 400 subjects 10 through 17 years of age
  - Group 1b: 500 subjects 18 through 55 years of age
- Group 2: MenQuadfi vaccine (Lot 2)
  - Group 2a: 400 subjects 10 through 17 years of age
  - Group 2b: 500 subjects 18 through 55 years of age
- Group 3: MenQuadfi vaccine (Lot 3)
  - Group 3a: 400 subjects 10 through 17 years of age
  - Group 3b: 500 subjects 18 through 55 years of age
- Group 4: Menactra vaccine
  - Group 4a: 300 subjects 10 through 17 years of age
  - Group 4b: 300 subjects 18 through 55 years of age

Subjects received a single dose of MenQuadfi vaccine (Lot 1, Lot 2, or Lot 3) or Menactra on Day 0. The subject and the investigator were unaware of the treatment assignments throughout

the trial. An unblinded vaccine administrator was not involved in safety data collection. The applicant and laboratory personnel who performed the serology testing, also remained blinded to treatment assignments throughout the trial until database lock.

Study duration was for ~6months and included the following:

- 2 study visits: Day 0, Day 30 (+14 days)
- 2 telephone calls: Day 8 (+2 days), Day 180 (+14 days)

6.1.3 Population

Individuals were eligible to be enrolled if they met all of the following inclusion criteria: Ages 10 through 55 years on the day of inclusion; informed consent form signed and dated by the subject (ages 18 through 55 years) or assent form signed and dated by the subject and informed consent form has been signed and dated by the parent/guardian (for subjects aged 10 to < 18 years); subject (≥ 18 years) or subject (10 to < 18 years) and parent / guardian are able to attend all scheduled visits and to comply with all trial procedures.

Individuals were not eligible to be enrolled if they met any of the following exclusion criteria: Pregnant, or lactating, or of childbearing potential (to be considered of nonchildbearing potential, a female must have been pre-menarche or post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination); participated in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure; receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination (could be received at least 2 weeks before or after the study investigational vaccines-includes monovalent pandemic/multivalent influenza vaccines); previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate) meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B vaccine; receipt of immune globulins, blood or blood-derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months); history of meningococcal infection, confirmed either clinically, serologically, or microbiologically; at high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease); known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances; verbal report of thrombocytopenia, as reported by the subject or the subject's parent/guardian, contraindicating intramuscular (IM) vaccination in the Investigator's opinion; bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination in the Investigator's opinion; personal history of Guillain-Barre syndrome (GBS); personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine within 10 years of the proposed study vaccination; deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily; current alcohol abuse or drug addiction; chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion; moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F) [prospective subject was not to be

included in the study until the condition had resolved or the febrile event had subsided]; receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw; and identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, spouse,
natural or adopted child) of the Investigator or employee with direct involvement in the proposed
study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi: Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

- Batch #: Lot 1 (UD18368); Lot 2 (UD18364); Lot 3 (UD18365)
- Dose: single 0.5mL intramuscular
- Composition: Serogroups A, C, Y, W: 10 ug (each meningococcal capsular polysaccharide); Tetanus toxoid protein carrier: (b) (4) ug
- Preparation: single-dose 0.5 mL vial

Menactra® (Sanofi Pasteur): MenACWY Diphtheria Toxoid Conjugate Vaccine

- Batch #: U5462AB
- Dose: single 0.5mL intramuscular
- Composition: Serogroups A, C, Y, W: 4 ug (each meningococcal capsular polysaccharide); Diphtheria toxoid protein carrier: 48 ug
- Preparation: single-dose 0.5mL vial

6.1.5 Directions for Use

See prior section.

6.1.6 Sites and Centers

90 sites in the US.

6.1.7 Surveillance/Monitoring

Study Oversight:
Study oversight was provided by (b) (4) Institutional Review Board (IRB) for all study sites, except Site 31. For Site 31, the IRB was (b) (4) . An internal Safety Management Team performed blinded safety analysis on safety data after vaccination.

Safety Monitoring:

- Immediate Adverse Events for 30 minutes postvaccination
  - Any unsolicited AEs during this time period
  - Documented in source document at site
- Solicited Adverse Events (AEs) for 7 days postvaccination
  - Solicited Reactions:
    - Local (Injection Site): pain, redness, swelling

    - Systemic: fever[15], headache, malaise, myalgia
  - Graded intensity[16] as 1, 2, or 3
  - Documented by subject, or parent/guardian daily on Diary Card, and transcribed by study personnel in the Case Report Form at Visit 2.
- Unsolicited AE data, including those leading to study withdrawal for 30 days postvaccination
  - Any other medical events that occur in the 30-day period after vaccination
  - Documented by site or parent/guardian on Diary Card, including start/stop dates, intensity, action taken, if any.
  - Graded intensity[17] as 1, 2, or 3
- Medically attended AEs (MAAEs) for 30 days postvaccination
  - Defined as new onset of a condition that prompts the subject or subject's parent / guardian to seek medical advice at a physician's office/by telephone consultation or Emergency Department visit.
  - Documented on
    - Diary card: MAAEs occurring between Day 0 to 30 (+14 days)
    - Memory aid: MAAEs occurring between Day 30 (+14days) to 180 (+14 days)
- Serious adverse events (SAEs) for 180 days (+14) postvaccination
  - Defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or an important medical event. The investigator assessed the causality to the investigational vaccine as either related or not related.

Immunogenicity Monitoring (Methods and Designated Testing Laboratory):
Blood samples were collected at Day 0 (pre-vaccination) & Day 30 (+14days): all subjects
Serum bactericidal antibody (SBA) assays

- SBA using human sera complement (hSBA) against serogroups A, C, W & Y strains
  - hBA testing performed at Global Clinical Immunology, Sanofi Pasteur, Swiftwater PA
  - lower limit of quantitation: 1:4
- Assessments included:
  - hSBA Geometric Mean Titer (GMTs) and Ratios (GMTRs): all subjects
  - hSBA seroresponse from Day 0 (pre-vaccination) to Day 30: all subjects

6.1.8 Endpoints and Criteria for Study Success

Please see Section 6.1.1 of the clinical review.

15 Temperature measurements: once per day, preferably same time, optimal time in evening. Additional measurements at time of apparent fever. Observed daily temperature and the route of measurement were to be recorded in diary card provided. The highest temperature was recorded in the CRF. Preferred route of temperature measurement was oral. Pre-vaccination temperature collected by investigator on source document. Tympanic thermometers were not permitted.
16 Grading for local -erythema & -swelling: Grade 1: ≥25mm to ≤50mm, Grade 2: ≥51 to ≤100mm; Grade 3 >100mm. Grading for local pain, headache, malaise, myalgia: Grade 1: no interference with activity; Grade 2: some interference with activity; Grade 3: significant, prevents daily activity. Grading for Fever: Grade 1: ≥38.0C to ≤38.4; Grade 2: ≥38.5C to ≤38.9C; Grade 3: ≥39.0C.
17 Grading for unsolicited AEs: Grade 1: No interference with activity, Grade 2: some interference with activity, Grade 3: significant, prevents daily activity.

6.1.9 Statistical Analysis Plan

Sample Size Calculations: Planned enrollment of 3300 subjects, assuming a 10% drop-out rate, would result in ~2970 evaluable subjects (810 evaluable subjects in each of the MenQuadfi lot groups and 540 evaluable subjects in the Menactra group), with 88% power to declare clinical equivalence of the 3 MenQuadfi lots and 99.9% power to declare non-inferiority of MenQuadfi (pooled lots) to Menactra. Overall, the study had 88% power to achieve both primary objectives simultaneously.

Subgroup Analyses: Immunogenicity and safety analyses were provided by age (10 years through 17 years, 18 years through 55 years); sex (male, female), and racial origin. In addition, the applicant conducted sensitivity analyses that excluded data from study sites that had GCP concerns (Site 38 and Site 22).

Statistical Methods:
Immunogenicity Data

- Missing data were not imputed
- For analysis purposes to manage extreme values (hSBA titers < lower limit of quantitation [LLOQ] and ≥ upper limit of quantitation [ULOQ]), the following computational rules were applied:
  For GMT calculations:
  - If a value w < LLOQ, then use the computed value LLOQ/2
  - If a value is between ≥ LLOQ and < ULOQ, then use the value
  - If a value is ≥ ULOQ, then use the computed value ULOQ
- For fold-rise calculations:
  - If the baseline computed value is < LLOQ and the post-baseline computed value is <LLOQ then the fold-rise is 1
  - If the baseline computed value is ≥ LLOQ and the post-baseline computed value is ≥LLOQ then the fold-rise is post-baseline computed value / baseline computed value
  - If the baseline computed value is ≥ LLOQ and the post-baseline computed value is <LLOQ then the fold-rise is (LLOQ/2) / baseline computed value
  - If the baseline computed value is < LLOQ and the post-baseline computed value is ≥LLOQ then the fold-rise is post-baseline computed value /LLOQ

Safety Data:

- Missing data were not replaced. In all subject listings, partial and missing data were indicated as missing

Protocol Amendments:

- Protocol: version 2.0, dated 02 June 2016, major revisions included:
  - Updated hSBA vaccine seroresponse definition as per CBER guidance
  - Indicated priority of hSBA testing in the event of insufficient sample volume

Significant Changes in the Conduct of the Study & Planned Analyses:

- Immunogenicity Analyses:
  - Site 38: The applicant investigated this site, due to concerns about unusual results following a dry-run of serology data for 83 subjects and determined that the laboratory technician at this site affixed blood sample #2 labels for sera collected at Visit 1 and affixed blood sample #1 labels for sera collected at Visit 2 for 18 subjects. The applicant and site staff remained blinded during these investigations. The subjects from Site #38

were included in the Per Protocol Analysis Set and Full Analysis Set populations for primary immunogenicity analyses. The applicant conducted a sensitivity analyses without these 18 subjects from Site #38, which demonstrated comparable immunogenicity results to those of the primary analyses that included these subjects.

- Safety Analyses:
  - Site #22: 6 subjects were removed from the Safety Analysis Set due to concerns associated with GCP at this site. The applicant had conducted an additional safety analyses population (Safety Analyses Set 2) which included these 6 subjects. The results of these analyses did not demonstrate any differences in the overall safety findings of the study.

Reviewer Comment*: The applicant appropriately notified the IRBs and FDA of these concerns in timely manner and conducted the relevant sensitivity analyses.*

6.1.10 Study Population and Disposition

A total of 3344 subjects were enrolled in the study. Study period: 15 July 2016 (first subject, first visit) to 28 February 2017 (last contact for 6-month safety follow-up).

6.1.10.1 Populations Enrolled/Analyzed

Relevant analysis populations:

- *Safety Analyses Set (SafAS)*: Subjects who received at least 1 dose of the study vaccine and had safety data available. Safety data was analyzed based on actual vaccine administered. There were 6 subjects excluded from Site #22 due to GCP concerns.
- *Full Analyses Set (FAS):* subjects who received at least 1 dose of the study vaccine and had a valid post-vaccination result, i.e., a result different from not reportable or missing for at least 1 serogroup. All subjects were analyzed according to the treatment group to which they were randomized. The FAS was used to confirm the findings of the primary immunogenicity analyses.
- *Per-Protocol Analyses Set (PPAS):* a subset of the FAS, which excluded those subjects with at least one of protocol deviations listed below. The PPAS was used for the primary immunogenicity analyses.

  Protocol Deviations: Subjects were excluded from the PPAS for the following protocol deviations:
  - did not meet all protocol-specified inclusion criteria or met at least one of the protocol specified exclusion criteria
  - did not receive vaccine, received a vaccine other than the one that he/she was randomized to receive; preparation/administration of vaccine was not done as per-protocol; subject did not receive vaccine in proper time window
  - did not provide post-dose serology sample in the proper time window (Visit 2: 30 to 44 days after vaccination at Visit 1) or a post-dose serology sample was not drawn;
  - subject received a protocol-prohibited Category 2 or 3 therapy/medication/vaccine; serology sample did not produce a valid test result, such as a result different from 'NR' or missing for at least 1 serogroup (either pre- or post-vaccination)
  - subject had other protocol violations that affected the subject's immune response, as determined by the applicant's team before locking the database.

6.1.10.1.1 Demographic and Baseline Characteristics

Table 1: Study MET43- Demographic Characteristics of MenQuadfi Study Groups (Lot 1, Lot 2, & Lot 3) and Menactra Study Group, SafAS

Demographic Characteristic	Lot 1 (N=895) X (%)	Lot 2 (N=883) X (%)	Lot 3 (N=898) X (%)	Menactra (N=635) X (%)
Sex Ratio M:F (%)	364:531 (41%:59%)	357:526 (40%:60%)	406:492 (45%:55%)	280:355 (44%:56%)
Age Group:	--	--	--	--
10 through 17years:	398 subjects:	391 subjects:	392 subjects:	323 subjects:
Mean Age (SD)	12.1y (1.9)	12.0y (1.9)	12.2y (1.9)	12.2y (2.1)
Median Age	11.5y	11.4y	11.5y	11.4y
Age Range	10.0y, 18.0y	10.0y, 17.9y	10.0y,17.8y	10.0y, 17.9 y
18 through 55years:	497 subjects:	492 subjects:	506 subjects:	312 subjects:
Mean Age (SD)	39.17y (9.9)	39.3y (10.4)	39.2y(10.2)	39.5y (10.0)
Median Age	39.6 y	39.3 y	39.2 y	39.5 y
Age Range	18.1y, 55.9y	18.6y, 55.9y	18.3y, 56.0y	18.1y, 56.0y
Racial origin:	--	--	--	--
Asian	9 (1.0)	19 (2.2%)	19 (3%)	14 (2.2%)
Black/A.A.	174 (19.4%)	183 (20.7%)	166 (18.5%)	120 (18.9%)
White	674 (75.3%)	639 (72.4%)	676 (75.3%)	473 (74.5%)
Am.Indian/A.N	1 (0.1%)	7(0.8%)	5 (0.6%)	3 (0.5%)
N.Hawaiian/P.I	6 (0.7%)	4(0.5%)	3 (0.3%)	2 (0.3%)
Mixed Origin	30 (0.4%)	29 (3.3%)	29 (3.2%)	21 (3.3%)
Ethnicity:	--	--	--	--
Hispanic/Latino	187 (20.9%)	202 (22.9%)	183 (20.4%)	137 (21.6%)
Not H/L	707 (79.0%)	680 (77.0)	713 (79.4%)	498 (78.4%)

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 4.3. SafAS: Safety Analyses Set. For Sex; Racial Origin, and Ethnicity: X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects for the Safety Analyses Set (subjects who received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female. For Age Groups: y indicates years. Additional Source: adapted from STN 125701.0, MET43 Appendix 15, Tables 13 and 14. Racial origin: Asian, Black/A.I: Black/African American; Am.Indian/A.N: American Indian/Alaska Native; N.Hawaiian/P.I.: Native Hawaiian/Pacific Islander; missing origin not listed (accounted for 5 subjects (0.2%) across all groups). Ethnicity: Hispanic/Latina; Not H/L: Not Hispanic/Latino.

There were more females enrolled (55% to 60%) than males (40% to 45%). Across study groups, the median age of each age cohort was consistent: 11.5 years in the adolescent (10 years to 17 years) cohorts and 39.5 years in the adult (18 years to 55 years) cohorts. Most subjects were White (74.4%), followed by Black/African American racial origin (19.4%). Across groups, most subjects were not of Hispanic/Latino ethnic origin, while 21.4% were of Hispanic/Latino origin.

Reviewer Comment: *The overall demographic characteristics across all 4 study groups were similar.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.1.10.1.3 Subject Disposition

Table 2: Study MET43- Subject Dispositions & Data Analyses Sets for MenQuadfi Groups (Lot 1, Lot 2, & Lot 3) and Menactra Study Group

Population	Lot 1(N=902) X (%)	Lot 2(N=895) X (%)	Lot 3 (N=906) X (%)	Menactra(N=641) X (%)
Enrolled	902 (100%)	895 (100%)	906 (100%)	641 (100%)
Vaccinated	895 (100%)	886 (99%)	900 (99.3%)	636 (99.2%)
Completed Study	849 (97.5%)	886 (99.0%)	900 (99.3%)	636 (99.2%)
Follow-Up	855 (94.8%)	847 (94.6%)	873 (96.4%)	608 (94.9%)
Safety Analysis Set	895 (99.2%)	883 (98.7)	898 (99.1%)	635 (99.1%)
Full Analysis Set	874 (96.9%)	861 (96.2%)	875 (96.6%)	615 (95.9%)
Per Protocol	843 (93.5%)	820 (91.6%)	845 (93.3%)	593 (92.5%)
≥1 Prot. Deviation	59 (6.5%)	75 (8.4%)	60 (6.6%)	48 (7.5%)

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 4.2. X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects enrolled. ≥1 Prot. Deviation: subjects with one or more protocol deviations.

The list of pre-specified protocol deviations was provided in Section 6.1.10.1 of this review memo. Across all study groups there were 242 subjects (7.2%) who experienced at least 1 protocol deviation, mainly due to post-dose blood sample at Visit 2 not drawn in the proper time window or a blood sample was not drawn (5.1% overall; range: 4.5% to 5.3%), or subjects did not meet all protocol-specified inclusion/exclusion criteria (0.9% overall; range:0.4% to1.6%) or not vaccinated (0.6% overall; range: 0.6% to 0.8%)

> ***Reviewer Comment*****:** *The distribution of protocol deviations was similar across the four study groups. The observed protocol deviations did not raise concerns about the interpretability of study results.*

6.1.11 Efficacy Analyses

Clinical endpoint vaccine efficacy was not evaluated in this trial.

6.1.11.1 Analyses of Primary Endpoints

Primary Objective #1: Lot-to-Lot Equivalence

The first primary immunogenicity objective evaluated the hSBA GMT 30 days following a single dose vaccination with one of 3 lots of MenQuadfi in adolescents and adults ages 10 years through 55 years. The 3 lots were considered equivalent if for each pairwise comparison of MenQuadfi vaccine lots, the 2-sided 95% CI of the ratio of GMTs was contained within the interval [0.5, 2.0] for each of the 4 serogroups. The primary objective was met.

The tables below provide the 30-day post-vaccination hSBA GMTs against each serogroup for each of the 3 lots [95% CI] and the ratio GMTs for each pairwise comparison for the Per Protocol Analyses Set.

Table 3: Study MET43 Primary Objective 1 - hSBA Geometric Mean Titers at 30-days Post-Vaccination for MenQuadfi Lot 1, Lot 2, Lot 3, PPAS

Serogroup	Lot 1 (N=841-843) GMT [95% CI]	Lot 2 (N=819-820) GMT [95% CI]	Lot 3 (N=843-845) GMT [95% CI]
A	84.9 [75.8; 95.1]	96.5 [86.4; 108]	97.9 [87.7; 109]
C	326 [286; 372]	305 [267; 349]	352 [307; 405]
Y	213 [191; 238]	210 [188; 234]	218 [194; 246]
W	84.5 [75.1; 95.1]	81.6 [72.7; 91.5]	87.2 [77.2; 98.5]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.1. hSBA: serum bactericidal antibody assay using human sera, PPS: Per Protocol Analyses Set, GMT: Geometric Mean Titers, N: #subjects in PPAS. Lot 1: Batch# UD18368; Lot 2: Batch# UD18364; Lot 3: Batch# UD18365.

Table 4: Study MET43 Primary Objective 1 - Geometric Mean Titer Ratios for Each Pairwise MenQuadfi Lot-to-Lot Comparison, PPAS

Serogroup	Lot 1/Lot 2 GMTR [95% CI]	Lot 2/Lot 3 GMTR [95% CI]	Lot 1/Lot 3 GMTR [95% CI]
A	0.880 [0.751; 1.03]	0.985 [0.843; 1.15]	0.867 [0.740; 1.02]
C	1.07 [0.888; 1.29]	0.866 [0.714; 1.05]	0.927 [0.766; 1.12]
Y	1.02 [0.869; 1.19]	0.961 [0.816; 1.13]	0.975 [0.829; 1.15]
W	1.04 [0.878; 1.22]	0.936 [0.791; 1.11]	0.970 [0.818; 1.15]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.1. PPAS: Per Protocol Analyses Set. GMTR: Geometric Mean Titer Ratio.

Primary Objective #2: hSBA Seroresponse Rates (All Subjects)

Since the lot consistency study objective was met, non-inferiority of hSBA serogroup-specific seroresponse[18] rates at Day 30 was evaluated after MenQuadfi (pooled lots [study groups 1, 2 and 3 combined]) vaccination compared corresponding responses after Menactra (Group 4) vaccination *in subjects 10 years through 55 years of age*. Non-inferiority was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroresponse rate was > -10% for each serogroup. The following table provides the hSBA seroresponse rates [95% CI] at Day 30 for the combined MenQuadfi groups compared to the Menactra group for the Per Protocol Analyses Set, as well as the differences in seroresponse rates [95%CI].

Table 5: Study MET43 Primary Objective 2 - hSBA Seroresponse Rates MenQuadfi (Pooled Lots) vs Menactra, PPAS

Serogroup	MenQuadfi Pooled Lots (N=2503-2505) % [95% CI]	Menactra (N=593) [95% CI]	Difference % [95% CI] (MenQuadfi- Menactra)
A	73.8% [72.0, 75.5]	54.6% [50.5, 58.7]	19.1% [**14.8**, 23.5])
C	88.8% [87.5, 90.0]	47.9% [43.8, 52.0]	40.9% [**36.7**, 45.0]
Y	91.4% [90.3, 92.5]	73.4% [69.6, 76.9]	18.1% [**14.5**, 21.9]
W	80.3% [78.7, 81.8]	61.2% [57.2, 65.2]	19.1% [**14.9**, 23.3]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.2. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates for each serogroup.

The non-inferiority criteria were met for all serogroups.

6.1.11.2 Analyses of Secondary Endpoints

Secondary Objectives #1 & 2: hSBA Seroresponse Rates by Age Cohort (Adults, Adolescents)

For these two analyses and the additional immunogenicity analyses for this study, the hSBA comparisons were between the 3 lots of MenQuadfi combined and the Menactra group, unless otherwise stated. hSBA serogroup-specific seroresponse rates at Day 30 were evaluated for the MenQuadfi combined group compared to Menactra group separately in adult subjects (18 years through 55 years) and adolescent subjects (10 years through 17 years), respectively. Non-inferiority of the immune response was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroresponse rate was > -10% for each serogroup.

18 hSBA seroresponse definition: pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

The following table provides the % difference [95% CI] in hSBA seroresponse rates between groups (MenQuadfi- Menactra) in the *adult participants (18 years through 55 years of age)* by serogroup for the PPAS.

Table 6: Study MET43 Secondary Objective 1 - hSBA Seroresponse Rates MenQuadfi (Pooled Lots) vs Menactra, Adults (18 through 55 years), PPAS

Serogroup	MenQuadfi Pooled Lots (N=1406-1408) % [95% CI]	Menactra (N=293) [95% CI]	Difference % [95% CI] (MenQuadfi- Menactra)
A	73.5% [71.2, 75.8]	53.9% [48.0, 59.7]	19.6% [13.5, 25.8]
C	83.4% [81.4, 85.3]	42.3% [36.6, 48.2]	41.1% [35.0, 46.9]
Y	88.1% [86.3, 89.8]	60.8% [54.9, 66.4]	27.4% [21.7, 33.3]
W	77.0% [74.7, 79.2]	50.2% [44.3, 56.0]	26.8% [20.7, 32.9]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.3. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates for each serogroup

The following table provides the % difference [95% CI] in hSBA seroresponse rates across groups *in adolescent participants (10 years through 17 years*) by serogroup for the PPAS.

Table 7: Study MET43 Secondary Objective 2 - hSBA Seroresponse Rates MenQuadfi (Pooled Lots) vs Menactra, Adolescents (10 through 17 years), PPAS

Serogroup	MenQuadfi Pooled Lots (N=1097) % [95% CI]	Menactra (N=300) [95% CI]	Difference % [95% CI] (MenQuadfi- Menactra)
A	74.0% [71.3, 76.6]	55.3% [49.5, 61.0]	18.7% [12.5, 24.9]
C	95.6% [94.2, 96.8]	53.3% [47.5, 59.1]	42.3% [36.6, 48.0]
Y	95.6% [94.2, 96.8]	85.7% [81.2, 89.4]	10.0% [6.18, 14.5]
W	84.5% [82.2, 86.6]	72.0% [66.6, 77.0]	12.5% [7.22, 18.2]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.4. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates for each serogroup

For both age cohorts, non-inferiority of MenQuadfi (pooled lots) to Menactra was demonstrated for each serogroup.

> ***Reviewer Comment:*** *When evaluated separately, the hSBA seroresponse rates in adults and adolescents who received MenQuadfi were non-inferior to those achieved by Menactra recipients in the respective age cohorts. The separate results support the overall findings of the primary analyses (all enrolled subjects) for each serogroup. The % difference in hSBA seroresponse rates demonstrated similar trends for serogroups A, C and W between adults and adolescents. However, for serogroup Y the % difference in hSBA responses across groups in adults were greater (27.4% [21.7, 33.3]) when compared to those in adolescents (10.0% [6.18, 14.5]).*

Secondary Objective #3:
hSBA seroresponse rates at Day 30 postvaccination were described for each MenQuadfi lot (Groups 1, 2 or 3). The point estimates for the % of subjects who achieved seroresponse across the 3 lots for each serogroup were generally comparable.

Secondary Objective #4:
Serogroup-specific hSBA GMTs at Day 30 postvaccination were compared for the combined MenQuadfi groups to corresponding hSBA GMTs in the Menactra group. The following table provides the hSBA GMTs across both groups based on the PPAS:

Table 8: Study MET43 Secondary Objective 4- hSBA Geometric Mean Titers MenQuadfi (Pooled Lots) vs Menactra, PPAS

Serogroup	MenQuadfi Combined (N=2505-2507) GMTs [95% CI]	Menactra (N=593) GMTs [95% CI]	GMT Ratio [95% CI] (MenQuadfi/Menactra)
A	92.9 [87.1, 99.1]	48.1 [41.8, 55.2]	1.93 [1.67, 2.24]
C	328 [303, 354]	40.7 [33.8, 49.0]	8.05 [6.58, 9.84]
Y	214 [200, 228]	66.4 [56.4, 78.0]	3.22 [2.71, 3.84]
W	84.4 [78.8, 90.4]	44.5 [38.3, 51.7]	1.90 [1.61, 2.24]

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 5.6. PPAS: Per Protocol Analyses Set.
N: #subjects in PPAS, hSBA: serum bactericidal antibody assay using human sera, GMTs: Geometric Mean Titers, N= #subjects in PPAS

The point estimates for the hSBA GMTs for the pooled MenQuadfi lots were higher than the hSBA GMTs for the Menactra group, with 95% CI that did not overlap; for serogroups C, the GMTs were ~8-fold [6.58, 9.84] higher, and for the other serogroups the hSBA GMTs were ~2 to 3-fold higher.

> ***Reviewer Comment****: The hSBA GMTs for the MenQuadfi recipients were higher for all serogroups when compared to the Menactra recipients. These findings support the primary immunogenicity analyses evaluating the hSBA seroresponse rates across treatment groups. The trends in hSBA GMTs are similar to those observed with hSBA seroresponse rates, with markedly higher results for the pooled MenQuadfi lots compared to Menactra group, especially for serogroup C.*

Observational Objectives:
The proportion of subjects with hSBA antibody titers ≥1:8 at Day 30 postvaccination, for each serogroup, in the pooled MenQuadfi groups (2508 subjects in PPAS) vs. the Menactra group (593 subjects in PPAS), with 95% confidence intervals (CIs), are as follows:
(n=# subjects with valid serology results for serogroup and time point):

- Serogroup A
  - MenQuadfi (n=2505): 94.7% [93.7. 95.5]
  - Menactra (n= 593): 88.5% [85.7, 91.0]
- Serogroup C
  - MenQuadfi (n=2506): 95.7% [94.8. 96.4]
  - Menactra (n= 593): 76.2% [72.6, 79.6]
- Serogroup Y
  - MenQuadfi (n=2507): 98.8% [98.3. 99.2]
  - Menactra (n= 593): 87.9% [85.0, 90.4]
- Serogroup W
  - MenQuadfi (n=2507): 96.2% [95.3. 96.9]
  - Menactra (n= 593): 87.0% [84.0, 89.6]

For each serogroup, a higher proportion of participants in the pooled MenQuadfi lots achieved a hSBA titer ≥1:8 compared to the Menactra participants, especially for serogroup C.

Reviewer Comment*: The proportion of participants with postvaccination hSBA titers ≥1:8 were higher in the MenQuadfi pooled lots for all serogroups (~95% to 99%) compared to the Menactra group (76% to 89%). These results support the results of the primary immunogenicity analyses.*

6.1.11.3 Subpopulation Analyses

Subpopulation Analyses by Age:
See Section 6.1.11.2 for subgroup analyses based on age.

Subpopulation Analyses by Sex
For MenQuadfi recipients, the hSBA immune responses observed in male and in female participants separately were similar to those observed overall in the primary analyses (data not shown). [19]

Subpopulation Analyses by Racial/Ethnic Group
No conclusions could be made due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

6.1.11.4 Dropouts and/or Discontinuations

Missing immunogenicity data was not imputed. No test or search for outliers were performed.

6.1.11.5 Exploratory and Post Hoc Analyses

No additional exploratory or post-hoc analyses were performed.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety datasets:

- Safety Analyses Set (SafAS): subjects who received at least 1 dose of the study vaccine and had safety data available. Data were analyzed according to the vaccine received. If the vaccine received by a subject did not correspond to any study group, the subject was excluded from the SafAS.
- In Study MET43, there were 6 subjects excluded from Site #22 due to GCP concerns.

Safety data surveillance:

- Solicited local injection site and systemic AEs for 7 days postvaccination
- Immediate AEs within 30 minutes postvaccination
- Unsolicited AE, including AEs leading to study withdrawal during the 30-day period postvaccination
- MAAEs and SAEs for 6 months postvaccination.

6.1.12.2 Overview of Adverse Events

Safety Overview:
The safety data will be presented for the 3 lots of MenQuadfi combined compared to the Menactra group. The following table provides an overview of the rates of adverse events in the

19 Reference: STN 125701.0, MET43 Clinical Study Report, Appendix 15 (Complementary Analyses), Table 2: Summary of GMTs by Sex-PPAS

MenQuadfi pooled lots compared to the Menactra group over the time period 6 months after vaccination.

Table 9: Study MET43-Safety Overview: Proportion of Subjects Reporting an Adverse Event Following Single Dose Vaccination, SafAS

AE Type: Monitoring Period*	MenQuadfi Pooled Lots (N=2619-2676) %	Menactra Group 4 (N=614-635) %
Immediate AE: 30 minutes	0.4%	0.5%
Solicited Local: 30 days	40.0%	39.4%
Solicited Systemic: 30 days	44.4%	45.7%
Unsolicited AE: 30 days	13.5%	13.5%
AEs leading to w/d: 30 days	0	0
MAAEs-1st: 1st 30 days*	5.1%	5.8%
MAAEs-2nd: Next 5 months**	12.9%	12.6%
SAEs: 6 months	1.0%	0.8%
Deaths: 6 months	0	0

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 6.1. SafAS: Safety Analyses Set. *Monitoring period: time interval that the relevant type of AE was monitored for postvaccination. %: #subjects who experienced the solicited event, N= #subjects in SafAS, AE: adverse event. AEs leading to w/d: adverse events leading to study withdrawal. MAAEs: Medically attended adverse events. *MAAEs-1st: collected for 1st 30 day postvaccination (Visit 1 to Visit 2). **MAAEs-2nd:collected from Visit 2 to the 6 month follow-up phone call (5 months total). SAEs: serious adverse events.

For any type of AE, the rates were similar between the MenQuadfi pooled groups and the Menactra group. For the MenQuadfi recipients, AE rates evaluated separately by age (adolescents 10 years to 17 years, adults 18 years to 55 years) or sex (male vs. female) were similar to corresponding AE rates in subjects overall (10 to 55 years of age). No conclusions could be made about racial/ethnic differences in AE rates due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

Solicited Adverse Reactions: 7 days Post-Vaccination
The following table includes the percentage of MenQuadfi and Menactra participants who reported any and grade 3 solicited reactions, including local injection site and systemic reactions within the 7 days following vaccination, based on the Safety Analyses Set.

Table 10: Study MET43- Percentage of Participants with Any & Grade 3 Solicited Reactions (Local and Systemic) 7 Days Postvaccination, SafAS

Solicited Adverse Reaction	MenQuadfi Pooled Lots (N=2676) %	Menactra (N=635) %
Local (Injection Site)	--	--
Pain:	--	--
Any	38.8%	38.3%
Grade 3*	1.8%	1.8%
Swelling	--	--
Any	4.2%	4.1%
Grade 3 (>100mm)	0.2 %	0.2%
Erythema:	--	--
Any	4.8%	4.1%
Grade 3 (>100mm)	0.3%	0.3%
Systemic	--	--
Myalgia:	--	--
Any	32.0%	31.2%
Grade 3*	2.9%	2.1%
Headache:	--	--
Any	27.9%	27.8%
Grade 3*	2.6%	2.3%
Malaise:	--	--
Any	21.4%	21.5%
Grade 3*	2.1%	2.3%
Fever:	--	--
Any ≥38.0C	1.1%	1.2%
Grade 3 ≥ 39.0C	0.2%	0.3%

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Tables 6.3 and 6.4. SafAS: Safety Analyses Set. x subjects: # subjects who experienced the solicited event. #n: #subjects with available data for relevant endpoint, N= #subjects in SafAS.
*Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

For both study groups, injection site pain was the most frequently reported local reaction (pooled MenQuadfi 38.8% vs. Menactra 38.3%). The percentage of participants reporting severe pain was low (1.8% for both study groups).

For both study groups, myalgia, headache, and malaise were the most commonly reported systemic reactions; for each of the three systemic adverse reactions, the rates were similar (~32%, 28%, and 21%, respectively) in the MenQuadfi and Menactra study groups. Severe myalgia, headache, and malaise were reported in <3% of subjects in each study group. Fever (≥38.0C) was reported by 1% of subjects in each study group.

> ***Reviewer Comment:*** *The rates of solicited adverse reactions after MenQuadfi vaccination were similar to the corresponding rates after Menactra vaccination. The rates of severe reactions were <3%, including any fever and grade 3 fever (T≥39.0C) in each study group.*

Immediate AEs within 30 minutes Postvaccination
Ten subjects in the MenQuadfi (pooled groups) and 3 subjects in the Menactra group reported an immediate AE within 30 minutes after vaccination. The majority of the reported events in the MenQuadfi groups were grade 1 (8 events) and included (by preferred term) the following events: dizziness, nausea, vomiting, nasal congestion, dizziness, dysgeusia, hypoaesthesia, and rash. All AEs resolved completely. The investigator considered nausea/vomiting in one subject, dizziness in 5 subjects (two Grade 2), dysgeusia in one subject, and rash in one subject, to be

related to MenQuadfi vaccination. The 3 subjects in the Menactra group experienced decreased appetite/nausea, fatigue, and dizziness/fatigue, respectively. All 3 participants recovered, though the dizziness and fatigue events were considered related to study vaccine Menactra.

Unsolicited AEs (Non-Serious): 30 days Postvaccination
The rates of unsolicited, non-serious AEs within 30 days postvaccination were similar in both study groups (MenQuadfi 13.3%, Menactra 13.4%). Unsolicited AE were most frequently classified in System Organ Class (SOC) Infections and Infestations (MenQuadfi 3.7%, Menactra 4.3%), of which upper respiratory tract infection was most common (MenQuadfi 0.6%, Menactra 0.8%). Most of the unsolicited non-serious AEs in the MenQuadfi and Menactra study group were Grade 1 or 2. Three percent of MenQuadfi recipients reported AEs that lasted ≥8 days, which was similar to the percentage of subjects in the Menactra group.

Medically Attended Adverse Events: through 6 months postvaccination
Medically attended adverse events were defined as a new onset condition that prompted the subjects or the parents to seek medical advice at a physician's office or Emergency Department. The proportion of participants who reported MAAEs within 30 days postvaccination were similar in both study groups (MenQuadfi 5.1%, Menactra 5.8%), and most frequently classified in the SOC Infections and Infestations; for both study groups, each of the following AEs in this SOC occurred in <0.3% of subjects: viral pharyngitis, upper respiratory tract infection, sinusitis, urinary tract infection, otitis externa, and pharyngitis streptococcal. There was one MenQuadfi recipient (Lot 2) that reported an injection site infection within the 30 days following vaccination that was considered by the investigator to be related to study vaccination, while all other MAAEs during this time period were not considered related to study vaccination. The proportion of participants who reported MAAEs between Visit 2 and Month 6 were similar across study groups.

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

During the time period between Day 0 through 6 months post-vaccination, 33 subjects reported a total of 39 nonfatal SAEs across both treatment groups, including 28 MenQuadfi recipients who reported 32 SAEs. Across the three MenQuadfi study groups, the percentages of subjects who experienced at least 1 SAE during the study were similar: Lot 1: 1% (9 subjects); Lot 2: 1.5% (13 subjects), and Lots 3: 0.7% (6 subjects).

During the 30-day postvaccination time period, a total of 5 subjects reported a SAE across both treatment groups, including 4 MenQuadfi recipients. None of these SAEs were considered related by the investigator to vaccination. Brief narratives for the 4 MenQuadfi participants who reported a SAE:

Subject #(b) (6) *: Unexplained Tingling in Left Arm & Leg*
37-year-old female (MenQuadfi lot 1) developed numbness/tingling in her left arm & leg and nausea 1 day after surgical removal of a left ovarian cyst (2 weeks postvaccination). Laboratory tests were within normal limits and symptoms improved without treatment.

Subject #(b) (6) *: Somatization Disorder*
11-year-old female (MenQuadfi Lot 2) was hospitalized for abdominal pain & muscle weakness 21 days following vaccination, recovered and went home 2 days later, then was hospitalized 12 days later due to symptoms of anxiety, rumination and other symptoms. During both hospitalizations, results from an extensive laboratory work-up were within normal limits. She was diagnosed with somatization disorder, and fully recovered without medical intervention

Subject #(b) (6) *: Worsening Depression*
34-year-old male (MenQuadfi Lot 2) with medical history of depression was hospitalized for suicidal ideation approximately 1 month after vaccination. He was treated with anti-depressive medications, and symptoms improved after a 4-day hospital stay.

Subject #(b) (6) *: Status Epilepticus*
24-year-old male (MenQuadfi Lot 2) with medical history of childhood seizures and drug/alcohol abuse was hospitalized 21 days postvaccination for a seizure precipitated by illegal drug use. Symptoms improved after treatment with anti-epileptic drugs, antihypertensive medications, and antibiotics. He was diagnosed with status epilepticus and discharged after an 8-day hospital stay.

During the time period from Day 30 through 6 months postvaccination, 28 MenQuadfi subjects reported 34 SAEs (Lot 1: 8 subjects-10 SAEs; Lot 2: 10 subjects-11 SAEs; Lot 3: 6 subjects-7 SAEs), and 4 Menactra subjects reported 6 SAEs. None of the SAEs were considered related to study vaccination. Four SAEs reported by 4 MenQuadfi recipients were ongoing at the time of study completion, including 3 SAEs that were diagnosed during study participation (Type 2 diabetes mellitus, multiple sclerosis, and coronary artery disease), and 1 SAE that was a pre-existing condition (lower back pain).

> ***Reviewer Comment:*** *This reviewer agrees with the study investigator's assessment that none of the SAEs were related to vaccination.*

6.1.12.5 Adverse Events of Special Interest [AESI]

Please see Section 8 for an overview of AESI across all studies.

6.1.12.6 Clinical Test Results

Not applicable

6.1.12.7 Dropouts and/or Discontinuations

Across study groups, a total of 3242 (96.9%) participants completed the study. There were no study discontinuations due to an AE. The subjects who prematurely withdrew from the study are listed below by group and by reason:

Table 11: Study MET43 Participant Disposition

Population	Lot 1(N=895) X (%)	Lot 2(N=883) X (%)	Lot 3(N=898) X (%)	Menactra(N=635) X (%)
Enrolled	902 (100%)	895 (100%)	906 (100%)	641 (100%)
Vaccinated	895 (100%)	886 (99%)	900 (99.3%)	636 (99.2%)
Completed Study	849 (97.5%)	886 (99.0%)	900 (99.3%)	636 (99.2%)
Withdrawal due to	--	--	--	--
Voluntary W/d	11 (1.2%)	13 (1.5%)	9 (1.0%)	8 (1.2%)
Lost to F/up	9 (1.0)	13 (1.5%)	9 (1.0%)	11 (1.7%)
Non-compliance	3 (0.3%)	7 (0.8%)	2 (0.2%)	5 (0.8%)
AE/SAE	0	0	0	0

Source: Adapted from STN 125701.0, MET43 Clinical Study Report, Table 4.1

6.1.13 Study Summary and Conclusions

Study MET43 was designed as a lot consistency, immunogenicity (inferred effectiveness) and safety study conducted in the US. Meningococcal vaccine-naïve adolescents 10 years through 17 years of age and adults 18 years through 55 years of age received 1 of 3 MenQuadfi lots or Menactra. The primary objectives, to demonstrate MenQuadfi lot consistency, and then immunological non-inferiority of MenQuadfi (pooled lots) to Menactra, were met. The safety profile of MenQuadfi was comparable to the safety profile of the US-licensed vaccine control group.

6.2 Trial #2 (Study MET35)

NCT03077438
Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to evaluate the immunogenicity and describe the safety of MenACYW conjugate vaccine compared to a licensed quadrivalent meningococcal conjugate vaccine in healthy children 2 to 9 years of age in the United States (US) and Puerto Rico[20]

Study Overview: Study MET35 was designed to demonstrate the immunogenicity and safety of MenQuadfi when compared to Menveo in children 2 years through 9 years of age administered as a single dose. The study was conducted between February 2017 to October 2017 and enrolled 1000 meningococcal vaccine-naïve individuals in the United States and Puerto Rico.

6.2.1 Objectives

The study objectives, endpoints and statistical success criteria, if applicable are described below.

Primary Immunogenicity:
To demonstrate the non-inferiority of the hSBA responses to meningococcal serogroups A, C, Y and W following the administration of a single dose of MenQuadfi vaccine compared to those observed following the administration of a single dose of Menveo in children ages 2 years through 9 years.

20 Study population included individuals between 2 years and 9 years of age, beginning on the day of the 2nd birthday and ending on the day before the 10th birthday.

- *Primary Endpoint:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA at 30 days (+14 days) after vaccination. *Seroresponse was defined as:*
  - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
  - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.*
- *Primary Hypothesis*: Thirty days after the administration of MenQuadfi or Menveo, the percentages of subjects who achieve an hSBA vaccine seroresponse for serogroups A, C, Y and Win Group 1 are non-inferior to the corresponding percentages in Group 2
    - *Criteria for Success*: If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions ($p_{\text{MenQuadfi}}$-p_{Menveo}) of subjects who achieved seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup.

Secondary Immunogenicity:

1. To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi vaccine to those observed following the administration of Menveo in children ages 2 through 9 years of age
   - *Secondary Endpoint #1*: GMTs measured by hSBA, for each serogroup
   - *Descriptive Analysis*

2. To evaluate the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi vaccine to those observed following administration of Menveo in children 2 through 5 years of age and in children 6 through 9 years of age, respectively.
   - *Secondary Endpoint #2*: GMTs as measured by hSBA, for each serogroup
   - *Descriptive Analysis*

3. To evaluate the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W in children 2 through 5 years of age and in children 6 through 9 years of age, respectively.
   - *Secondary Endpoint 3:* Seroresponse, as measured by hSBA in specific age cohorts for each serogroup
   - *Descriptive Analysis*

Observational Safety: Descriptive statistics without hypothesis testing
To describe the safety profile of MenQuadfi compared to Menveo after single vaccination.

- Safety Endpoints: Defined previously in Section 6.1.1

6.2.2 Design Overview

Study MET35 was a modified double-blind, randomized, parallel-group, active controlled multicenter study in the United States and Puerto Rico. The planned enrollment included 1000 healthy, meningococcal vaccine naïve individuals, stratified into two age cohorts (2 years to 5 years or 6 years to 9 years) and randomized 1:1 between MenQuadfi and Menveo as follows:

- Group 1: MenQuadfi (N=500)
  - Group 1a: 2 years through 5 years (250 subjects)
  - Group 1b: 6 years through 9 years (250 subjects)
- Group 2: Menveo (N=500)
  - Group 2a: 2 years through 5 years (250 subjects)
  - Group 2b: 6 years through 9 years (250 subjects)

6.2.3 Population

Inclusion (in summary):
Children were eligible to be enrolled if they met any of the following inclusion criteria: ages 2 through 9 year on the day of inclusion; signed the assent form, if applicable; parents/guardians had provided informed consent; would be able to attend all scheduled visits; and would comply with all trial procedures.

Children were not eligible to be enrolled if they met any of the following exclusion criteria: pregnant, lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination; participation in the 4 weeks preceding the trial vaccination or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure; receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to Visit 2 except for influenza vaccination, which may be received at least 2 weeks before or after the study investigational vaccines; previous vaccination against meningococcal disease with either the trial vaccine or another vaccine (i.e., mono- or polyvalent, polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W; or meningococcal B serogroup containing vaccine); receipt of immune globulins, blood or blood-derived products in the past 3 months; history of meningococcal infection, confirmed either clinically, serologically, or microbiologically; at high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects traveling to countries with high endemic or epidemic disease); known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances; verbal report of thrombocytopenia, contraindicating intramuscular vaccination by the Investigator's judgment; bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion contraindicating intramuscular vaccination in the Investigator's opinion; personal history of Guillain-Barré syndrome (GBS); personal history of an Arthus-like reaction after vaccination with a tetanus toxoid-containing vaccine; chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion; moderate or severe acute illness/infection (according to Investigator's judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F); a prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided; receipt of oral or injectable antibiotic therapy within 72 hours prior to the first blood draw; and identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study.

> ***Reviewer Comment:*** *The eligibility criteria for enrollment was considered acceptable at the time of the protocol review under IND 14171.*

6.2.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi (Sanofi Pasteur Inc): Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

- Batch # UD18366
- Dose: single 0.5 mL intramuscular
- Composition:
  - Serogroups A, C, Y, W: 10 ug each meningococcal capsular polysaccharide
  - Tetanus toxoid protein carrier: (b) (4) ug

- Preparation: single-dose 0.5 mL vial

Menveo® (Formerly- Novartis Vaccines and Diagnostics, Now GSK): Meningococcal Oligosaccharide (Serogroups A, C, Y, and W) CRM_{197} Conjugate Vaccine

- Batch # M16005
- Dose: single 0.5mL intramuscular
- Composition:
  - Serogroups A (10 ug), C (5 ug), Y (5 ug), and W (5 ug) oligosaccharides
  - CRM_{197} carrier protein: 32.7 to 64.1 ug
- Preparation: single-dose 0.5 mL vial

6.2.5 Directions for Use

See prior section.

6.2.6 Sites and Centers

36 study sites in the United States, including Puerto Rico

6.2.7 Surveillance/Monitoring

Study Oversight:
Study oversight was provided for all study sites by (b) (4) IRB. An internal Safety Management Team performed blinded safety analysis on safety data after vaccination.

Safety Monitoring

- Solicited AE data for 7 days postvaccination:
  - Solicited Reactions:
    - Local Injection Site: pain, redness, swelling
    - Systemic: fever[21], headache, malaise, myalgia
  - Graded intensity[22] as 1, 2, or 3
  - Recorded by the subject, or parent/guardian on a Diary Card. Data transcribed into the Case Report Form at Visit 2.
- Adverse Events of Special Interest (AESI):
  The following AESI were assessed during the study: Generalized seizures (febrile/non-febrile), Kawasaki Disease, Guillain Barre Syndrome (GBS), and Idiopathic Thrombocytopenic Purpura (ITP). These AESIs were reported as SAEs.
- Immediate AEs, Unsolicited AE data, MAAEs, SAEs:
  Previously described in Section 6.1.7 of this review memo.

Immunogenicity Monitoring: Serum bactericidal antibody (SBA) assays
Previously described in Section 6.1.7 of this review memo.

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21 Temperature measurements: once per day, preferably same time, optimal time in evening. Additional measurements at time of apparent fever. Observed daily temperature and the route of measurement were to be recorded in diary card provided. The highest temperature was to be recorded in the CRF. Preferred route of temperature measurement was axillary. Pre-vaccination temperature collected by investigator on source document. Tympanic thermometers were not permitted.
22 Grading for local -erythema & -swelling: Grade 1: ≥0mm to <25mm, Grade 2: ≥25 to <50mm; Grade 3: ≥50mm. Grading for local pain: Grade 1: Easily tolerated, Grade 2: Sufficiently discomforting to interfere with normal behavior or activities; Grade 3: Incapacitating, unable to perform usual activities. Grading for solicited systemic headache, malaise, myalgia: Grade 1: no interference with activity; Grade 2: some interference with activity; Grade 3: significant, prevents daily activity. Grading for Fever: Grade 1: ≥38.0C to ≤38.4; Grade 2: ≥38.5C to ≤38.9C; Grade 3: ≥39.0C.

6.2.8 Endpoints and Criteria for Study Success

Previously defined in Section 6.2.1

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations: Planned enrollment for 1000 subjects, assuming 20% drop-out rate, would result in ~800 evaluable subjects (400 evaluable subjects per treatment group) with 90% power to declare non-inferiority of hSBA antibody responses of MenQuadfi compared to Menveo.

Subgroup Analyses: The applicant conducted complementary analyses of select immunogenicity outcomes and safety analyses stratified by age group (2 years through 5 years, 6 years through 9 years); sex (male, female), and racial origin.

Statistical Methods: Previously described in Section 6.1.9

Protocol Amendments:

- Original Protocol: version 1.0, dated 11 July 2016
- Two Amended Protocols:
  - Protocol Amendment 1, version 2.0, dated 23 August 2017: revisions included
    - Puerto Rico was included in the protocol as a study location
  - Protocol Amendment 2, version 3.0, dated 23 February 2018
    - The analyses of (b) (4) immunogenicity data was done when all (b) (4) testing was completed. The (b) (4) immunogenicity data analyses were done separately from other analyses in order to prevent delay in available data, including hSBA data analyses and safety data analyses.

Significant Changes in the Conduct of the Study & Planned Analyses:

- There were no reported changes in the conduct or planned analyses

6.2.10 Study Population and Disposition

A total of 1000 subjects were enrolled: the first subject was enrolled on 17 February 2017 and the last subject visit occurred on 25 May 2017.

6.2.10.1 Populations Enrolled/Analyzed

Relevant analysis populations: (see Section 6.1.10 for study population definitions)

- *Safety Analyses Set (SafAS)*
- *Full Analyses Set (FAS)*
- *Per-Protocol Analyses Set (PPAS)*

Protocol Deviations:
Previously defined in Section 6.1.10

6.2.10.1.1 Demographics
The demographic characteristics of participants across study groups are provided in table below.

Table 12: Study MET35- Demographic Characteristics of MenQuadfi & Menveo, SafAS

Demographic Characteristic	MenQuadfi (N=498) X (%)	Menveo (N=494) X (%)
Sex Ratio M:F (%)	254:244 (51%:49%)	262:232 (53%:47%)
Age Group:	--	--
2 through 5 years:	250 subjects:	245 subjects:
Mean Age (SD)	4.0y (1.2)	• 3.9y (1.2)
Median Age	4.0y	• 3.9y
Age Range	2.0y, 6.0y	• 2.0y, 6.0y
6 through9 years:	248 subjects:	249 subjects:
Mean Age (SD)	7.9y (1.2)	• 8.1y (1.1)
Median Age	8.0y	• 8.1y
Age Range	6.0y, 10.0y	• 6.0y, 10.0y
Racial origin:	--	--
White	401 (80.5%)	411 (83.2%)
Black/A.A.	66 (13.3%)	60 (12.1%)
Mixed Origin	21 (4.2%)	21 (4.3%)
Asian	2 (0.4)	2 (0.4%)
N.Hawaiian/P.I	4 (0.8%)	0
Am.Indian/A.N	1 (0.2%)	0
Ethnicity:	--	--
Hispanic/Latino	114 (22.9%)	115 (23.3%)
Not H/L	383 (76.9%)	379 (76.7)

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Table 4.4. SafAS: Safety Analyses Set. For Sex; Racial Origin, and Ethnicity: X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects for the Safety Analyses Set (subjects who received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female. For Age Groups: y indicates years. Racial origin: Asian, Black/A.I: Black/African American; Am.Indian/A.N: American Indian/Alaska Native; N.Hawaiian/P.I.: Native Hawaiian/Pacific Islander; missing origin not listed (accounted for 3 subjects in Group 1 only. Ethnicity: Hispanic/Latina; Not H/L: Not Hispanic/Latino.

The demographic characteristics across groups were generally similar with 52% of male subjects and 48% subjects. Across groups, the median age in each of the two age cohorts (2 years through 5 years and 6 years through 9 years) were consistent across groups, 4.0 years in the younger age cohort and 8.0 years in the older age cohort. Most subjects across groups were of White racial origin (~82%), followed by Black/African American racial origin (12.7%) and Mixed racial origin (4.2%). The Asian, American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander groups had low enrollment across both groups. Most subjects were not of Hispanic/Latino ethnic origin, while 23.1% were of Hispanic/Latino origin.

Reviewer Comment: *The overall demographic characteristics across both study groups were similar.*

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.2.10.1.3 Subject Disposition

Table 13: Study MET35-Subject Dispositions & Data Analyses Sets for MenQuadfi & Menveo

Population	MenQuadfi (N=499) X (%)	Menveo (N=501) X (%)
Enrolled	499 (100%)	501 (100%)
Vaccinated	497 (99.6%)	495 (98.8%)
Completed Study	487 (97.6%)	487 (97.2%)
Follow-Up after Last Visit	483 (96.8%)	486 (97.0%)
Safety Analysis Set	498 (100%)	494 (100%)
Full Analysis Set	480 (96.2%)	482 (96.2%)
Per Protocol	458 (91.8%)	460 (91.8%)
≥1 Prot. Deviation	41 (8.2%)	41 (8.2%)

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Table 4.1, 4.2, and 4.3. X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects enrolled. ≥1 Prot. Deviation: subjects with one or more protocol deviations.

The list of pre-specified protocol deviations was provided in Section 6.1.10.1 of this review memo. Across all study groups there were 82 subjects (8.2%) who experienced at least 1 protocol deviation, of which the most common deviation was that the post-dose blood sample at Visit 2 was not provided or was not in the proper time window (30 days to 44 days post-vaccination), observed in 6.2% of MenQuadfi subjects and 5.0% of Menveo subjects. All other reported protocol deviations occurred in <1% of subjects across both groups.

> ***Reviewer Comment*:** *The distribution of protocol deviations was generally low and similar across groups. The observed protocol deviations did not raise concerns about the interpretability of the study results.*

6.2.11 Efficacy Analyses

Clinical endpoint vaccine efficacy was not evaluated in this trial.

6.2.11.1 Analyses of Primary Endpoint(s)

Primary Analyses: hSBA Seroresponse Rates

The primary immunogenicity analyses evaluated the hSBA serogroup-specific seroresponse rates[23] at Day 30 for the MenQuadfi group compared to the Menveo group in all subjects 2 years through 9 years of age. Non-inferiority of the immune response was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroresponse rates >-10% for each serogroup. The following table provides the hSBA seroresponse rates [95% CI] at Day 30 for the MenQuadfi group compared the Menveo group for the Per Protocol Analyses Set, as well as the differences in seroresponse rates [95%CI]. The table also includes the hSBA GMTs and the GMT ratio (GMTR) across groups (MenQuadfi/Menveo) with the 95% CI.

23 hSBA seroresponse definition: pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

Table 14: Study MET35 Primary/Secondary Objectives – hSBA Seroresponse Rates & hSBA GMTs, All Subjects, MenQuadfi vs Menveo, PPAS

Serogroup	MenQuadfi (N=455-458) %Seroresponse [95% CI] GMTs [95% CI]	Menveo (N=458-459) %Seroresponse [95%CI] GMTs [95% CI]	% Difference [95% CI] GMTR [95% CI]
A	55.4% [50.7, 60.0] 24.8 [21.9, 27.9]	47.8% [43.2, 52.5] 22.6 [19.7, 26.0]	7.6% [**1.1**, 14.0] 1.09 [0.91, 1.32]
C	95.2% [92.8, 97.0] 238 [209, 270]	47.8% [43.2, 52.5] 17.0 [14.3, 20.2]	47.4% [**42.2**, 52.2] 14.0 [11.3, 17.3]
Y	91.5% [88.5, 93.9] 68.8 [61.3, 77.3]	79.3% [75.3, 82.9] 43.5 [37.7, 50.4]	12.2% **[7.7,** 16.7] 1.58 [1.31, 1.9]
W	78.8% [74.8, 82.5] 37.5 [33.7, 41.8]	64.1% [59.5, 68.4] 26.2 [23.0, 29.9]	14.8% [**8.9**, 20.5] 1.43 [1.2, 1.69]

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Tables 5.1 & 5.2. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menveo). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers, GMTR: GMT ratio (MenQuadfi/Menveo).

Non-inferiority criteria were met for all serogroups.

Reviewer Comment:

1. *Notably, the seroresponse rates against serogroup C in MenQuadfi recipients (95.2%) were higher than in the Menveo recipients (47.8%).*
2. *Across groups, the GMTs corresponded accordingly with the observed hSBA seroresponse rates. The GMT ratios (MenQuadfi/Menveo) was highest against serogroup C, with (14.0).*
3. *The serogroup-specific hSBA seroresponse rates and GMTs observed in children 2 years through 9 years of age followed similar trends as those observed in adolescent/adult subjects (10 years through 55 years) in Study MET43. The seroresponse rate differences across study groups in children 2 years through 9 years (as noted above) were higher than the rate differences across study groups observed in adolescents/adults (Section 6.1.11.1).*

6.2.11.2 Analyses of Secondary Endpoints

Secondary Analyses: hSBA Seroresponse Rates & hSBA GMTs and by Age

The hSBA serogroup specific seroresponse rates and GMTs at Day 30 were evaluated descriptively without hypothesis testing in participants 2 years through 5 years and participants 6 years through 9 years as two separate analyses. The results are provided in the table below.

Table 15: Study MET35 Secondary Objectives - hSBA Seroresponse Rates & hSBA GMTs by Age, MenQuadfi vs Menveo, PPAS

Serogroup	MenQuadfi (N=227-229 per age cohort) %Seroresponse [95% CI] GMTs [95% CI]	Menveo (N=221-237 per age cohort) %Seroresponse [95%CI] GMTs [95% CI]	% Difference [95% CI] GMTR [95% CI]
Age: 2y - 5y	--	--	--
A	52.4% [45.7, 59.1] 21.6 [18.2, 25.5]	44.8% [38.1, 51.6] 18.9 [15.5, 23.0]	7.6% [-1.6, 16.7] 1.14 [0.883, 1.47]
C	94.3% [90.5, 96.9] 208 [175, 246]	43.2% [36.3, 50.0] 11.9 [9.79, 14.6]	51.1% [43.5, 57.8] 17.4 [13.4, 22.6]
Y	88.2% [83.3, 92.1] 49.8 [43.0, 57.6]	77.0% [70.9, 82.4] 36.1 [29.2, 44.7]	11.2% [4.2, 18.1] 1.38 [1.07, 1.78]
W	73.8% [67.6, 79.4] 28.8 [24.6, 33.7]	61.3% [54.5, 67.7] 20.1 [16.7, 24.2]	12.5% [3.9, 20.9] 1.43 [1.12, 1.83]
Age: 6y - 9y	--	--	--
A	58.3% [51.6, 64.8] 28.4 [23.9, 33.8]	50.6% [44.1, 57.2] 26.8 [22.0, 32.6]	7.7% [-1.1, 16.6] 1.06 [0.816, 1.38]
C	96.1% [92.7, 98.2] 272 [224, 330]	52.1% [45.5, 58.6] 23.7 [18.2, 31.0]	44.0% [36.8, 50.6] 11.5 [8.24, 16.0]
Y	94.8% [91.0, 97.3] 95.1 [80.2, 113]	81.4% [75.9, 86.2] 51.8 [42.5, 63.2]	13.3% [7.6, 19.2] 1.84 [1.41, 2.38]
W	83.8% [78.4, 88.4] 48.9 [42.5, 56.3]	66.7% [60.3, 72.6] 33.6 [28.2, 40.1]	17.2% [9.4, 24.7] 1.45 [1.16, 1.82]

Source: Adapted from STN 125701.0, MET35 Clinical Study Report Tables 5.4 & 5.3. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menveo). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers, GMTR: GMT ratio (MenQuadfi/Menveo).

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When evaluated separately, the hSBA seroresponse rates and hSBA GMTs in children 2 through 5 years and children 6 through 9 years were similar to the overall results in all subjects and followed similar trends. The hSBA GMT ratios were similar across groups as well for each of the two age cohorts when compared to the overall study GMT ratios.

Clinical Reviewer Comment:

In the current Menveo USPI (Table 7),[24] the following seroresponse rates and GMTs were observed by serogroup:

- *Children 2 through 5 years:*
  - *A: 72% [68, 75], GMT 26 [22, 30]*
  - *C: 60% [56, 64], GMT 18 [15, 20]*
  - *Y: 66% [62, 70], GMT 24 [20, 28]*
  - *W: 72 [68, 75], GMT 43 [38, 50]*
- *Children 6 through 9 years:*
  - *A: 77% [73, 80]], GMT 35 [29, 42]*
  - *C: 63% [59, 67], GMT 36 [29,45]*
  - *Y: 58% [54, 62], GMT 34 [28, 41]*
  - *W: 57 [53,61], GMT 61 [52, 72]*

The seroresponse rates in the Menveo USPI incorporate a 4-fold rise in its definition, and study sites were in US and Canada. MET35 seroresponse definition also incorporated a 4-

24 Reference: Menveo USPI: https://www.fda.gov/media/78514/download (accessed 4/17/2020).

fold rise in its seroresponse definition, and the study was conducted in the US, including Puerto Rico. The seroresponse rates and GMTs for Menveo that are cited in the USPI are greater than those observed in Study MET35 for serogroups A and C in both age cohorts. The observed responses in Study MET35 may differ from those cited in the Menveo USPI due to differences across assays (both validated) and/or baseline characteristics of the evaluated populations.

6.2.11.3 Subpopulation Analyses

Subpopulation Analyses by Age:
The secondary analyses provided the hSBA seroresponse rates and hSBA GMTs in two age cohorts: 2 years through 5 years and 6 years through 9 years. These results were included in the prior section of this review memo.

Subpopulation Analyses by Sex
The hSBA immune responses evaluated separately in male and female subjects were similar to those observed in the primary analyses.

Subpopulation Analyses by Racial/Ethnic Group
No conclusions could be made due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

6.2.11.4 Dropouts and/or Discontinuations

Missing immunogenicity data were not imputed. No test or search for outliers was performed.

6.2.11.5 Exploratory and Post Hoc Analyses

No additional exploratory or post-hoc analyses wereprovided.

6.2.12 Safety Analyses

6.2.12.1 Methods

Safety Analyses Set (SafAS) and the duration of adverse event safety monitoring were previously defined in this memo (Section 6.1.12.1). For this study, the applicant also evaluated adverse events of special interest (AESI), which were considered events for which ongoing monitoring and rapid communication by the investigator to the applicant were conducted. The following AESIs were assessed during the study: Generalized seizures (febrile/non-febrile), Kawasaki Disease, Guillain Barre Syndrome (GBS), and Idiopathic Thrombocytopenic Purpura (ITP). These AESIs were reported as SAEs.

6.2.12.2 Overview of Adverse Events

Observational Safety Objective: Descriptive statistics without hypothesis testing
To describe the safety profile of MenQuadfi compared to Menveo after single vaccination.

Safety Overview:
The following table provides an overview of the rates of adverse events in the MenQuadfi group compared to the Menveo group over the time period 6-month after vaccination.

Table 16: Study MET35-Safety Overview: Proportion of Subjects Reporting an Adverse Event Following Single Dose Vaccination, SafAS

AE Type: Monitoring Period*	MenQuadfi (N=498) % (x subjects/n)	Menveo (N=494) % (x subjects/n)
Immediate AE: 30 minutes	0 (0/498)	0 (0/494)
Solicited Local: 30 days	46.8% (228/487)	53.9% (262/486)
Solicited Systemic: 30 days	34.5% (168/487)	37.0% (180/486)
Unsolicited AE: 30 days	24.3% (121/498)	29.4% (145/494)
AEs leading to w/d: 30 days	0 (0/498)	0 (0/494)
MAAEs-1st: 1st 30 days*	13.1% (65/498)	15.4% (76/494)
MAAEs-2nd: Next 5 months**	31.1% (155/498)	27.5% (136/494)
SAEs: 6 months	1.4% (7/498)	0.6% (3/494)
Deaths: 6 months	0	0

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Table 6.1. SafAS: Safety Analyses Set. Monitoring Period*: time interval that the relevant type of AE was monitored for postvaccination. x subjects: #subjects who experienced the solicited event; n: #subjects with available data for relevant endpoint, N= #subjects in SafAS, AE: adverse event. AEs leading to w/d: adverse events leading to study withdrawal. MAAEs: Medically attended adverse events. *MAAEs-1st: collected for 1st 30 day postvaccination (Visit 1 to Visit 2). **MAAEs-2nd: collected from Visit 2 to the 6 month follow-up phone call (5 months total). SAEs: serious adverse events.

For any type of AE, the rates were similar between the MenQuadfi group and the Menveo group. When evaluated separately by age (2 years through 5 years, 6 years through 9 years), the rates of solicited and unsolicited AEs were similar across study groups. No conclusions could be made about racial/ethnic differences in AE rates due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

Solicited Adverse Events: 7 days Post-Vaccinations
The following table provides the proportion of subjects across groups who experienced a solicited reaction of any severity and Grade 3 severity.

Table 17: Study MET35- Proportion of Participants with Any & Grade 3 Solicited Reactions (Local Injection Site and Systemic) 7 Days Postvaccination, SafAS

Solicited Adverse Reaction	MenQuadfi (N=484-487) %	Menveo (N=494) %
Local (Injection Site)	--	--
Pain:	--	--
Any	38.6%	42.4%
Grade 3*	0.6%	1.0%
Swelling	--	--
Any	13.8%	21.5%
Grade 3 (>100mm)	1.4%	5.6%
Erythema:	--	--
Any	22.6%	31.5%
Grade 3 (>100mm)	3.1%	9.9
Systemic	--	--
Myalgia:	--	--
Any	20.1%	23.0%
Grade 3*	0.4%	0.8%
Headache:	--	--
Any	12.5%	11.5%
Grade 3*	0	0.4%
Malaise:	--	--
Any	21.1%	20.4%
Grade 3*	1.8%	1.0%
Fever:	--	--
Any ≥38.0C	1.9%	2.7%
Grade 3 ≥ 39.0C	0%	0.4%

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Tables 6.3 and 6.4. SafAS: Safety Analyses Set. x subjects: # subjects who experienced the solicited event. #n: #subjects with available data for relevant endpoint, N= #subjects in SafAS. *Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

For both study groups, injection site pain was the most frequently reported local reaction (MenQuadfi 38.6% and Menveo 42.4%). The number of participants reporting severe pain was low, 3 in the MenQuadfi group and 5 in the Menveo group. The rates across groups of 'any' and 'severe' injection site swelling and injection site erythema were higher in the Menveo group than the MenQuadfi group with 95% CI that did not overlap.[25]

For both study groups, myalgia and malaise were the most frequently reported solicited systemic events (myalgia: MenQuadfi 20.1% and Menveo 23.0%; malaise: 21% both groups). Severe solicited reactions were rare. The rates of fever were low in both groups, 1.9% & 2.7% for MenQuadfi recipients and Menveo recipients, respectively. There were no participants who reported severe fever in the MenQuadfi group, compared to 2 in the Menveo group.

> ***Reviewer Comment:*** *The rates of any/severe injection site erythema and swelling are higher in the Menveo group than the MenQuadfi group with 95% CI that do not overlap.*

25 The rates of injection site swelling were 21.5% [17.9, 25.5] in Menveo recipients and 13.8% [10.9, 17.2] in MenQuadfi recipients. The rates of local injection site erythema were 31.5% [27.4, 35.9] in Menveo recipients compared to 22.6% [18.9, 26.6] in MenQuadfi recipients. The rates of severe swelling and severe erythema were higher in Menveo recipients (5.6% & 9.9%, respectively) compared to the rates observed in MenQuadfi recipients (1.4% & 3.1%, respectively) with 95% CI that also did not overlap.

Immediate AEs within 30 minutes Postvaccination
There were no subjects in either group who reported an immediate unsolicited AE within 30 minutes of vaccination.

Unsolicited AEs Non-Serious AEs: 30 days Postvaccination
The rates of unsolicited AEs non-serious AEs within 30 days postvaccination were similar across groups (MenQuadfi 24.3%, Menveo 29.4%). The rates of grade 3 unsolicited AEs were also comparable across groups (MenQuadfi 3.8%, Menveo 2.8%). The unsolicited AEs were most frequently reported under the SOC Infections and Infestations (MenQuadfi 10.8%, Menveo 11.5%). Across groups, the most frequently reported AE by preferred term were cough, upper respiratory infection (URI), and pharyngitis/pharyngitis streptococcal. Most AEs were reported as either Grade 1 or 2 in intensity.

There were 19 MenQuadfi subjects (3.8% of MenQuadfi recipients) who experienced 22 Grade 3 AEs; and 14 Menveo subjects (2.8% of Menveo recipients) who experienced 17 Grade 3 AEs. The most frequently reported Grade 3 unsolicited AEs were pharyngitis, vomiting, and pyrexia. Unsolicited AEs that lasted ≥8 days were observed in 7.4% of MenQuadfi recipients compared to 9.1% of Menveo recipients.

> ***Reviewer Comment:*** *As previously cited in a prior reviewer comment, the rates of unsolicited AEs in this study were higher than those observed in adolescents/adults 10 years through 55 year of age (Study MET43), likely due to higher rates of URIs/cough in children compared to older age cohorts.*

Medically Attended Adverse Events: 30 Day Postvaccination & to 6-month Contact
MAAEs were previously defined in this review (Section 6.1.12.2). The proportion of participants who reported MAAEs within 30 days postvaccination were similar across groups (MenQuadfi 13.1%, Menveo 15.4%). Across groups, most of these events were graded Grade 1 or 2 in intensity, occurred ≥15 days following vaccination, and lasted for either 4-7 days or ≥8 days. Within 30 days of vaccination, there were 105 MAAEs in the MenQuadfi group, of which 1 was considered related to vaccination – generalized rash. In the same time there were 114 MAAEs in the Menveo group, of which 2 were considered related to vaccination- injection site urticaria and injection site warmth. During the time between Visit 2 and the 6-month follow-up contact, the rates of MAAEs were similar across groups (MenQuadfi 31.1%, Menveo 27.5%), and none of the MAAES were considered by the investigator to be related to vaccination.

6.2.12.3 Deaths

There were no deaths reported during the study.

6.2.12.4 Nonfatal Serious Adverse Events

There were 8 SAEs in the MenQuadfi group (7 participants) and 4 SAEs in the Menveo group (3 participants) during the study, most of which were events commonly observed in the general population in this age group, such as asthma and hypertrophy of the tonsils & adenoids. None of the reported SAEs were considered by the investigator to be related to study vaccination. There were 2 SAEs reported in MenQuadfi recipients within 30 days of vaccinations and included the following case narratives:

Subject #(b) (6) (MenQuadfi): Tethered Cord
Due to a family history of tethered cord, 3-year-old asymptomatic male had a scheduled magnetic resonance imaging study 3 days postvaccination. The findings demonstrated tethered cord necessitating surgical repair. The SAE was not considered by the study investigator as related to study vaccine.

Subject #(b) (6) (MenQuadfi): Asthma Exacerbation
4-year-old female with past medical history significant for asthma developed wheezing 16 days postvaccination. The subject was admitted to the hospital for management and improved. The SAE was not considered by the study investigator as related to study vaccine.

There was one Menveo recipient who experienced asthma exacerbation 26-hour postvaccination that was not considered by the study investigator as related to study vaccine.

Reviewer Comment: *This reviewer agrees with the study investigator's assessment that none of the SAEs were related to vaccination.*

6.2.12.5 Adverse Events of Special Interest (AESI)

The applicant pre-specified the following AESI as part of their safety assessments during the study: Generalized seizures (febrile/non-febrile), Kawasaki Disease, GBS, and ITP. There was one AESI reported during the study in the Menveo study group: Subject #(b) (6) experienced epilepsy event 43 days postvaccination that was considered not related to study vaccine. There were no AESI reported in the MenQuadfi group.

6.2.12.6 Clinical Test Results

Not applicable.

6.2.12.7 Dropouts and/or Discontinuations

Across study groups, there were a total of 974 subjects (97.4%) who completed the study. There were no reports of study discontinuations due to SAEs or other AEs. The subjects who prematurely withdrew from the study are listed below by group and by reason:

Table 18: MET35-Participant Disposition

Population	**MenQuadfi (N=498) X (%)**	**Menveo (N=494) X (%)**
Enrolled	499 (100%)	501 (100%)
Vaccinated	497 (99.6%)	495 (98.8%)
Completed Study	487 (97.6%)	487 (97.2%)
Withdrawal due to	--	--
Voluntary W/d	3 (0.6%)	6 (1.2%)
Lost to F/up	6 (1.2)	3 (0.6%)
Non-compliance	3 (0.6%)	6 (1.2%)
AE/SAE	0	0

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Table 4.1

Reviewer Comment: *There were no reports of study discontinuations due to adverse events. Most premature withdrawals were due to either lost-to-follow-up or voluntary withdrawal, which occurred at low rates in each group.*

6.2.13 Study Summary and Conclusions

Study MET35 was designed to demonstrate the immunogenicity and safety of MenQuadfi when compared to Menveo, a licensed meningococcal A, C, Y, W conjugate vaccine in children. The primary objective, to demonstrate immunological non-inferiority of MenQuadfi to Menveo in children 2 years through 9 years of age as a single dose was met. The safety and immunogenicity data from this study support the use of MenQuadfi in this age cohort.

6.3 Trial #3 (Study MET49)

NCT#02842866
Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenACYW conjugate vaccine to Menomune® – A/C/Y/W-135 in adults ≥ 56 years of age in the United States and Puerto Rico.

Study Overview: Study MET49 was designed to evaluate the immunogenicity and safety of a single dose of MenQuadfi when compared to a single dose of Menomune® – A/C/Y/W-135 in adults 56 years of age and older. The study was conducted between July 2016 and February 2017 and enrolled 907 meningococcal vaccine-naïve individuals in the US and Puerto Rico.

6.3.1 Objectives

Primary Immunogenicity:
To demonstrate the non-inferiority of the vaccine seroresponses of meningococcal serogroups A, C, Y and W following the administration of a single dose of MenQuadfi vaccine compared to those observed following the administration of a single dose of Menomune vaccine.

- *Primary Endpoint:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination.
  Seroresponse was defined as:
  - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
  - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.*

- *Primary Hypothesis:* 30 days after the administration of MenQuadfi or Menomune, the percentages of subjects who achieve hSBA seroresponse for serogroups A,C,Y, and W in Group 1 are non-inferior to the corresponding percentages in Group 2.
  - *Criteria for Success:* If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions ($p_{\text{MenQuadfi}}$-p_{Menomune}) who achieved seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup

Clinical Reviewer Comment*:*
Menomune is the only meningococcal quadrivalent (A, C Y, W) vaccine licensed for use in adults 55 years of age and older in the US. Menomune is a polysaccharide vaccine that is not conjugated to a carrier protein.

Secondary Immunogenicity:
To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi vaccine to those observed following

the administration of Menomune.

- *Secondary Endpoint 1:* GMTs as measured by hSBA, for each serogroup
- *Descriptive analyses*

Observational Immunogenicity:
To describe the antibody titers against meningococcal serogroups A, C, W, Y measured by hSBA assessed at Day 0 and Day 30 after vaccination with either MenQuadfi or Menomune.

- *Observational Endpoint 1:* Antibody titers against vaccine serogroups measured by hSBA before and 30 days (+14 days) after vaccination with MenQuadfi or Menomune
- *Descriptive analyses*

Observational Safety: Descriptive analyses
To describe the safety profile of MenQuadfi compared to Menomune after single vaccination.

- *Safety Endpoints:* Defined previously in Section 6.1.1

6.3.2 Design Overview

Study MET49 was a Phase 3 randomized, parallel-group, active-controlled multicenter study in the United States and Puerto Rico. The study design was modified double-blind, which included an unblinded vaccine administrator as MenQuadfi was administered by intramuscular route and Menomune by subcutaneous route. The remaining study staff, including those collecting safety data, the investigator, and the subject remained blinded throughout the trial. The planned enrollment included 900 healthy, meningococcal vaccine-naïve individuals stratified into two age cohorts (≥56 years through 64 years or ≥65 years) and randomized 1:1 between MenQuadfi and Menomune. The older age cohort was further stratified into two age cohorts: 65 through 74 years or ≥75 years, with at least 25% in the oldest cohort.
Planned Enrollment:

- Group 1: MenQuadfi (N=450)
  - Subjects 56 through 64 years: 200 subjects
  - Subjects ≥65 years: 250 subjects
    - 65 through 74 years: 70-180 subjects
    - ≥75 years: 70-180 subjects
- Group 2: Menomune (N=450)
  - Subjects 56 through 64 years: 200 subjects
  - Subjects ≥65 years: 250 subjects
    - 65 through 74 years: 70-180 subjects
    - ≥75 years: 70-180 subjects

6.3.3 Population

Inclusion (in summary):
Individuals were eligible to be enrolled if they met any of the following inclusion criteria: ≥56years old on day of enrollment, had provided informed consent, and would be able to attend all scheduled visits and comply with all trial procedures.

Exclusion (in summary):
Individuals were not eligible to enrolled if they met any of the following exclusion criteria: pregnant, lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination; participation in the 4 weeks preceding the trial vaccination or planned participation

during the present trial in another clinical trial investigating a vaccine, drug, medical device or medical procedure; receipt of any vaccine in the 28 days preceding the study or planned receipt of any vaccine before Day 30 except for influenza vaccination-which may be received 2 weeks before or after study investigational vaccination, this exception include monovalent pandemic influenza vaccines and multivalent influenza vaccines; previous vaccinations against meningococcal disease with either the trial vaccine or another meningococcal vaccine contained serogroups A,C,W, or Y or a meningococcal B vaccine; receipt of immune globulins, blood or blood derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency , or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months); history of meningococcal infection, confirmed either clinically, serologically or microbiologically; at high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease; known systemic hypersensitivity to any vaccine components, or history of a life threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances; history of GBS; personal history of Arthus-like reaction after vaccination with a tetanus toxoid containing vaccine within at least 10 years of the proposed study vaccination; verbal report of thrombocytopenia, contraindicating IM vaccination in the PI's opinion; bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion contraindicating IM vaccination in the PI's opinion; deprived of freedom by an administrative or court order, or in an emergency setting or hospitalized involuntarily, current alcohol abuse or drug addiction, chronic illness that in the opinion of the PI is at a stage where is might interfere with trial conduct or completion, moderate or severe acute illness/infection (according to the PI judgment) on the day of vaccination or febrile illness (temp≥100.4F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided; receipt of oral or injectable antibiotic therapy within 72 hours prior to the 1st blood draw, identified as a PI or employee of the PI or study center with direct involvement in the proposed study, or identified as an immediate family member (parent/spouse, natural or adopted child) of the PI or the employee with direct involvement in the proposed study.

> ***Reviewer Comment:*** *The eligibility criteria for enrollment were considered acceptable at the time of the protocol review under IND 14171.*

6.3.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi (Sanofi Pasteur Inc): Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

- Batch # UD18367
- Dose: single 0.5 mL intramuscular injection
- Composition:
  - Serogroups A, C, Y, W: 10 ug each meningococcal capsular polysaccharide
  - Tetanus toxoid protein carrier: (b) (4) ug
- Preparation: single-dose 0.5 ml vial

Menomune® (Sanofi Pasteur Inc): Meningococcal Polysaccharide Vaccine, Groups A, C, Y, and W Combined Vaccine

- Batch # UI041AA
- Dose: single 0.5 mL subcutaneous injection
- Composition:

- Serogroups A, C, Y, and W: 50 ug of each polysaccharide
- Preparation: Lyophilized single-dose vial with 0.6 mL vial of diluent (sterile, pyrogen free distilled water without preservatives)

6.3.5 Directions for Use

See prior section.

6.3.6 Sites and Centers

35 study sites in the United States, including Puerto Rico

6.3.7 Surveillance/Monitoring

Study Oversight:
Study oversight was provided for all study sites by (b) (4) IRB. An internal Safety Management Team performed blinded safety analysis on safety data after vaccination.

Safety Monitoring:
Previously described in Section 6.1.7

Immunogenicity Monitoring: Serum bactericidal antibody (SBA) assays
Previously described in Section 6.1.7

6.3.8 Endpoints and Criteria for Study Success

See Section 6.3.1

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations: Planned enrollment for 900 subjects, assuming 15% drop-out rate, would result in ~765 subjects (382 evaluable subjects per treatment group) with 90% power to declare non-inferiority of MenQuadfi to Menomune for all serogroups.

Subgroup Analyses:
The applicant conducted complementary analyses of select immunogenicity and safety analyses stratified by age group (56 through 64 years; ≥65 years; 65 through 74 years; ≥75 years); sex (male, female), and racial origin.

Statistical Methods:
See Section 6.1.9

Protocol Amendments:
- Original Protocol: version 2.0, dated 22 December 2015
- One Amended Protocol:
  - Protocol Amendment, version 3.0, dated 20 May 2016: revisions included
    - Stratification of older age groups: subjects 65 years of age and older were further stratified into 2 sub-group as 65 through74 years of age and ≥75 years of age, with at least 25% of the 250 subjects enrolled in each of these age groups
    - hSBA vaccine seroresponse definition for serogroups A, C, Y and W modified as per FDA recommendations.
    - Estimated sample size calculations were updated.

Significant Changes in the Conduct of the Study & Planned Analyses:

- There were no reported changes in the conduct or planned analyses.

6.3.10 Study Population and Disposition

A total of 907 subjects were enrolled: the first subject was enrolled on 15 July 2016 and the last subject visit occurred on 13 February 2017.

6.3.10.1 Populations Enrolled/Analyzed

Relevant analysis populations: (see Section 6.1.10 for study population definitions)

- *Safety Analyses Set (SafAS)*
- *Full Analyses Set (FAS)*
- *Per-Protocol Analyses Set (PPAS)*

Protocol Deviations:
Previously defined in Section 6.1.10

6.3.10.1.1 Demographics
The demographic characteristics across study groups are provided in the table below.

Table 19: Study MET49- Demographic Characteristics of MenQuadfi & Menomune, All Randomized

Demographic Characteristic	MenQuadfi (N=448) X (%)	Menomune (N=453) X (%)
Sex Ratio M:F (%)	192:259 (43%:57%)	194:261 (43%:57%)
Age Group:	--	--
56 years through 64 years:	202 subjects:	200 subjects:
Mean Age (SD)	60.4y (2.7)	60.4y (2.5)
Median Age	60.1y	60.2y
Age Range	56.0y, 64.9y	56.0y, 65.0y
≥65 years:	249 subjects:	255subjects:
Mean Age (SD)	72.2y (5.77)	72.7y (5.47)
Median Age	70.8y	71.8y
Age Range	65.1y, 89.8y	65.0y, 97.2y
Racial origin:	--	--
White	389 (86.3%)	404 (88.8%)
Black/A.A.	54 (12.0%)	47 (10.3%)
Mixed Origin	0	0
Asian	5 (1.1)	1 (0.2%)
N.Hawaiian/P.I	0	1 (0.2%)
Am.Indian/A.N	2 (0.4%)	2 (0.4%)
Ethnicity:	--	--
Hispanic/Latino	35 (7.8%)	32 (7.0%)
Not H/L	415 (92.0%)	421 (92.5)

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Table 4.3. SafAS: Safety Analyses Set. For Sex; Racial Origin, and Ethnicity: X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects for the Safety Analyses Set (subjects who received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female. For Age Groups: y

indicates years. Racial origin: Asian, Black/A.I: Black/African American; Am.Indian/A.N: American Indian/Alaska Native; N.Hawaiian/P.I.: Native Hawaiian/Pacific Islander; missing origin not listed (accounted for 1 subject in Group 1 only). Ethnicity: Hispanic/Latina; Not H/L: Not Hispanic/Latino.

The demographic characteristics across groups were generally similar with 43% of male subjects and 57% female subjects. Across groups, the median age in each of the two age cohorts (56 through 64 years, ≥65 years) were consistent across study groups, 60.1 years in the younger age cohort and 71.2 years in the older age cohort. Most subjects across groups were of White racial origin (~88%), followed by Black/African American racial origin (11%). All other racial groups had very low or no enrollment in the study. Most subjects were not of Hispanic/Latino ethnic origin, while 7.8% were of Hispanic/Latino origin.

Reviewer Comment: *The overall demographic characteristics across both study groups were similar.*

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The study design included enrollment of 200 subjects/group who were 56 through 64 years of age; and 250 subjects/group who were ≥65 years of age. Subjects in the latter age cohort were further stratified into two cohorts, with at least ~63 subjects (25% of 250) who were 65 through74 years of age and ~63 subjects who were ≥75 years of age. The following table provides the age stratification of enrolled subjects included in the Per Protocol Analyses Set (PPAS), used for primary analyses. As noted in the table, the number of subjects in the ≥75 years of age cohort across groups included 69 subjects and 67 subjects enrolled in the MenQuadfi and Menomune groups, respectively.

Table 20: Study MET49- Number of Subjects per Age Strata for MenQuadfi (Group 1) & Menomune (Group 2), PPAS

Age (in years)	MenQuadfi (N=433)	Menomune (N=431)
56 through 64 years	N=192	N=189
≥ 65 years	N=241	N=242
65 through 74 years	N=172	N=175
≥ 75 years	N=69	N=67

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Appendix 15, Tables 1 and 4. PPAS: Per Protocol Analyses Set. N: # subjects in PPAS.

Reviewer Comment: *The number of subjects enrolled in the ≥ 75 years age cohort per group was adequate to allow for a meaningful evaluation of safety and immunogenicity in this age cohort. The upper age range for the MenQuadfi group was 89.8 years and 97.2 years for the Menomune group.*

6.3.10.1.3 Subject Disposition

Table 21: Study MET49- Subject Dispositions & Data Analyses Sets for MenQuadfi (Group 1) & Menomune (Group 2)

Population	MenQuadfi (N=451) X (%)	Menomune (N=455) X (%)
Enrolled	451 (100%)	455 (100%)
Vaccinated	448 (99.3%)	453 (99.6%)
Completed Study	444 (98.4%)	452 (99.3%)
Follow-Up after Last Visit	440 (97.6%)	447 (98.2%)
Safety Analysis Set	448 (99.3%)	453 (99.6%)
Full Analysis Set	443 (98.2%)	450 (98.9%)
Per Protocol	433 (96.0%)	431 (94.7%)
≥1 Prot. Deviation	18 (4.0%)	24 (5.3%)

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Table 4.1, 4.2, and 4.3. X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects enrolled. ≥1 Prot. Deviation: subjects with one or more protocol deviations.

The list of pre-specified protocol deviations for Study MET49 was provided in Section 6.1.10.1 of this review memo. Across both study groups there were 42 subjects (4.6%) who experienced at least 1 protocol deviation, of which the most common deviation was that the post-dose blood sample at Visit 2 was not provided or was not in the proper time window (30 days to 44 days post-vaccination), observed in 10 (2.2%) MenQuadfi subjects and 20 (4.4%) of Menomune subjects. All other reported protocol deviations occurred in <1% of subjects across both groups.

> ***Reviewer Comment*:** *The distribution of protocol deviations was generally low and similar across groups.*

6.3.11 Efficacy Analyses

Efficacy data were not collected in this trial.

6.3.11.1 Analyses of Primary Endpoints

Primary & Secondary Analyses: hSBA Seroresponse Rates & GMTs

The primary immunogenicity analyses evaluated the hSBA serogroup-specific seroresponse rates[26] at Day 30 post vaccination for the MenQuadfi group compared to the Menomune group in all subjects ≥56 years of age. Non-inferiority of the immune response was based on a lower limit of the 2-sided 95% CI of the difference in seroresponse rates >-10% for each serogroup. The following table provides the hSBA seroresponse rates [95% CI] at Day 30 for the MenQuadfi group compared to the Menomune group for the Per Protocol Analyses Set, as well as the differences (MenQuadfi-Menomune) in seroresponse rates [95%CI] across groups. The table also includes the results of the secondary analyses evaluating the hSBA GMTs and the GMT ratio (GMTR) across groups (MenQuadfi/Menomune) with the 95% CI.

26 hSBA seroresponse definition: pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

Table 22: Study MET49 Primary/Secondary Objectives – hSBA Seroresponse Rates & hSBA GMTs, All Subjects, MenQuadfi vs Menomune, PPAS

Serogroup	MenQuadfi (N=433) %Seroresponse [95% CI] GMTs [95% CI]	Menomune (N=431) %Seroresponse [95%CI] GMTs [95% CI]	% Difference [95% CI] GMTR [95% CI]
A	58.2 % [53.4, 62.9] 55.1 [46.8, 65.0]	42.5% [37.7, 47.3] 31.4[26.9, 36.7]	15.7% [**9.08**, 22.2] 1.75 [1.4, 2.0]
C	77.1% [72.9, 81.0] 101 [83.8, 123]	49.7% [44.8, 54.5] 24.7 [20.7, 29.5]	27.5% [**21.2**, 33.5] 4.10 [3.16, 5.33]
Y	74.4% [70.0, 78.4] 69.1 [58.7, 81.4]	43.4% [38.7, 48.2] 21.0 [17.4, 25.3]	31.0% **[24.6,** 37.0] 3.30 [2.57, 4.23]
W	62.6% [57.8, 67.2] 28.1 [23.7, 33.3]	44.8% [40.0, 49.6] 15.5 [13.0,18.4]	17.8% [**11.2**, 24.2] 1.81 [1.42, 2.31]

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Tables 5.2 & 5.7. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menomune). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers, GMTR: GMT ratio (MenQuadfi/Menomune).

The non-inferiority criteria were met for all 4 serogroups.

Reviewer Comment:

1. *The highest seroresponse rates in the MenQuadfi group were observed against serogroups C and Y, with 77.1% and 74.4% of MenQuadfi recipients, respectively compared to 49.7% and 43.4% of Menomune recipients, respectively.*
2. *Across groups, the trends in the GMT responses corresponded accordingly with the observed hSBA seroresponse rates. The GMT ratio (MenQuadfi/Menomune) was highest against serogroup C, with 4-fold greater GMTs in MenQuadfi recipients compared to Menomune recipients.*
3. *Higher immune responses observed following MenQuadfi vaccination compared to Menomune vaccination in meningococcal vaccine-naïve adults are consistent with hSBA responses that can be observed following immunization with a polysaccharide conjugate vs polysaccharide only vaccines, respectively.*

6.3.11.2 Analyses of Secondary Endpoints

The findings of the secondary analyses were provided in the prior section.

6.3.11.3 Subpopulation Analyses

Subpopulation Analyses by Age: hSBA Seroresponse Rates & hSBA GMTs

The number of MenQuadfi recipients and Menomune recipients with available data in each of the age cohort for the PPAS were as follows:

- 56 through 64 years: 192 MenQuadfi subjects & 189 Menomune subjects
- 65 through 74 years: 172 MenQuadfi subjects and 175 Menomune subjects
- ≥75 years: 69 MenQuadfi subjects & 67 Menomune subjects

The hSBA seroresponse rates and GMTs by age cohort (56 through 64 years, 65 through 74 years, and ≥75 years) are provided in the table below. In addition, the % difference in hSBA seroresponse rates and GMT ratios across groups are presented (descriptive analyses).

Table 23: Study MET49 – hSBA Seroresponse Rates & hSBA GMTs by Age, MenQuadfi vs Menomune, PPAS

Serogroup	MenQuadfi (N=69-192 per age cohort) %Seroresponse [95% CI] GMTs [95% CI]	Menomune (N=67-189 per age cohort) %Seroresponse [95%CI] GMTs [95% CI]
Age: 56y through 64y	--	--
A	58.9% [51.5, 65.9] 64.9 [50.8, 83.0]	44.4% [37.2, 51.8] 31.6 [24.9, 40.3]
C	80.2% [73.9, 85.6] 130 [99.6, 170]	52.9% [45.5, 60.2] 27.6 [21.2, 36.0]
Y	78.6% [72.2, 84.2] 98.7 [76.7, 127]	47.1% [39.8, 54.5] 22.3 [16.7, 29.8]
W	67.2% [60.1, 73.8] 35.8 [27.7, 46.2]	46.0% [38.8, 53.4] 17.2 [13.2, 22.4]
Age: 65y through 74y	--	--
A	57.6% [49.8, 65.0] 47.1 [36.5, 60.8]	41.7% [34.3, 49.4] 32.9 [25.7, 42.1]
C	73.8% [66.6, 80.2] 86.6 [62.7, 120]	48.6% [41.0, 56.2] 23.6 [17.8, 31.2]
Y	73.8% [66.6, 80.2] 60.7 [47.4, 77.8]	42.9% [35.4, 50.5] 21.9 [16.3, 29.4]
W	62.8% [55.1, 70.0] 25.4. [19.6, 33.0]	45.1% [37.6, 52.8] 14.4 [11.0, 18.92]
Age: ≥75 years	--	--
A	58.0% [45.5, 69.8] 51.8 [33.3, 80.6]	38.8% [27.1, 51.5] 27.4 [19.0, 39.5]
C	76.8% [65.1, 86.1] 75.2 [45.8, 123]	43.3% [31.2, 56.0] 20.5 [12.6, 33.3]
Y	63.8% [51.3, 75.0] 35.4 [23.9, 52.4]	34.3% [23.2, 46.9] 15.7 [9.8, 25.1]
W	49.3% [37.0, 61.6] 18.2 [11.6, 28.6]	40.3% [28.5, 53.0] 13.7 [8.76, 21.4]

Source: Adapted from STN 125701.0, MET49 Clinical Study Report Tables 5.4 and 5.9. Data on % difference in seroresponse rates and GMTR provided under IR response submitted to STN 125701.11: MET49 Appendix15b Complementary Listings and Analyses: Tables 4 and 5. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS, n: #subjects with available data. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menomune).

For all age cohorts, the hSBA GMTs were higher in the MenQuadfi group compared to the Menomune group for each serogroup.

Reviewer Comment:

Except for adults ≥75 years, the seroresponse rates and GMTs when categorized by separate age cohorts and study group trended in the same direction as corresponding responses in the overall study population. The seroresponse rates in adults ≥75 years following MenQuadfi vaccination were numerically lower for serogroup Y and W when compared to the rates observed in all adults for these two serogroups, however the study was not powered to show differences based on age.

Subpopulation Analyses by Sex
The hSBA seroresponse rates and GMTs when evaluated separately in male and female subjects were similar to those observed in all enrolled subjects.

Subpopulation Analyses by Racial/Ethnic Group
No conclusions could be made due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

6.3.11.4 Dropouts and/or Discontinuations

Missing immunogenicity data were imputed. No test or search for outliers were performed.

6.3.11.5 Exploratory and Post Hoc Analyses

No additional exploratory or post-hoc analyses were requested.

6.3.12 Safety Analyses

6.3.12.1 Methods

Safety Analyses Set (SafAS) and the duration of adverse event safety monitoring were previously defined in this memo (Section 6.1.12.1).

6.3.12.2 Overview of Adverse Events

Observational Safety Objective:
To describe the safety profile of MenQuadfi compared to Menomune after single vaccination.

Safety Overview:
The following table provides an overview of the rates of adverse events in the MenQuadfi group compared to the Menomune group over the course of 6-month study period.

Table 24: Study MET49-Safety Overview: Proportion of Subjects Reporting an Adverse Event Following Single Vaccination, SafAS

AE Type: Monitoring Period*	**MenQuadfi (N=448) % (x subjects/n)**	**Menomune (N=453) % (x subjects/n)**
Immediate AE: 30 minutes	0.2 (1/448)	0 (0/453)
Solicited Local: 30 days	26.6% (118/443◊)	9.5% (43/451⊓)
Solicited Systemic: 30 days	31.2% (138/442◊)	24.2% (109/451⊓)
Unsolicited AE: 30 days	17.9% (80/448)	13.5% (61/453)
AEs leading to w/d: 30 days	0 (0/448)	0.2% (1/453)
MAAEs-1st: 1st 30 days*	5.8% (26/448)	3.5% (16/453)
MAAEs-2nd: Next 5 months**	10.5% (47/448)	13.9% (63/453)
SAEs: 6 months	3.3% (15/448)	3.3% (15/453)
Deaths: 6 months	0 (0/448)	0.4 (2/453)

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Table 6.1. SafAS: Safety Analyses Set. Monitoring Period*: time interval that the relevant type of AE was monitored for postvaccination. x subjects: #subjects who experienced the solicited event; n: #subjects with available data for relevant endpoint, N= #subjects in SafAS, AE: adverse event. AEs leading to w/d: adverse events leading to study withdrawal. MAAEs: Medically attended adverse events. *MAAEs-1st: collected for 1st 30-day postvaccination (Visit 1 to Visit 2). **MAAEs-2nd: collected from Visit 2 to the 6-month follow-up phone call (5 months total). ◊: Data on solicited injection site and systemic reactions were missing for 5 subjects, and data on systemic reactions were missing for 1 additional subject. ⊓: Data on solicited injection site and systemic reactions were missing for 2 subjects. SAEs: serious adverse events.

The rates of local solicited reactions were 26.6% [22.6, 31.0] in the MenQuadfi group compared to 9.5% [7.0, 12.6] in the Menomune group, and the rates of systemic reactions were 31.2% [26.9, 35.8] in the MenQuadfi group compared to 24.2% [20.3, 28.4] in the Menomune group. The rates of unsolicited AEs in the MenQuadfi group (17.9% [14.4, 21.7]) were also higher than the Menomune group (13.5% [10.5, 17.0]), but with overlapping 95% CIs. The rates of MAAEs and SAEs were comparable across groups. There were two SAEs reported during the study, both of which were in the Menomune treatment group; please see section 6.3.12.3 of the clinical review for details.

Subgroup Analyses: Age[27]
By age cohorts, the rates of solicited and unsolicited AEs were as follows:

- 56 through 64 years: MenQuadfi (n=195-196) vs Menomune (n=197)
  - Local injection site rates: 36.2% [28.5, 43.4] vs 10.7% [6.7, 15.8]
  - Systemic rates: 37.4% [30.6, 44.6] vs 27.4% [21.3, 34.2]
  - Unsolicited AEs: 14.1% [9.6, 19.7] vs 9.0 [5.4, 13.9]
- 65 through 74 years: MenQuadfi (n=178) vs Menomune (n=183)
  - Local injection site rates: 21.5% [15.7, 28.3] vs 8.7% [5.1, 13.8]
  - Systemic rates: 27.1% [20.7, 34.3] vs 22.4% [16.6, 29.1]
  - Unsolicited AEs: 15.7% [10.7, 21.9] vs 12.6% [8.1, 18.3]
- ≥75 years: MenQuadfi (n=71) vs Menomune (n=71)
  - Local injection site rates: 12.9% [6.1,23.0] vs 8.5% [3.2,17.5]
  - Systemic rates: 24.3% [14.8,36.0] vs 19.7% [11.2, 30.9]
  - Unsolicited AEs: 12.7% [6.0, 22.7] vs 6.0 [22.7]

Reviewer Comment: *In MenQuadfi recipients, the rates of solicited and unsolicited AEs stratified by age followed similar trends observed with those observed in the entire cohort.*

Subgroup Analyses: Sex and Race
The rates of AEs stratified by sex were similar for male and females subjects across treatment groups. No conclusions could be made about racial/ethnic differences in AE rates due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

Solicited Adverse Events: 7 days Post-Vaccinations
The following table provides the proportion of subjects across groups who experienced a solicited reaction of any severity and Grade 3 severity.

27 Source: STN 125701.11, Tables 1, 2, and 3

Table 25: Study MET49- Proportion of Participants with Any & Grade 3 Solicited Reactions (Local Injection Site and Systemic) 7 Days Postvaccination, SafAS

Solicited Adverse Reaction	MenQuadfi (N=436-443) %	Menomune (N=449-451) %
Local (Injection Site)	--	--
Pain:	--	--
Any	25.5%	9.6%
Grade 3*	0.7%	0.7%
Swelling	--	--
Any	4.5%	0%
Grade 3 (>100mm)	0%	0%
Erythema:	--	--
Any	5.2%	0%
Grade 3 (>100mm)	0.2%	0%
Systemic	--	--
Myalgia:	--	--
Any	21.9%	15.3%
Grade 3*	1.6%	1.3%
Headache:	--	--
Any	19.0%	14.6%
Grade 3*	0.7%	0.7%
Malaise:	--	--
Any	14.5%	11.3%
Grade 3*	1.4%	1.8%
Fever:	--	--
Any ≥38.0C	2.1%	0.4%
Grade 3 ≥ 39.0C	0.2%	0

Source: Adapted from STN 125701.0, MET49 Clinical Study Report, Tables 6.3 and 6.4. SafAS: Safety Analyses Set. x subjects: # subjects who experienced the solicited event. #n: #subjects with available data for relevant endpoint, N= #subjects in SafAS.
*Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

In the MenQuadfi group, injection site pain, myalgia, and headache were the most frequently reported solicited reaction, reported in 25.5%, 21.9%, 19.0% of recipients, respectively. In the Menomune group, injection site pain, myalgia and headache were also the most frequently reported solicited reaction (9.6%, 15.3%, and 14.6%, respectively), but reported at lower rates than MenQuadfi group. Fever (≥38.0C) was reported in 9 MenQuadfi recipients and 2 Menomune recipients; and Grade 3 fever (≥ 39.0C) was reported in 1 MenQuadfi recipient, and no Menomune recipients.

> ***Reviewer Comment:*** *In enrolled subjects (56 years through 97 years age range), MenQuadfi was more reactogenic than Menomune. These findings are consistent with observed safety profiles of conjugate vaccines, which can be more reactogenic than polysaccharide vaccines.*

Unsolicited Adverse Events: Immediate AEs within 30 minutes Postvaccination
There were minimal reports across groups of immediate unsolicited AE within 30 minutes of vaccination.

Unsolicited AEs Non-Serious AEs: 30 days Postvaccination
The rates of unsolicited AEs non-serious AEs within 30 days postvaccination were similar across groups (MenQuadfi 17.9%, Menomune 13.5%). The number of grade 3 unsolicited AEs were higher in the MenQuadfi group, with 10 subjects reporting 16 grade 3 AEs compared to in the Menomune group that had 2 subjects reporting 2 grade 3 AEs. Unsolicited AEs were most frequently reported in SOC Musculoskeletal and Connective Tissue Disorders (MenQuadfi 26, Menomune 9), of which arthralgia and back pain were the most frequently reported AE.

> ***Reviewer Comment:*** *The observed unsolicited AEs were similar in nature and frequency across groups, and nature of the AEs were consistent with medical conditions and/or clinical signs/symptoms reported commonly in the population studied.*

Medically Attended Adverse Events: 30 Day Postvaccination & to 6-month Contact
MAAEs were previously defined in this memo (Section 6.1.12.2). Within 30 days of vaccination, there were 26 subjects who reported 38 MAAEs in the MenQuadfi group (5.8%) and there were 16 subjects who reported 18 MAAEs in the Menomune group (3.5%). Except for one, all MAAEs reported during this time period were considered to be unrelated to study vaccination. One participant in the MenQuadfi group experienced Grade 2 non-serious bilateral rash on legs and arms 3 days after study vaccination, which required medical intervention after which it resolved 19 days following onset.

6.3.12.3 Deaths

There were 2 deaths reported in the study, both of which were reported in the Menomune group and included a 60-year-old who died secondary to Chronic Obstructive Pulmonary Disease 60-year-old male and a 78-year-old female who died secondary to a cervical spinal cord injury following an automobile accident. Neither of these events were related to study vaccination.

6.3.12.4 Nonfatal Serious Adverse Events

There were 15 subjects in each group who experienced a SAE in the study (MenQuadfi 19 SAEs, Menomune 20 SAEs), none of which were considered related to study vaccination. During the first 30 days following vaccinations, there were 3 MenQuadfi recipients who experienced 3 SAEs, and 3 Menomune subjects who experienced 3 SAEs. The following case narratives are provided for the 3 MenQuadfi SAEs:

Subject #(b) (6) *: Biliary Colic*
58-year-old female was hospitalized for biliary colic 14 days after MenQuadfi vaccination. The subject recovered, and the event was considered not related to vaccination.

Subject #(b) (6) *: Knee Replacement*
67-year-old female was hospitalized for worsening of osteoarthritis of the right knee 23 days after MenQuadfi vaccination. She underwent knee replacement, recovered, and the event was considered not related to vaccination.

Subject #(b) (6) *: Urinary Tract Infection*
78-year-old female was hospitalized for *E. coli* septicemia secondary to a urinary tract infection 20 days after MenQuadfi vaccination. She was treated, recovered, and the events was considered not related to vaccination.

In the Menomune Group, 3 subjects experienced the following SAEs: suicide attempt, non-ST elevation myocardial infarction, and worsening coronary artery disease necessitating open heart surgery. None of these SAEs were considered related to study vaccination.

6.3.12.5 Adverse Events of Special Interest (AESI)

Please see Section 8 for an overview of AESI across all studies.

6.3.12.6 Clinical Test Results

Not applicable.

6.3.12.7 Dropouts and/or Discontinuations

Across study groups, there were a total of 907 subjects who were enrolled[28] of which 901 (99.3%) were vaccinated, 896 (98.8%) completed the trial, and 11 subjects did not complete the trial.
26 subjects (2.6%) who did not complete the trial. There was one report of study discontinuation due to a SAE in the Menomune group (Subject #(b) (6)) in a 58 years old male who underwent open heart surgery and withdrew from the study.

Table 26: MET49-Study Disposition

Population	**MenQuadfi (N=451) X (%)**	**Menomune (N=455) X (%)**
Enrolled	451 (100%)	455 (100%)
Vaccinated	448 (99.3%)	453 (99.6%)
Completed Study	444 (98.4%)	451 (99.1%)
Withdrawal due to	--	--
Voluntary W/d	1 (0.2%)	0
Lost to F/up	2 (0.4)	0
Non-compliance	4 (0.9%)	2 (0.4%)
AE	0	0
SAE	0	1 (0.2%)

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Table 4.1

Reviewer Comment: *Most premature withdrawals were due to lost-to-follow-up or non-compliance, both of which occurred in <1% of subjects across groups.*

6.3.13 Study Summary and Conclusions

Study MET49 was designed to demonstrate the immunogenicity and safety of MenQuadfi compared to Menomune, a licensed meningococcal A, C, Y, W polysaccharide vaccine in individuals ≥55 years of age. The primary objective, to demonstrate immunological non-inferiority of MenQuadfi to Menomune in adults ≥55 years as a single dose was met. The safety and immunogenicity data from this study support the use of MenQuadfi in this age cohort.

28 Includes one subject who was enrolled, but not randomized or vaccinated and did not complete the trial.

6.4 Trial #4 (Study MET56)

NCT02752906
Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a booster dose of MenACYW conjugate vaccine to a licensed vaccine in quadrivalent meningococcal conjugate vaccine primed adolescents (≥ 15 to < 18 years) and adults (≥ 18 years) in the United States and Puerto Rico

Study Overview: Study MET56 was designed to demonstrate the immunogenicity and safety of a single booster dose of MenQuadfi compared to a single booster dose of Menactra in adolescents/adults 15 years of age and older. The enrolled subjects had received a meningococcal A, C, Y, W conjugate vaccine 4 to 10 years earlier. The study was conducted between April 2016 to December 2016 and enrolled 810 individuals in the United States and Puerto Rico.

6.4.1 Objectives

The study objectives, endpoints and statistical success criteria, if applicable are described below.

Primary Immunogenicity
To demonstrate the non-inferiority of the hSBA responses to meningococcal serogroups A, C, Y and W following the administration of a booster dose of MenQuadfi vaccine compared to those observed following the administration of a booster dose of Menactra in adolescents/adults 15 years of age and older who had previously received a prior dose of a meningococcal conjugate A, C, W, Y vaccine 4 to 10 years prior to enrollment.

- *Primary Endpoint:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA at 30 days (+14 days) after booster dose vaccination.
  Seroresponse was defined as:
  - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
  - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer.*
- *Primary Hypothesis and Criteria for Success*: Thirty days after the administration of MenQuadfi or Menactra, the percentages of subjects who achieve an hSBA seroresponse for serogroups A, C,Y and W in Group 1 are non-inferior to the corresponding percentages in Group 2
  - *Criteria for Success*: If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions ($p_{MenQuadfi}$-$p_{Menactra}$) of subjects who achieved seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup.

Clinical Reviewer Comment:
Menactra is approved for use as a single booster dose in individuals 15 years through 55 years of age.

Secondary Immunogenicity:
1. To evaluate the vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured using hSBA in serum specimens collected 6 days (± 1 day) after booster dose vaccination in a subset of 120 subjects.

- *Secondary Endpoint 1*: Seroresponse, as measured by hSBA assessed at 6 days post-vaccination in a subset of 120 subjects
- *Descriptive analyses*

2. To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y and W following booster dose administration of MenQuadfi to those observed following booster dose administration of Menactra in adolescents and adults.
   - *Secondary Endpoint 2*: GMTs as measured by hSBA for each serogroup assessed at 30 days post-vaccination
   - *Descriptive analyses*

Observational Immunogenicity Objectives: Descriptive statistics

1. To describe the antibody titers against meningococcal serogroups A,C,W,Y measured by hSBA assessed at D0, D06, D30 after vaccination
   - *Observational Endpoint 1:* Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at D0, D06, and D30 after vaccination.

2. To describe the antibody responses to the meningococcal serogroup A,C,Y, and W before and 30 days (+14days) after vaccination with MenQuadfi or Menactra measured by serum bactericidal assay using (b) (4) in a subject of subjects
   - *Observational Endpoint 2:* Antibody titers against meningococcal serogroups A, C, Y, and W measured by (b) (4) before and 30 days after vaccination with MenACYW conjugate vaccine or Menactra

Observational Safety Objective: Descriptive Statistics

To describe the safety profile of MenQuadfi compared to that of the licensed Menactra after booster vaccination

- *Safety Endpoints:* Defined previously in Section 6.1.1

6.4.2 Design Overview

Study MET56 was a modified double-blind, randomized, parallel-group, active- controlled multicenter study in the US and Puerto Rico. The planned enrollment included 800 meningococcal conjugate ACYW vaccine primed subjects randomized 1:1 between MenQuadfi and Menactra study groups.

6.4.3 Population

Inclusion (in summary): ≥15 years old on day of inclusion who have received 1 dose of a meningococcal quadrivalent conjugate vaccine 4 to 10 years prior to enrollment; subjects between 15 to 18 years of age must have assent form signed and dated by the subject and ICF signed and dated by the parent/guardian, and must be able to attend all scheduled visits with parent/guardian and will be able to comply with all trial procedures; subjects ≥18 years must have ICF signed and dated by the subjects, and must be able to attend all study visits and comply with all trial procedures.

Exclusion (in summary): Any subjects who is pregnant, lactating, or of childbearing potential (to be considered non-child bearing potential must be pre-menarche or post-menopausal for at least 1 years, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination; in the 4 weeks prior to study participation- if subject had participated in a clinical trial evaluating a vaccine, drug,

medical device or medical procedure; receipt of any vaccine in the 28 days preceding the study or planned receipt of any vaccine before Day 30 except for influenza vaccination-which may be received 2 weeks before study investigational vaccination, this exception include monovalent pandemic influenza vaccines and multivalent influenza vaccines; previous vaccinations against meningococcal disease with either an investigational or approved meningococcal B vaccine; receipt of immune globulins, blood or blood derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than consecutive weeks within the past 3 months); history of meningococcal infection, confirmed either clinically, serologically or microbiologically; at high risk for meningococcal infection during the trial (specifically, but not limited to, subjects with persistent complement deficiency, with anatomic or functional asplenia, or subjects travelling to countries with high endemic or epidemic disease; known systemic hypersensitivity to any vaccine components, or history of a life threatening reaction to the vaccine(s) used in the trial or to a vaccine containing any of the same substances; personal history of Arthus-like reaction after vaccination with a tetanus toxoid containing vaccine, history of GBS; verbal report of thrombocytopenia, contraindicating IM vaccination in the PI's opinion; bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion contraindicating IM vaccination in the PI's opinion; deprived of freedom by an administrative or court order, or in an emergency setting or hospitalized involuntarily, current alcohol abuse or drug addiction, chronic illness that in the opinion of the PI is at a stage where is might interfere with trial conduct or completion, moderate or severe acute illness/infection (according to the PI judgment) on the day of vaccination or febrile illness (temp≥100.4F). A prospective subject should not be included in the study until the condition has resolved or the febrile event has subsided; receipt of oral or injectable antibiotic therapy within 72 hours prior to the 1st blood draw, identified as a PI or employee of the PI or study center with direct involvement in the proposed study, or identified as an immediate family member (parent/spouse, natural or adopted child) of the PI or the employee with direct involvement in the proposed study.

6.4.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi: Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

- Batch # UD18363
- Dose: single 0.5 mL intramuscular
- Composition:
  - Serogroups A, C, Y, W: 10 ug each meningococcal capsular polysaccharide
  - Tetanus toxoid protein carrier: (b) (4) ug
- Preparation: single-dose 0.5 ml vial

Menactra® (Sanofi Pasteur): MenACWY Diphtheria Toxoid Conjugate Vaccine

- Batch #: U5260AA (provided by applicant)
- Dose: single 0.5mL intramuscular
- Composition: Serogroups A, C, Y, W: 4 ug (each meningococcal capsular polysaccharide); Diphtheria toxoid protein carrier: 48 ug
- Preparation: single-dose 0.5 mL vial

6.4.5 Directions for Use

See prior section.

6.4.6 Sites and Centers

30 sites in the United States, including Puerto Rico.

6.4.7 Surveillance/Monitoring

Study Oversight:
Study oversight was provided by for all study sites by (b) (4) IRB. An internal Safety Management Team performed blinded safety analysis on safety data after vaccination.

Safety Monitoring:
Previously described in Section 6.1.7

Immunogenicity Monitoring: Serum bactericidal antibody (SBA) assays
Previously described in Section 6.1.7

6.4.8 Endpoints and Criteria for Study Success

See Section 6.4.1

6.4.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations: Planned enrollment for 800 subjects, assuming 15% drop-out rate, would result in 765 subjects (340 evaluable subjects per treatment group) with 99.9% power to declare the non-inferiority of MenQuadfi to Menactra.

Subgroup Analyses:
The applicant conducted immunogenicity and safety analyses stratified by age at time of the booster dose (≥ 15 to < 18 years of age; ≥ 18 years of age), time elapsed since the first quadrivalent meningococcal conjugate vaccination (7 years; ≥ 7 years), and by vaccine administered as primary meningococcal conjugate ACYW vaccine 4 to 10 years earlier (Menactra or Menveo).

Statistical Methods:
See Section 6.4.9

Protocol Amendments:
- Original Protocol: version 2.0, dated 20 November 2015
- 3 Amended Protocols:
  - Protocol Amendment 1, version 3.0, dated 15 January 2016
    - Included clarifications on inclusion criteria and on actions needed in case of subjects receiving antibiotics within 3 days of blood draw
  - Protocol Amendment 2, version 4.0., dated 25 March 2016
    - Updated hSBA vaccine seroresponse definition as per CBER guidance
    - SBA testing laboratories and priority of hSBA testing
  - Protocol Amendment 3, version 5.0, dated 29 November 2016
    - Updates pertaining to Coordinating Investigator

Significant Changes in the Conduct of the Study & Planned Analyses:
- There were no reported changes in the conduct or planned analyses

6.4.10 Study Population and Disposition

A total of 810 subjects were enrolled in Study MET56: the first subject was enrolled on 15 April 2016 and last subject visit occurred on 19 December 2016.

6.4.10.1 Populations Enrolled/Analyzed

Relevant analysis populations: (see Section 6.1.10 for study population definitions)

- *Safety Analyses Set (SafAS)*
- *Full Analyses Set (FAS)*
- *Per-Protocol Analyses Set (PPAS)*

The FAS and PPAS immunogenicity sets each included analysis at Day 6 and at Day 30.

Protocol Deviations:
Previously defined in Section 6.1.10

6.4.10.1.1 Demographics
The demographic characteristics of participants across study groups are provided in table below:

Table 27: Study MET56- Demographic Characteristics of MenQuadfi & Menactra SafAS

Demographic Characteristic	**MenQuadfi (N=402) X (%)**	**Menactra (N=407) X (%)**
Sex Ratio M:F (%)	195:207 (49%:52%)	207:200 (51%:49%)
Age (Years)	--	--
Mean Age (SD)	20.0y (5.97)	19.9y (5.59)
Median Age	17.8y	17.9y
Age Range	16.5y, 55.5y	15.0y, 58.7y
Age Group: # subjects (%)		
15 to 17 years	201 (52.3%)	201(51.7%)
≥18 years	183 (47.7%)	188 (48.3%)
Racial origin:	--	--
White	342 (85.1%)	340 (83.5%)
Black/A.A.	39 (9.7%)	46 (11.3%)
Mixed Origin	8 (2.0%)	17 (4.2%)
Asian	11 (2.7)	3 (0.7%)
N.Hawaiian/P.I	0	1 (0.2%)
Am.Indian/A.N	1 (0.2%)	0
Ethnicity:	--	--
Hispanic/Latino	63 (15.7%)	71 (17.4%)
Not H/L	338 (84.1%)	336 (82.6%)

Source: Adapted from STN 125701.0, MET55 Clinical Study Report, Table 4.4. SafAS: Safety Analyses Set. For Sex; Racial Origin, and Ethnicity: X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects for the Safety Analyses Set (subjects who received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female. For Age Groups: y indicates years. Racial origin: Asian, Black/A.I: Black/African American; Am.Indian/A.N: American Indian/Alaska Native; N.Hawaiian/P.I.: Native Hawaiian/Pacific Islander; missing origin not listed (accounted for 3 subjects in Group 1 only. Ethnicity: Hispanic/Latina; Not H/L: Not Hispanic/Latino.

The demographic characteristics across groups were generally similar with ~50% male subjects and 50% female subjects. Across groups, the median age was 17.8 years were consistent across groups, with the youngest subject 15 years and the oldest 58.7 years. Most subjects across

groups were of White racial origin (~84%), followed by Black/African American racial origin (10.5%) and Mixed racial origin (3.1%). The Asian, American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander groups had low enrollment across both groups. Most subjects were not of Hispanic/Latino ethnic origin, while 17% were of Hispanic/Latino origin.

Reviewer Comment: *The overall demographic characteristics across both study groups were similar.*

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.4.10.1.3 Subject Disposition

Table 28: Study MET56- Subject Dispositions & Data Analyses Sets for MenQuadfi (Group 1) & Menactra (Group 2)

Population	MenQuadfi (N=403) X (%)	Menactra (N=407) X (%)
Enrolled	403 (100%)	407 (100%)
Vaccinated	402 (99.8%)	407 (100%)
Completed Study	396 (98.3%)	402 (98.8%)
Follow-Up after Last Visit	391 (97.0%)	399 (98.0%)
Safety Analysis Set	498 (100%)	494 (100%)
Full Analysis Set-Day 6	56 (13.9%)	63 (15.5%)
Per Protocol Set- Day 6	55 (13.6%)	62 (15.5%)
Full Analyses Set -Day 30	396 (98.3%)	402 (98.8%)
Per Protocol Set – Day 30	384 (95.3%)	389 (95.6%)
For PPAS-Day 30: subjects with ≥1 Prot. Deviation	19 (4.7%)	18 (4.4%)

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 4.1, 4.2, and 4.3. X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects enrolled. ≥1 Prot. Deviation: subjects with one or more protocol deviations.

The list of pre-specified protocol deviations for Study MET56 was provided in Section 6.4.10.1 of this review memo. Across all study groups for the PPAS-Day 30 there were 37 subjects (4.6%) who experienced at least 1 protocol deviation, of which the most common deviation was that the post-dose blood sample at Day 30 visit was not provided or was not in the proper time window (30 days to 44 days post-vaccination), observed in 3.0% of MenQuadfi subjects and 3.0% of Menactra subjects. All other reported protocol deviations occurred in <1% of subjects across both groups.

Reviewer Comment: *The number of protocol deviations was generally low and similar across groups. The observed protocol deviations did not raise concerns about study conduct.*

6.4.11 Efficacy Analyses

Efficacy data were not collected in this trial.

6.4.11.1 Analyses of Primary & Secondary Endpoints at 30 days Post-Vaccination

Immunogenicity Analyses: hSBA Seroresponse Rates & GMTs (Day 30)

The primary immunogenicity objective was to evaluate the hSBA serogroup-specific seroresponse rates[29] at Day 30 following a booster dose vaccination of MenQuadfi compared to Menactra. Non-inferiority of the immune response was demonstrated if the lower limit of the 2-sided 95% CI of the difference in seroresponse rates >-10% for each serogroup. The following table provides the hSBA seroresponse rates [95% CI] at Day 30 for the MenQuadfi group compared to the Menactra group for the Per Protocol Analyses Set-Day 30, as well as the differences in seroresponse rates [95%CI]. The table also includes the hSBA GMTs and GMT ratio (GMTR) across groups (MenQuadfi/Menactra) with the 95% CI.

Table 29: Study MET56 Primary/Secondary Objectives – hSBA Seroresponse Rates & hSBA GMTs at Day 30 Post-Booster Vaccination, MenQuadfi vs Menactra, PPAS-Day30

Serogroup	MenQuadfi (N=384) %Seroresponse [95% CI] GMTs [95% CI]	Menactra (N=389) %Seroresponse [95%CI] GMTs [95% CI]	% Difference [95% CI] GMTR [95% CI]
A	92.2% [89.0, 94.7] 497 [436, 568]	87.1% [83.4, 90.3] 296 [256, 343]	5.0% [**0.735**, 9.38] 1.68 [1.38, 2.05]
C	97.1% [94.9, 98.6] 2618 [2227, 3078]	91.8% [88.6, 94.3] 599 [504, 711]	5.4% [**2.16**, 8.76] 4.37 [3.45, 5.53]
Y	97.4% [95.3, 98.7] 2070 [1807, 2371]	95.6% [93.1, 97.4] 811 [699, 941]	1.8% **[-0.907,** 4.55] 2.55 [2.09, 3.12]
W	98.2% [96.3, 99.3] 1747 [1508, 2025]	90.7% [87.4, 93.4] 723 [614, 853]	7.4% [**4.3**, 10.9] 2.42 [1.94, 3.01]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Tables 5.1 & 5.3. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi - Menactra). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers, GMTR: GMT ratio (MenQuadfi/Menactra).

The non-inferiority criteria were met for each of the 4 serogroups.

Reviewer Comment:

1. *Overall, the seroresponse rate for any serogroup was >92% and >85% after MenQuadfi and Menactra vaccination, respectively. For serogroups C and W, the seroresponse rates for the MenQuadfi group were higher than those for the Menactra group, with 95% CI that did not overlap.*
2. *Across study groups, serogroup-specific GMTs were consistent with the corresponding serogroup-specific hSBA seroresponse rates.*

6.4.11.2 Analyses of Secondary Endpoints at Day 6 Post-Vaccination

Immunogenicity Analyses: hSBA Seroresponse Rates & GMTs (Day 6)

The hSBA serogroup specific seroresponse rates and GMTs were evaluated descriptively at Day 6 post-booster dose vaccination across treatment groups in a subset of subjects. The following table provides the hSBA seroresponse rates [95% CI] at Day 6 for the MenQuadfi group compared to the Menactra group for the Per Protocol Analyses Set-Day 6, as well as the

29 hSBA seroresponse definition: pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer

differences in seroresponse rates across treatment groups [95%CI]. The table also includes the Day 6 post-vaccination hSBA GMTs with the 95% CI for each treatment group.

Table 30: Study MET56 Secondary Objectives – hSBA Seroresponse Rates & hSBA GMTs at Day 6 Post-Booster Vaccination, MenQuadfi vs Menactra, PPAS-Day 6

Serogroup	MenQuadfi (N=55) %Seroresponse [95% CI] GMTs [95% CI]	Menactra (N=62) %Seroresponse [95%CI] GMTs [95% CI]
A	72.7% [59.0, 83.9] 173 [102, 294]	66.1% [53.0, 77.7] 226 [141, 363]
C	83.6% [71.2, 92.2] 334 [191, 583]	87.1% [76.1, 94.3] 448 [277, 724]
Y	90.9% [80.0, 97.0] 302 [176, 516]	83.9% [72.3, 92.0] 335 [219, 512]
W	94.5% [84.9, 98.9] 499 [293, 850]	83.9% [72.3, 92.0] 346 [216, 555]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Tables 5.2 & 5.4. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS. GMTs: hSBA Geometric Mean Titers

At Day 6, the hSBA seroresponse rates in the Menquadfi study group were numerically higher than seroresponses rates in the Menactra study group for each serogroup, but with overlapping 95% CI. For the MenQuadfi group, the Day 6 hSBA GMTs were higher than the Day 0 pre-vaccination hSBA GMTs[30] for each serogroup and were comparable to the Menactra group's hSBA GMTs.

> ***Reviewer Comment****: The Day 6 hSBA immune responses were evaluated descriptively without formal hypothesis testing. For both study groups, hSBA seroresponse rates at Day 6 and at Day 30 followed similar trends for each serogroup. Though the hSBA GMTs generated 6 days following MenQuadfi booster vaccination are numerically higher than at baseline, they are modest compared to the hSBA GMTs generated at Day 30. The data show that most participants achieved seroresponse as early as Day 6, indicative of kinetics of an immunological memory response.*
>
> .

6.4.11.3 Subpopulation Analyses

Immunogenicity analyses were stratified by age at time of the booster dose (≥ 15 to < 18 years of age or ≥ 18 years of age); by time elapsed since the first quadrivalent meningococcal conjugate vaccination (7 years or ≥ 7 years); and by vaccine administered as primary meningococcal conjugate ACYW vaccine 4 to 10 years earlier (Menactra or Menveo). These analyses were descriptive without pre-specified hypothesis testing. The following table provides the number of subjects in each of these stratified subgroups in the PPAS-Day 30.

30 hSBA GMTs at Day 0, not shown. Source: STN 125701.0, MET56 CSR, Table 5.4

Table 31: MET56-Subgroup Populations for MenQuadfi & Menactra, PPAS-Day 30

Subgroup	MenQuadfi *(N=384)* *X (%)*	Menactra *(N=389)* *X (%)*
Age: 15 years to <18 years	201 (52.3%)	201(51.7%)
Age: ≥18 years	183 (47.7%)	188 (48.3%)
Time since Priming: < 7y	276 (71.9%)	281 (72.2%)
Time since Priming: ≥7y	108 (28.1%)	108 (27.8%)
Primary Vaccine: Menactra	327 (85.2%)	340 (87.4%)
Primary Vaccine: Menveo	48 (12.5%)	39 (10.0%)
Primary Vaccine Unknown	9 (2.3%)	10 (2.6%)

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 4.3. Section 5.1.4 of CSR. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. X indicates number of subjects fulfilling the item followed by % (percentage of subjects fulfilling the item relative to # subjects in PPAS-Day 30)

More subjects had received a first dose of a meningococcal conjugate vaccine < 7 years earlier (~72%) compared to those who received a dose ≥7 years earlier. Most subjects had received a prior dose of Menactra (~86%) as compared to Menveo (~11%), with 19 subjects across groups for whom the primary vaccine was unknown.

> ***Reviewer Comment***: *These findings were anticipated due to the timing of the study, which was initiated in April 2016 and the greater market availability of Menactra in the US (licensed in 2005) ~11 years prior to study initiation compared to Menveo (licensed in 2010) 6 years prior to study initiation.*

Subpopulation Analyses by Age at Booster Dose (≥ 15 to <18 years vs ≥ 18 years)
The following table provides the hSBA seroresponse rates for subjects stratified by age (≥ 15 to <18 years vs ≥ 18 years) at time of booster dose vaccination across treatment groups. The upper age range in the MenQuadfi group was ~55 years of age and in the Menactra group was ~58 years of age.

Table 32: MET56- Subgroup Analyses by Age, hSBA Seroresponse Rates, Day 30 Post-Booster Vaccination, MenQuadfi vs Menactra, and % Difference Across Groups, PPAS-Day 30

Serogroup	MenQuadfi (N=384) %Seroresponse [95%CI]	Menactra (N=389) %Seroresponse [95%CI]	% Difference* [95%
Age: ≥ 15 to <18	n=201	n=201	--
A	91.0% [86.2, 94.6]	90.0 % [85.1, 93.8]	1.0% [-4.86, 6.87]
C	97.5% [94.3, 99.2]	94.5% [90.4, 97.2]	3.0 % [-1.01, 7.29]
Y	98.5% [95.7, 99.7]	97.0% [93.6, 98.9]	1.5 % [-1.74, 5.01]
W	98.0% [95.0, 99.5]	93.5% [89.2, 96.5]	4.5 % [0.465, 8.93]
Age: ≥ 18 years	n=183	n=188	--
A	93.4% [88.8, 96.6]	84.1% [78.0, 89.0]	9.4 % [2.97; 15.9)
C	96.7% [93.0, 98.8]	88.8% [83.4, 93.0]	7.9 % [2.63; 13.5)
Y	96.2% [92.3, 98.4]	94.1% [89.8, 97.0]	2.0 % [-2.60; 6.77)
W	98.4% [95.3, 99.7]	87.8% [82.2, 92.1]	10.6 % [5.60; 16.2)

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Tables 5.16 and 5.18. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. n=number of subjects with valid serology results for each subgroup's treatment group. *These analyses were descriptive without pre-specified hypothesis testing.

Reviewer Comment:
For both treatment groups, the proportion of participants in each age cohort who achieved seroresponse at Day 30 post booster dose vaccination were generally comparable to the overall seroresponse rates in all participants, however success criteria were not prespecified, and those data are descriptive only.

The following table provides hSBA GMTs at Day 0 and Day 30 stratified by age across treatment groups. The observed GMTs based on age cohort were comparable to the overall GMTs for all subjects.

Table 33: MET56- Subgroup Analyses by Age, hSBA GMTs, Day 0 & Day 30 Post-Booster Vaccination, MenQuadfi vs Menactra, PPAS-Day 30

Serogroup		MenQuadfi [N=384] GMTs [95% CI]	Menactra [N=389] GMTs [95% CI]
Age: ≥ **15 to <18 y**		n=201	n=201
A	**Day 0**	13.5 [11.5; 15.9]	14.0 [12.0; 16.3]
	Day 30	528 [444; 628]	313 [257; 380]
C	**Day 0**	10.7 [8.46; 13.5]	9.81 [7.94; 12.1]
	Day 30	2952 [2401; 3629]	654 [522; 819]
Y	**Day 0**	6.03 [4.87; 7.46]	6.55 [5.30; 8.09]
	Day 30	2279 [1903; 2729]	895 [748; 1071]
W	**Day 0**	9.98 [8.26; 12.0]	9.84 [8.18; 11.8]
	Day 30	1847 [1520; 2243]	841 [671; 1055]
Age: ≥ **18 years**		n=183	n=188
A	**Day 0**	14.0 [11.7; 16.7]	16.3 [13.8; 19.3]
	Day 30	466 [379; 572]	280 [224; 350]
C	**Day 0**	11.4 [8.93; 14.6]	11.5 [9.22; 14.4]
	Day 30	2294 [1781; 2956]	545 [419; 709]
Y	**Day 0**	10.1 [7.94; 12.8]	8.12 [6.42; 10.3]
	Day 30	1863 [1517; 2288]	729 [573; 928]
W	**Day 0**	9.52 [7.67; 11.8]	11.4 [9.27; 14.1]
	Day 30	1644 [1312; 2060]	616 [485; 782]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 5.14. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. X indicates number of subjects fulfilling the item followed

Reviewer Comment:
One month after a MenQuadfi booster dose, hSBA GMTs were 1.5-4.5 times higher, depending on the serogroup, than corresponding hSBA GMTs following a Menactra booster dose. For both vaccines (MenQuadfi or Menactra), the post-booster responses among individuals ≥ 15 to <18 years of age and ≥ 18 years of age were similar for each serogroup.

Subpopulation Analyses by Time Elapsed Since Primary Dose [7 years or ≥ 7 years]:
The following table provides the hSBA seroresponse rates and differences across groups [95% CI] stratified based on the time elapsed since receipt of the primary dose of a meningococcal conjugate ACWY vaccine (7 years vs ≥7 years).

Table 34: MET56- Subgroup Analyses by Time Since Primary Meningococcal Conjugate ACWY Vaccination, hSBA Seroresponse Rates, Day 30 Post-Booster Vaccination, MenQuadfi vs Menactra, and % Difference Across Groups, PPAS-Day 30

Serogroup	MenQuadfi (N=384) % Seroresponse [95%CI]	Menactra (N=389) % Seroresponse [95%CI]
<7 years	n=276	n=281
A	92.0% [88.2, 94.9]	89.0% [84.7, 92.4]
C	97.5% [94.8, 99.0]	93.2 % [89.6, 95.9]
Y	98.2 % [95.8, 99.4]	97.5 % [94.9, 99.0]
W	98.6% [96.3, 99.6]	91.1 % [87.1, 94.2]
≥ 7 years	n=108	n=108
A	92.6 % [85.9, 96.7]	82.4% [73.9, 89.1]
C	96.3 % [90.8, 99.0]	88.0 % [80.3, 93.4]
Y	95.4 % [89.5, 98.5]	90.7 % [83.6, 95.5]
W	97.2 % [92.1, 99.4]	89.8 % [82.5, 94.8]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Tables 5.22 & 5.24. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. n=number of subjects with valid serology results for each subgroup's treatment group

The hSBA GMTs when stratified by time since primary dose (data not shown) were also comparable to the overall hSBA GMTs across treatment groups (shown in Section 6.4.11.1).

Subpopulation Analyses by Primary Dose Vaccine [Menactra or Menveo]:
The following table provides the hSBA seroresponse rates and differences across groups [95% CI] stratified based on the primary meningococcal conjugate ACWY vaccine (Menactra vs Menveo) administered 4 to 10 years earlier.

Table 35: MET56- Subgroup Analyses by Primary Meningococcal Conjugate ACWY Vaccine Administered 4 to 10 years Earlier, hSBA Seroresponse Rates, Day 30 Post-Booster Vaccination, MenQuadfi vs Menactra, and % Difference Across Groups, PPAS-Day 30

Serogroups	MenQuadfi (N=384) % Seroresponse [95%CI]	Menactra (N=389) % Seroresponse [95%CI]
Menactra	n=327	n=340
A	92.7% [89.3, 95.2]	87.6% [83.7, 91.0]
C	96.9% [94.4, 98.5]	91.5% [88.0, 94.2]
Y	97.2% [94.8, 98.7]	95.6 % [92.8, 97.5]
W	98.5% [96.5, 99.5]	90.0% [86.3, 93.0]
Menveo	n=48	n=39
A	89.6% [77.3, 96.5]	79.5% [63.5, 90.7]
C	100.0% [92.6, 100.0]	92.3% [79.1, 98.4]
Y	100.0% [92.6, 100.0]	94.9% [82.7, 99.4]
W	97.9 % [88.9, 99.9]	94.9 % [82.7, 99.4]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Tables 5.28 & 5.30. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. n=number of subjects with valid serology results for each subgroup's treatment group

The following table provides hSBA GMTs at Day 0 and Day 30 stratified by age across treatment groups.

Table 36: MET56- Subgroup Analyses by Primary Meningococcal Conjugate ACWY Vaccine Administered 4 to 10 years Earlier, hSBA GMTs, Day 0, Day 30 Post-Booster Dose Vaccination, MenQuadfi vs Menactra, PPAS-Day 30

Serogroup		MenQuadfi [N=384) GMTs [95% CI]	Menactra [N=389) GMTs [95% CI]
Menactra		n=327	n=340
A	**Day 0**	13.2 [11.6, 14.9]	15.1 [13.4, 17.1]
	Day 30	490 [424, 565]	298 [255, 349]
C	**Day 0**	11.1 [9.20, 13.3]	11.0 [9.36, 13.0]
	Day 30	2505 [2096, 2993]	575 [478, 691]
Y	**Day 0**	7.67 [6.44, 9.13]	7.09 [5.99, 8.40]
	Day 30	2009 [1737, 2324]	771 [660, 902]
W	**Day 0**	9.40 [8.04, 11.0]	10.7 [9.19, 12.4]
	Day 30	1758 [1497, 2065]	671 [563, 800]
Menveo		n=48	n=39
A	**Day 0**	17.4 [11.8, 25.9]	14.4 [9.79, 21.1]
	Day 30	636 [439, 920]	238 [148, 384]
C	**Day 0**	11.2 [7.44, 16.7]	7.72 [4.84, 12.3]
	Day 30	4096 [2745, 6113]	771 [439, 1351]
Y	**Day 0**	7.13 [4.74, 10.7]	9.39 [5.61, 15.7]
	Day 30	2981 [2011, 4420]	1245 [738, 2101]
W	**Day 0**	11.0 [7.69, 15.7]	10.3 [6.74, 15.6]
	Day 30	1773 [1185, 2651]	1202 [697, 2071]

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 5.26. PPAS-Day 30: number of subjects included in the Per Protocol Analyses Set at Day 30. N: total number of subjects in the PPAS-Day 30. X indicates number of subjects fulfilling the item followed. n=number of subjects with valid serology results for each subgroup's treatment group

Reviewer Comment*:*
Overall (all serogroups), hSBA GMTs after MenQuadfi booster vaccination were 1.5 to 5.0 times higher than the hSBA GMTs after a Menactra booster dose, regardless if Menactra or Menveo was administered as the primary vaccination. hSBA GMTs prior to booster dose vaccination were similar, regardless if subjects had received a dose 4 to 10 years earlier with Menactra or Menveo.

Subpopulation Analyses by Sex and Race:
The hSBA immune responses evaluated separately in male and female subjects were similar to those observed in all enrolled subjects. No conclusions could be made due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

6.4.11.4 Dropouts and/or Discontinuations

Missing immunogenicity data was not imputed. No test or search for outliers were performed.

6.4.11.5 Exploratory and Post Hoc Analyses

No additional exploratory or post-hoc analyses were required.

6.4.12 Safety Analyses

6.4.12.1 Methods

Datasets:
Safety Analyses Set (SafAS) and the duration of adverse event safety monitoring were previously defined in this memo (Section 6.1.12.1).

6.4.12.2 Overview of Adverse Events

Observational Safety Objective: Descriptive statistics without hypothesis testing
To describe the safety profile of MenQuadfi compared to that of the licensed Menactra after booster vaccination.

Safety Overview:
The following table provides an overview of the rates of adverse events in the MenQuadfi group compared to the Menveo group over the course of 6-month study period.

Table 37: Study MET56-Safety Overview: Proportion of Subjects Reporting an Adverse Event Following Single Booster Dose Vaccination, SafAS

AE Type: Monitoring Period*	**MenQuadfi (N=402) % (x subjects/n)**	**Menveo (N=407) % (x subjects/n)**
Immediate AE: 30 minutes	0.5% (2/402)	0 (0/407)
Solicited Local: 30 days	46.5% (185/398)	49.3% (198/402)
Solicited Systemic: 30 days	55.3% (220/398)	54.2% (218/402)
Unsolicited AE: 30 days	26.4% (106/402)	25.8% (105/407)
AEs leading to w/d: 30 days	0 (0/402)	0 (0/407)
MAAEs-1st: 1st 30 days*	7.5% (30 /402)	6.1% (25/407)
MAAEs-2nd: Next 5 months**	17.4% (70/402)	23.1% (94/407)
SAEs: 6 months	1.2% (5/402)	1.0% (4/407)
Deaths: 6 months	0	0

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 6.1. SafAS: Safety Analyses Set. Monitoring Period*: time interval that the relevant type of AE was monitored for postvaccination. x subjects: #subjects who experienced the solicited event; n: #subjects with available data for relevant endpoint, N= #subjects in SafAS, AE: adverse event. AEs leading to w/d: adverse events leading to study withdrawal. MAAEs: Medically attended adverse events. *MAAEs-1st: collected for 1st 30-day postvaccination (Visit 1 to Visit 2). **MAAEs-2nd: collected from Visit 2 to the 6-month follow-up phone call (5 months total). SAEs: serious adverse events.

The rates of adverse events following booster dose vaccination across treatment groups were comparable.

> ***Reviewer Comment***:
> *When compared to the rates of adverse events following a primary dose vaccination (Section 6.1, Study MET43), the safety profile of MenQuadfi following a booster dose vaccination are comparable.*

Subgroup Analyses: Age, Sex, and Race[31]
The rates of adverse events stratified by age (15 to 17 years, ≥18 years) followed similar trends observed with those in all subjects. The rates of AEs stratified by sex were similar for male and

31, Safety overview stratified by age, sex and race were provided in IR response submitted to STN 125701.17

females subjects across treatment groups. No conclusions could be made about racial/ethnic differences in AE rates due to small number of subjects who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

Solicited Adverse Events: 7 days Post-Vaccinations
The following table provides the proportion of subjects across groups who experienced a solicited reaction of any severity and Grade 3 severity.

Table 38: Study MET56- Proportion of Participants with Any & Grade 3 Solicited Reactions(Local and Systemic) 7 Days Postvaccination, SafAS

Solicited Adverse Reaction	**MenQuadfi (N=390-398) % (x subjects/n)**	**Menactra (N=390-402) % (x subjects/n)**
Local (Injection Site)	--	--
Pain:	--	--
Any	44.7%	48.8%
Grade 3*	1.0%	2.0%
Swelling	--	--
Any	4.0%	0.7%
Grade 3 (>100mm)	0	0
Erythema:	--	--
Any	5.0%	1.5%
Grade 3 (>100mm)	0	0
Systemic	--	--
Myalgia:	--	--
Any	36.7%	38.8%
Grade 3*	2.0%	2.2%
Headache:	--	--
Any	37.9%	33.3%
Grade 3*	2.3	3.5%
Malaise:	--	--
Any	27.6%	26.9%
Grade 3*	2.8%	3.5%
Fever:	--	--
Any ≥38.0C	0%	0.5%
Grade 3 ≥ 39.0C	0%	0.3%

Source: Adapted from STN 125701.0, MET35 Clinical Study Report, Tables 6.3 and 6.4. SafAS: Safety Analyses Set. x subjects: # subjects who experienced the solicited event. #n: #subjects with available data for relevant endpoint, N= #subjects in SafAS.
*Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity.

For both study groups, injection site pain was the most frequently reported local reaction (MenQuadfi 44.7%, Menactra 48.8%). The number of participants reporting severe pain was low, 4 in the MenQuadfi group and 8 in the Menactra group. Across treatment groups, myalgia, headache, and malaise were reported at similar rates across groups.

Reviewer Comment: *The rates of solicited local injection site and systemic AEs following a primary dose of MenQuadfi (Section 6.1, Study MET43) were similar to those observed following a booster dose of MenQuadfi (table above, Study MET56) in adolescents/adult population: (primary dose rates vs booster dose rates):*

Local Injection Site:	*Systemic:*
Pain: 38.8% vs 44.7%	*Myalgia: 32% vs 36.7%*
Swelling: 4.2% vs 4.0%	*Headache: 27.9% vs 37.9%*
Erythema: 4.8% vs 5%	*Malaise: 21.4% vs 27.6%*
	Fever: 1.1% vs 0

Unsolicited Adverse Events: Immediate AEs within 30 minutes Postvaccination
There were 2 subjects in the MenQuadfi group that reported an immediate unsolicited AE within 30 minutes of vaccination, including a 16-year-old female and 17-year-old female both reporting Grade 1 dizziness following vaccination. Both subjects recovered and completed the study, however both events were considered related to study vaccination. There were no reports of immediate AEs in the Menactra group.

> ***Reviewer Comment:*** *The clinical reviewer concurs with the assessment by the investigators that the 2 reported immediate AEs of dizziness following MenQuadfi vaccination in two adolescent subjects were related to study vaccination. Of note, the USPI for Menactra and Menveo include Syncope (fainting) following vaccination in the Warnings & Precaution section.*

Unsolicited AEs Non-Serious AEs: 30 days Postvaccination
The rates of unsolicited AEs non-serious AEs within 30 days postvaccination were similar across groups (MenQuadfi 26.4%, Menactra 25.8%). The rates of grade 3 unsolicited AEs were also comparable across groups (MenQuadfi 3.7%, Menactra 4.4%). The reported unsolicited AEs were most frequently reported under the SOC Infections and Infestations (MenQuadfi 7.5%, Menactra 6.6%) and Respiratory/Thoracic & Mediastinal Disorders (MenQuadfi 6.0%, Menactra 5.5%), the most frequently reported AE by preferred term were cough, upper respiratory infection (URI), nasopharyngitis, and headache. The majority of reported unsolicited AEs were reported as Grade 1 or 2 in intensity.

> ***Reviewer Comment:*** *The observed unsolicited AEs were similar in nature and frequency across groups.*

Medically Attended Adverse Events: 30 Day Postvaccination & to 6-month Contact
MAEEs were previously defined in this memo (Section 6.1.12.2). The proportion of participants who reported MAAEs within 30 days postvaccination were similar across groups, (MenQuadfi, 7.5%, Menactra). Across groups, most of these events were graded Grade 1 or 2 in intensity, occurred ≥15 days following vaccination, and lasted for either 4-7 days or ≥8 days. Within 30 days of vaccination, there were 40 MAAEs in 30 MenQuadfi recipients, of which 3 MAAEs were considered related to study vaccinations: one event of injection site pruritus and two events of dizziness. In the same time there were 29 MAAEs in 25 Menactra recipients, of which 1 MAAE was considered related to vaccination: an AE of injection site discoloration. During the time between Visit 2 and the 6-month follow-up contact, 18.9% [15.2, 23.1] of MenQuadfi recipients and 24.6% [20.5, 29.1] of Menactra recipients reported a MAAE. None of these MAAEs were considered related to vaccination.

6.4.12.3 Deaths

No deaths were reported during the study.

6.4.12.4 Nonfatal Serious Adverse Events

There were 5 SAEs in MenQuadfi group (5 participants) and 4 SAEs in the Menactra group (4 participants) during the study, none of which were considered by the investigator to be related to study vaccination. Within 30 days of study vaccination there was 1 SAE reported in the MenQuadfi group and includes the following case narrative:

Subject #(b) (6) *:* Pulmonary Embolism
24-year-old male was hospitalized for bilateral pulmonary embolism 8 days after MenQuadfi vaccination. The subject had a past medical history of superficial blood clot in the left leg 3 months prior to the event and had a history of Factor V mutation. The subject recovered, and the events were considered not related to vaccination.

There were 2 SAEs reported in the Menactra group within 30 days of study vaccination that were not considered related to study vaccination and included a hospitalization due to depressive disorder 3 days post-vaccination, and chest pain 28 days post-vaccination.

Reviewer Comment: *This reviewer agrees with the study investigator's assessment that none of the SAEs were related to vaccination*

6.4.12.5 Adverse Events of Special Interest [AESI]

Please see Section 8 for an overview of AESI across all studies.

6.4.12.6 Clinical Test Results

Not applicable.

6.4.12.7 Dropouts and/or Discontinuations

Across study groups, there were a 798 (98.5%) subjects who completed the trial. There were no reports of study discontinuations due to SAEs or other AEs. The proportion of subjects who prematurely withdrew from the study are listed below by group and by reason:

Table 39: MET56-Subject Disposition by Treatment Group, MenQuadfi vs Menactra, -All Enrolled Subjects

Population	**MenQuadfi (N=403) X (%)**	**Menactra (N=407) X (%)**
Enrolled	403 (100%)	407 (100%)
Vaccinated	402 (99.8%)	407 (100.0%)
Completed Study	396 (98.3%)	402 (98.8%)
Withdrawal due to	--	--
Voluntary W/d	2 (0.5%)	2 (0.5%)
Lost to F/up	3 (0.7)	2 (0.5%)
Non-compliance	2 (0.5%)	1 (0.2%)
AE/SAE	0	0

Source: Adapted from STN 125701.0, MET56 Clinical Study Report, Table 4.1

6.4.13 Study Summary and Conclusions

Study MET56 was designed to demonstrate the immunogenicity and safety of a single booster dose of MenQuadfi when compared to a single booster dose of Menactra in adolescents and adults who had received a meningococcal A, C, Y, W conjugate vaccine 4 to 10 years earlier. Menactra is a meningococcal conjugate quadrivalent vaccine licensed for use as a booster dose in the evaluated age cohort. MenQuadfi was immunologically non-inferior to Menactra based on hSBA seroresponse rates. The safety and immunogenicity data from this study support the use of MenQuadfi, administered as a single booster dose, in adolescents/adults 15 years of age and older and received a meningococcal A, C, Y, W conjugate vaccine 4 to 10 years earlier.

6.5 Trial #5 (Study MET50)

NCT#002199691
A Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenACYW conjugate vaccine compared to that of the licensed vaccine MENVEO®, and when MenACYW conjugate vaccine is given with Tdap and HPV vaccines, in healthy adolescents 10 to 17 years of age in the US

Study Overview: Study MET50 was designed to demonstrate the immunogenicity and safety of MenQuadfi compared Menveo in meningococcal vaccine-naïve adolescents 10 years through 17 years, and to evaluate for immune interference when MenQuadfi was administered concomitantly with Tdap vaccine (Adacel®) and HPV Quadrivalent (Types 6, 11, 16, & 18) vaccine (GARDASIL®). This phase 2 study was conducted from July 2014 to October 2015 in the US.

6.5.1 Objectives

Primary Objective
To demonstrate the non-inferiority of the hSBA responses to meningococcal serogroup A, C, Y and W following administration of a single dose of MenQuadfi vaccine compared to a single dose of Menveo.

- *Primary Endpoint:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA at 30 days (+14 days) after vaccination.
  Seroresponse was defined as:
  - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
  - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer*.
- *Primary Hypothesis*: Thirty days after the administration of MenQuadfi or Menveo, the percentages of subjects who achieve an hSBA vaccine seroresponse for serogroups A, C, Y and W in Group 1 are non-inferior to the corresponding percentages in Group 2
  - *Criteria for Success*: If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions ($p_{\text{MenQuadfi}}$-p_{Menveo}) of subjects who achieved seroresponse was > -10%, then non-inferiority was demonstrated for each serogroup.

Clinical Reviewer Comment:
The immunogenicity data presented for this study incorporate the CBER-recommended hSBA seroresponse definition (Type C meeting, 11 April 2016) and includes:

- *For subjects with pre-vaccination titers <1:8, the post vaccination titer must be ≥1:16.*
- *For subjects with titers ≥1:8, the post vaccination titer must be at least four-fold greater than the pre-vaccination titer.*

For Study MET50, this hSBA seroresponse definition was included with revised primary and secondary immunogenicity analyses submitted to the BLA in response to an information request (STN 125701, Amendment 17).

Secondary Objective
1. To evaluate the antibody responses to the antigens, present in MenQuadfi vaccine, when MenQuadfi vaccine is given concomitantly with Tdap and HPV vaccines, compared to those when MenQuadfi is given alone

- *Secondary Endpoints:* The proportion of subjects with seroresponse to meningococcal serogroups A, C, Y, and W measured by hSBA at 30 days (+14 days) after vaccination. *Seroresponse was defined as:*
  - *pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; or*
  - *pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer*
- *Secondary Hypothesis & Criteria for Success:* For each serogroup (A, C, Y, and W), if the lower limit of the 2-sided 95% CI of the difference between the 2 percentages across groups who achieved seroresponse was > -10%, then non-inferiority was assumed.

2. To evaluate the antibody responses to the antigens present in Tdap vaccine, when Tdap vaccine is given concomitantly with MenQuadfi vaccine and HPV vaccine, compared to those when Tdap vaccine is given with *HPV vaccine only*
- *Secondary Endpoints:*
  - Anti-pertussis antibody concentrations (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM]) for Group 3 and Group 4 at 30 days post vaccinations
  - Anti-tetanus and anti-diphtheria antibody concentrations for Group 3 and Group 4 at 30 days post vaccinations
- *Secondary Hypothesis & Criteria for Success:*
  - For each pertussis antigen: If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups is > 2/3 for each antigen, the inferiority assumption was rejected
  - For tetanus and diphtheria tested separately: If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption was rejected.

3. To evaluate the antibody responses to the antigens present in HPV vaccine after the 3-dose series, when the first dose of HPV vaccine is given concomitantly with MenQuadfi vaccine and Tdap vaccine, compared to those when the first dose of HPV vaccine is given with Tdap vaccine only
   - *Secondary Endpoints:* Anti-HPV antibody concentrations (Type 6, 11, 16, 18) for Groups 3 and 4) at Day 0 and Day 30 after the 3rd dose of HPV vaccine.
   - *Secondary Hypothesis & Criteria for Success:* If the lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups is > 2/3 for each antigen, the inferiority assumption was rejected.

Observational Objective:
To describe the antibody titers against meningococcal serogroups (A, C, Y, and W) after MenQuadfi, Menveo, or MenQuadfi administered concomitantly with licensed vaccines (Tdap and HPV)
- *Observational Endpoint:*
  - Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenQuadfi or Menveo for Group 1, Group 2, and Group 3
- *Descriptive Analyses*

6.5.2 Design Overview

MET50 was a Phase 2 open-label study in adolescents 10 through 17 years of age in the US evaluating MenQuadfi compared to Menveo. For the purpose of this review memo, the primary importance of this study was to evaluate the interaction of MenQuadfi with TdaP (Adacel) and HPV-4 (Gardasil) vaccines which are routinely recommended for use in this age population. At the time of study conduct, the Advisory Committee on Immunization Practices recommended that adolescents receive Tdap vaccine at 11-12 years of age and HPV vaccine as a 3-dose series at 0, 2, and 6 months.

Subjects were randomized into 4 groups as follows (anticipated # of subjects):

- Group 1: MenQuadfi-1 dose
  - 500 subjects
- Group 2: Menveo-1 dose
  - 500 subjects
- Group 3: MenQuadfi-1 dose + TdaP (Adacel)-1dose + HPV-4 (Gardasil-4)-3 doses
  - 400 subjects
- Group 4: TdaP (Adacel)-1 dose + HPV-4 (Gardasil-4)-3 doses
  - 300 subjects

Clinical Reviewer Comment:
MET50 evaluated concomitant administration with HPV-4 (Gardasil) vaccine, not HPV-9 (Gardasil-9) vaccine, as the latter vaccine had not been licensed/marketed at the time of study conduct. CBER advised the applicant that description of the MET50 study design in the USPI for MenQuadfi would characterize the product evaluated in the trial.

The study design was open-label because of different vaccinations schedules across study groups. The following table includes the vaccination schedules for the 4 study groups.

Table 40: Study MET50- Vaccination Schedule

Group	Day 0, Visit 1	Day 60, Visit 3	Day 180, Visit 4
Group 1: MenQuadfi	MenQuadfi	N/A	N/A
Group 2: Menveo	Menveo	N/A	N/A
Group 3: MenQuadfi+Tdap+HPV4	MenQuadfi Tdap HPV4-1st dose	HPV4-2nd dose	HPV4-3rd dose
Group 4: Tdap+HPV4	Tdap HPV4-1st dose	HPV4-2nd dose	HPV4-3rd dose

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Table 3.1. N/A: Not applicable- indicates that no vaccines were administered at the visit.

6.5.3 Population

Inclusion (in summary): Healthy participants between 10 through 17 years of age; signed informed consent by parent or an assent form signed by subject; able to attend all visits.

Exclusion (in summary): Pregnant/lactating/childbearing potential who is not using an effective method of contraception/abstinence for 4 weeks; participation in another clinical trial within 4 wks; receipt of any other licensed vaccine within 4 weeks of any study vaccine dose (except flu vaccine-can be given within 2 weeks); prior vaccination with any meningococcal vaccine (ACWY); Tdap vaccine within prior 4 years; any prior HPV vaccine; receipt of blood (or any

products) therapy within 3 month or immunosuppressive, chemotherapy, radiation treatments within 6months or long term systemic corticosteroids within prior 3months; history of meningococcal infection (either clinical/serological/microbiologic confirmed); at risk for meningococcal infection during trial (persistent complement deficiency, anatomic/functional asplenia; travel to high endemic areas); known systemic hypersensitivity to vaccine components or other concomitant vaccines planned for study; GBS; congenital or acquired immunodeficiency; bleeding disorder; receipt of anticoagulants in 3 weeks; unable to give voluntary consent; alcohol or drug abuse/addiction; chronic illness (HIV, Hep B, Hep C); moderate or severe acute illness/ or febrile illness on day of vaccination; antibiotic within 72 hours; involved with study or family member involved in study.

6.5.4 Study Treatments or Agents Mandated by the Protocol

MenQuadfi (Sanofi Pasteur Inc): MenQuadfi: Meningococcal (Groups A, C, Y, W) Conjugate Vaccine

- Batch # UD16710
- Dose: single 0.5 mL intramuscular
- Composition:
  - Serogroups A, C, Y, W: 10 ug each meningococcal capsular polysaccharide
  - Tetanus toxoid protein carrier: (b) (4) ug
- Preparation: single-dose 0.5 ml vial

Menveo® (Formerly- Novartis Vaccines and Diagnostics, Now GSK): Meningococcal Oligosaccharide (Serogroups A, C, Y, and W) CRM_{197} Conjugate

- Commercial product was supplied by each site
- Dose: single 0.5 mL intramuscular
- Composition:
  - Serogroup A: 10 ug meningococcal capsular polysaccharide
  - Serogroups C, Y, W135: 5 ug each meningococcal capsular polysaccharide
  - CRM_{197} protein: 32.7 to 64.1 ug
- Preparation: 2 vials, lyophilized MenA component and MenCYW135 liquid components. A single dose after reconstitution was 0.5 mL.

Adacel®: (Sanofi Pasteur Limited, Toronto Ontario Canada): Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)

- Batch #U4825AA
- Dose: single 0.5mL dose in left deltoid muscle on Day 0 (Groups 3, 4)
- Composition:
  - Detoxified pertussis toxin (PT): 2.5 µg
  - Filamentous hemagglutinin (FHA): 5 µg
  - Pertactin (PRN): 3 µg
  - Fimbriae types 2 and 3 (FIM): 5 µg
- Preparation: Single-dose prefilled syringe, 0.5mL suspension

Gardasil®:(Merck & Co., Inc., Whitehouse Station, NJ, USA) Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant (HPV)

- Commercial product was supplied by the sites
- Dose: 3 doses of 0. 5 mL in left deltoid muscle on Day 0, day 60, Day 180 (Groups 3, 4)
- Composition:
  - HPV 6 L1 protein: 20 µg

  - HPV 11 L1 protein: 40 µg
  - HPV 16 L1 protein: 40 µg
  - HPV 18 L1 protein: 20 µg
- Preparation: Single dose vial, 0.5 mL suspension

6.5.5 Directions for Use

See prior section.

6.5.6 Sites and Centers

41 study sites in the United States.

6.5.7 Surveillance/Monitoring

Study Oversight:
Study oversight was provided by for all study sites by (b) (4) IRB.

Safety Monitoring:
- Previously described in Section 6.1.7

Immunogenicity Monitoring:
Serum bactericidal antibody (SBA) assays: Previously described in Section 6.1.7.
Anti-pertussis, anti-tetanus, anti-diphtheria assays were performed at Sanofi Pasteur, Inc.
Anti-HPV antibody assay were performed at (b) (4)

6.5.8 Endpoints and Criteria for Study Success

See Section 6.5.1

6.5.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculations: Planned enrollment for 1700 subjects, assuming 15% drop-out rate, would result in ~1445 subjects (425 evaluable subjects per treatment group) with 87% power to declare non-inferiority of Group 1 versus Group 2 based on A, C, Y, and W antibodies.

Subgroup Analyses:
There were no complementary or subgroup (subpopulation) analyses conducted as part of the analyses of this study.

Statistical Methods:
See Section 6.1.9

Protocol Amendments:
- Original protocol: version 2.0, dated 09 April 2014
- 4 amended protocols (latest version 6.0, dated 23 October 2017), noteworthy revisions across all protocol versions include:
  - Clarifications on the timing of study events and study procedures
  - Corrected the window for Visits 3 and 4 to comply with ACIP recommendations for HPV vaccination schedule
  - Revision of the non-inferiority margin for HPV assessment: the lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups was changed from ½ to

2/3, a more stringent equivalence margin at the request of CBER for consistency with current CBER recommendations

Significant Changes in the Conduct of the Study & Planned Analyses:

- After the final database lock, the definition of the (b) (4) seroresponse in the statistical analysis plan was found to be incorrect and was subsequently revised in June 2018.

6.5.10 Study Population and Disposition

A total of 1715 subjects were enrolled in Study MET50: the first subject was enrolled on 22 July 2014 and the last subject visit occurred on 02 October 2015.

6.5.10.1 Populations Enrolled/Analyzed

Relevant analysis populations: (see Section 6.1.10 for study population definitions)

- *Safety Analyses Set (SafAS)*
- *Full Analyses Set (FAS)*
- *Per-Protocol Analyses Set (PPAS)*
    - *PPAS1:* defined for accessing the ACWY and Tdap immune response data for all subjects after they had received vaccinations at Visit 1 and completed the 2nd blood draw collection.
    - *PPAS2:* defined for accessing the HPV immune response data for subjects in Group 3 and in Group 4 after they received the 3rd HPV vaccination at Visit 4 and completed the 3rd blood draw collection.

Protocol Deviations:
Previously defined in Section 6.1.10

6.5.10.1.1 Demographics
The demographic characteristics for each of the 4 study groups are shown in the table below.

Table 41: Study MET50- Demographic Characteristics of MenQuadfi-Group 1, Menveo-Group 2, MenQuadfi+Tdap+HPV-Group 3, Tdap+HPV-Group 4, Safety Analyses Set

Demographic Characteristic	**Group 1 N=503 X (%)**	**Group 2 N=501 X (%)**	**Group 3 N=392 X (%)**	**Group 4 N=296 X (%)**
M:F Sex Ratio %	243:260 48%:52%	272:229 54%:46%	201:191 51%:49%	155:141 52%:48%
Mean Age [SD]	11.4y [1.4y]	11.4y [1.4y]	11.3y[1.1y]	11.4y [1.4y]
Median Age	11.1y	11.1y	11.1y	11.1y
Age Range	10.0y - 18.0y	10.0y–18.0y	10.0y- 17.5y	10.0y-17.9y
Racial origin:	--	--	--	--
White	439 (87.3%)	451 (90.0%)	350 (89.3%)	258 (87.2%)
Black/A.A.	30 (6.0%)	22 (4.4)	15 (3.8%)	18 (6.1%)
Mixed Origin	26 (5.2%)	24 (4.8%)	20 (5.1%)	12 (4.1%)
Asian	4 (0.8%)	2 (0.4%)	1 (0.3%)	0
N.Hawaiian/P.I	1 (0.2%)	2 (0.4%)	2 (0.5%)	5 (1.7%)
Am.Indian/A.N	3 (0.6%)	0	4 (1.0%)	1 (0.3%)
Ethnicity:	--	--	--	--
Hispanic/Latino	88 (17.5%)	95 (19.0%)	83 (21.2%)	60 (20.3%)
Not H/L	412 (81.9%)	404 (80.6%)	309 (78.8%)	236 (79.7%)

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Table 4.5. For Sex; Racial Origin, and Ethnicity: X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects for the Safety Analyses Set (subjects who

received 1 dose and had any safety data available). Sex Ratio M:F indicates Male:Female. For Age Groups: y indicates years. Racial origin: Asian, Black/A.I: Black/African American; Am.Indian/A.N: American Indian/Alaska Native; N.Hawaiian/P.I.: Native Hawaiian/Pacific Islander; missing origin not listed (accounted for 1 subject in Group 1 only). Ethnicity: Hispanic/Latina; Not H/L: Not Hispanic/Latino.

The demographic characteristics across the 4 study groups were generally similar with an overall sex ratio of 51.5% males and 48.5% females. The median age was 11.1 years, with an age range between 10 years to 11.9 years of age. Most subjects were of White racial origin (~88.5%), followed by Black/African American racial origin (5%), and mixed origin (4.8%). There were few subjects (<25 subjects total) representative of other racial groups. Most subjects were not of Hispanic/Latino ethnic origin, while 19.3% were of Hispanic/Latino origin.

Reviewer Comment: *The overall demographic characteristics across study groups were similar.*

6.5.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
No additional characterizations of the enrolled population were considered necessary.

6.5.10.1.3 Subject Disposition

Table 42: Study MET50- Demographic Characteristics of MenQuadfi-Group 1, Menveo-Group 2, MenQuadfi+Tdap+HPV-Group 3, Tdap+HPV-Group 4, All Randomized Subjects

Population	Group 1 N=505 X (%)	Group 2 N=507 X (%)	Group 3 N=403 X (%)	Group 4 N=300 X (%)
Enrolled	505 (100%)	507 (100%)	403 (100%)	300 (100%)
Vaccinated◊ at Visit 1 Visit 3 Visit 4	 499 (98.8%) NA	 504 (99.4%) NA	 392 (97.3%) 383 (95%) 377 (93.5%)	 297 (99.0%) 282 (94.0%) 273 (91.0%)
Completed Study	495 (98.0%)	500 (98.6%)	376 (93.3%)	270 (90.0%)
Safety Analysis Set	503 (99.6%)	501 (98.8%)	392 (97.3%)	296 (98.7%)
Full Analysis Set	492 (97.4%)	499 (98.4%)	388 (96.3%)	286 (95.3%)
Per Protocol Analyses Set 1*	463 (91.7%)	464 (91.5%)	360 (89.3%)	263 (87.7%)
PPAS1 ≥1 Prot. Deviation	42 (8.3%)	43 (8.5%)	43 (10.7%)	37 (12.3%))
Per Protocol Analyses Set 2**	N/A	N/A	242 (60%)	164 (54.7%)
PPAS2 ≥1 Prot. Deviation	N/A	N/A	161 (40.0%)	136 (45.3%)

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Table 4.1, 4.2, and 4.3.N indicates number of subjects enrolled. X indicates number of subjects fulfilling the item followed by (%). N: total number of subjects enrolled. ≥1 Prot. Deviation: subjects with one or more protocol deviations. Vaccinated◊: Groups 1 & 2 include one vaccination visit at Visit 1, Groups 3 & 4 include three vaccinations visits at Visit 1, Visit 3 and Visit 4. Per Protocol Analyses Set 1*: includes subjects who had immune responses assessed for A,C,Y and W and Tdap after completing the 1st blood sample collection. PPAS1: Per Protocol Analyses Set 1. Per Protocol Analyses Set 2: includes subjects who had HPV immune responses assessed after completing the 3rd blood sample collection. PPAS2: Per Protocol Analyses Set 2. N/A: not applicable

The list of pre-specified protocol deviations for Study MET50 was provided in Section 6.5.10.1 of this review memo. Across all 4 study groups, 9.5% of subjects were excluded from Per Protocol Analyses Set 1. The majority of these deviations were due to Visit 2 blood sample either not provided or not provided in the appropriate time window, including 4.6% of subjects in Group 1 (23 subjects), 4.9% of subjects in Group 2 (25 subjects), 4.7% of subjects in Group 3 (19 subjects), and 7.7% of subjects in Group 4 (23 subjects). Across Study Groups 3 and 4, 42.2% of subjects experienced at least 1 protocol deviation. The majority of which were associated with the Visit 5 blood sample either not provided or not provided in the appropriate time window including 25.6% of subjects in Group 3 (103 subjects) and 28.3% of subjects in Group 4 (85 subjects). The higher proportion of Visit 5 blood draw protocol deviation likely represents the latter time point in the study for this blood draw, which was at Visit 210 (one-month post dose 3 of HPV4 vaccine), compared to Visit 2 blood draw which was earlier at Day 30 (one-month after the 1st dose of study vaccines for all subjects).

Clinical Reviewer Comment
The PPAS2 was used to evaluate the HPV immune responses after the 3rd blood sample collection. A large proportion of participants were excluded from the PPAS2 which included only 60% of enrolled participants in Group 3, and 54.7% of enrolled participants in Group 4. The large proportion of non-evaluable participants (40-45%) limits the reviewer's ability to draw definitive conclusions about the HPV responses.

6.5.11 Efficacy Analyses

Efficacy data were not collected in this trial.

6.5.11.1 Analyses of Primary Endpoint

Primary Analyses: hSBA Seroresponse Rates

The primary immunogenicity analyses evaluated the hSBA serogroup specific seroresponse rates[32] at Day 30 for the MenQuadfi group (Group 1) compared to the Menveo group (Group 2). Non-inferiority of the immune responses was based on a lower limit of the 2-sided 95% CI of the difference between the 2 percentages across groups who achieved seroresponse was > -10% for each serogroup. The following table provides the hSBA seroresponse rates [95% CI] based on the CBER requested seroresponse definition at Day 30 for the MenQuadfi group compared to the Menveo group for the Per Protocol Analyses Set, as well as the differences in seroresponse rates [95%CI] across groups.[33] The table also includes the results of the observational analyses evaluating the antibody GMTs [95% CI] for each meningococcal serogroup for each study group at Day 30.

32 hSBA seroresponse definition: pre-vaccination titer < 1:8, then post-vaccination titer must be ≥ 1:16; pre-vaccination titer ≥1:8, then post-vaccination titer must be at least 4-fold greater than the pre-vaccination titer
33 Revised primary and secondary analyses provided to STN 125701, Am.17.

Table 43: Study MET50 - hSBA Seroresponse Rates & hSBA GMTs, MenQuadfi-Group 1 vs Menveo-Group 2, PPAS1

Serogroup	Group 1 (N=462-463) %Seroresponse [95% CI] GMTs [95% CI]	Group 2 (N=463-464) %Seroresponse [95%CI] GMTs [95% CI]	% Difference [95% CI] -
A	70.2 % [65.8, 74.3] 44.1 [39.2, 49.6]	60.3% [55.7, 64.8] 35.2[30.3, 41.0]	9.8% [**3.7**, 15.9] --
C	96.1% [93.9, 97.7] 387 [329, 456]	61.6% [57.0, 66.0] 51.4 [41.2, 64.2]	34.5% [**29.7**, 39.3] --
Y	91.1% [88.2, 93.6] 75.7 [66.2, 86.5]	66.8% [62.3, 71.1] 27.6 [23.8, 32.1]	24.3% [**19.2**, 29.3] -
W	84.2% [80.6, 87.4] 86.9 [77.8, 97.0]	56.0% [51.4, 60.6] 36.0 [31.5,41.0]	28.2% [**22.5**, 33.7 --

Source: Adapted from STN 125701.0.17, MET50 (response to Information Request sent October 11, 2019) for hSBA seroresponse rates; STN 125701.0, MET50 CSR Table 5.10 for GMTs. hSBA: serum bactericidal antibody assay using human sera, PPAS: Per Protocol Analyses Set 1. N: #subjects in PPAS1. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menveo). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers

The non-inferiority criteria were met for all 4 serogroups.

Clinical Reviewer Comment:

The hSBA seroresponse rates observed in adolescents following MenQuadfi vaccination in Study MET50 are comparable to those observed following MenQuadfi vaccination in adolescents in Study MET43 (see Section 6.1.11.2).

6.5.11.2 Analyses of Secondary Endpoints

Secondary Analyses #1:

Secondary objective #1 evaluated the antibody responses to the antigens present in MenQuadfi when it was given concomitantly with Tdap and HPV vaccines (Group 3), compared to those when MenQuadfi was given alone (Group 1). Non-inferiority of the meningococcal immune responses was based on a lower limit of the lower limit of the 2-sided 95% CI of the difference between the two percentages across groups (Group 3- Group 1) who achieved seroresponse > -10% for each serogroup. The table also includes the results of the observational analyses evaluating the antibody GMTs [95% CI] for each meningococcal serogroup for each study group at Day 30.

Table 44: Study MET50 - hSBA Seroresponse Rates & hSBA GMTs, MenQuadfi-Group 1 vs MenQuadfi+Tdap+HPV-Group 3, PPAS1

Serogroup	Group 1 N=462-463 %Seroresponse [95% CI] GMTs [95% CI]	Group 3 N=360 %Seroresponse [95% CI] GMTs [95% CI]	% Difference [95% CI] -
A	70.2% [65.8, 74.3] 44.1 [39.2, 49.6]	73.6% [68.7, 78.1] 47.9 [41.7, 55.0]	3.4% [-2.8, 9.5] --
C	96.1% [93.9, 97.7] 387 [329, 456]	96.4% [93.9, 98.1] 335 [280, 399]	0.3% [-2.6, 2.9] --
Y	91.1% [88.2, 93.6] 75.7 [66.2. 86.5]	90.6% [87.1, 93.4] 77.3 [66.5, 89.9]	-0.6% [-4.7, 3.4] -
W	84.2% [80.6, 87.4] 86.9 [77.8, 97.0]	82.2% [77.9, 86.0] 91.0 [80.2. 103]	-2.0% [-7.3, 3.1] --

Source: Adapted from STN 125701.0.17, MET50 (response to Information Request sent October 11, 2019) for hSBA seroresponse rates; STN 125701.0, MET50 CSR Table 5.10 for GMTs. hSBA: serum bactericidal antibody assay using human sera, PPAS1: Per Protocol Analyses Set 1. N: #subjects in PPAS1. Difference %: % difference in hSBA seroresponse rates across groups (MenQuadfi -Menveo). Bold numbers indicate lower limits of 95% CI of the difference in seroresponse rates across study groups for each serogroup. GMTs: hSBA Geometric Mean Titers

Non-inferiority of MenQuadfi administered concomitantly with Tdap and HPV vaccines compared to MenQuadfi administered alone was demonstrated for the meningococcal antibody responses for each serogroup.

Secondary Analyses #2:
Secondary objective #2 evaluated the antibody responses to the antigens present in Tdap vaccine, when Tdap vaccine is administered concomitantly with both HPV vaccine and MenQuadfi (Group 3), compared to the antibody responses when Tdap vaccine and HPV vaccine are co-administered only (Group 4).

Pertussis Antigens:
Non-inferiority of the immune responses to each pertussis antigens (PT, FHA, PRN, FIM) was determined if the lower limit of the 2-sided 95% CI of the ratio of GMCs (Group 3/Group 4) was >2/3 (0.667). The following table includes the GMC point estimates for each group, and the ratio of GMCs (Groups 3/Group4) with [95%CI] for each of the pertussis antigens.

Table 45: Study MET50 Secondary Objective – GMCs of PT, FHA, PRN, and FIM Pertussis Antigens) for MenQuadfi+Tdap+HPV Group 3 and Tdap+HPV Group 4, and GMC Ratio Across Groups (Group3/Group4), PPAS1

Pertussis Antigen	Group 3 (N=339-360) GMC [95% CI]	Group 4 (N=258-263) GMC [95% CI]	GMC Ratio (Group 3/Group 4) [95% CI]
PT	37.5 [33.8, 41.7]	44.4 [39.5, 49.9]	0.845 [**0.722**, 0.990]
FHA	180 [168, 194]	242 [218, 268]	0.746 [**0.661**, 0.842]
PRN	200 [177, 225]	265 [231, 304]	0.753 [**0.627**, 0.903]
FIM	339 [285, 403]	499 [414, 601]	0.679 [**0.525**, 0.878]

Source: Adapted from STN 125701.0, Study MET50 CSR, Table 5.3, PPAS1 Per Protocol Analyses Set 1 N: #subjects in PPAS1

The non-inferiority criteria were not met for three pertussis antigens (FHA, PRN and FIM) with each of the lower limits of the 95% CI for the GMC ratio <0.667, though for FHA and PRN they were only marginally lower. In addition, the GMC point estimates for these three antigens were lower in concomitant vaccination group (Group 3) compared to Group 4, with 95% CI that did not overlap. For PT antigen, the GMCs in Group 3 and Group 4 were comparable with overlapping 95% CIs and the lower limit of the 95% CI for the GMC ratio >0.667.

An additional (observational) immunogenicity analysis evaluated the proportion of subjects with a vaccine response[34] against pertussis antigens at Day 30 post-vaccination compared to baseline for each of the study groups. The following table provides the proportion of subjects (%) with

34 Pertussis antigen vaccine response definitions for PT, PRN and FIM: vaccine response for baseline concentration < 16, then post-vaccination concentration ≥ 4x baseline, and for baseline concentration ≥ 16, then post-vaccination concentration ≥ 2 x baseline. Pertussis antigen vaccine response definition for FHA: vaccine response for baseline concentration < 12, then post-vaccination concentration ≥ 4 x baseline, or baseline concentration ≥ 12, then post-vaccination concentration ≥ 2 x baseline

vaccine response to each pertussis antigen for each study group using the Per Protocol Analyses Set.

Table 46: Study MET50 – Proportion of Participants with Pertussis Vaccine Response for MenQuadfi+Tdap+HPV Group 3 and Tdap+HPV Group 4, PPAS1

Pertussis Antigen	Group 3 (N=315-360)) % Response [95% CI]	Group 4 (N=250-263) % Response [95% CI]
PT	82.2% [77.5, 86.3]	85.2% [80.1, 89.4]
FHA	92.1% [88.8, 94.7]	89.7% [85.4, 93.1]
PRN	95.6% [92.9, 97.4]	97.0% [94.1, 98.7]
FIM	93.4% [90.2, 95.8]	96.8% [93.8, 98.6]

Source: Adapted from STN 125701.0, Study MET50 CSR, Table 5.14, PPAS1 Per Protocol Analyses Set 1. N: #subjects in PPAS1

The proportion of participants in each study group that demonstrated vaccine response to each pertussis antigens (PT, FHA, PRN, and FIM) were similar with 95% CIs that overlapped.

Reviewer Comment:
The immune responses (GMCs) to pertussis antigens when Tdap and HPV vaccines were administered concomitantly with MenQuadfi were lower for 3 of the 4 pertussis antigens (FHA, PRN, FIM) than when these two routinely administered adolescent vaccines were not concomitantly administered with MenQuadfi. Because a serologic correlate of protection for pertussis antigens have not been established, it is unclear from these findings if concomitant administration will result in increased susceptibility to pertussis infection. The reviewer recommends that these results are described in the USPI.

The additional exploratory pertussis analyses demonstrated comparable vaccine response rates to each pertussis antigen across study groups, which provide some assurance of adequate pertussis immune responses when MenQuadfi and Tdap vaccines are co-administered.

Tetanus and Diphtheria Antigens:
Non-inferiority of the immune responses to the tetanus and diphtheria antigens in Group 3 participants compared to Group 4 participants were determined if the lower limits of the 95% CI of the difference between the proportion of participants who achieved ≥1.0 IU/ml anti-tetanus and anti-diphtheria antibody concentrations were > -10%. The following list includes the proportion (%) of subjects who achieve antibody concentration ≥1.0 IU/ml with 95% CI for each antigen
and the % difference in rates across groups (Group 3- Group 4) with 95% CIs.
(n= # subjects with valid serology results)

- Diphtheria antigen
  - Group 3: 97.8% [95.7, 99.0] n=360
  - Group 4: 98.9% [96.7, 99.8] n=263
  - % difference: -1.1% **[-3.3,** 1.3]
- Tetanus antigen:
  - Group 3: 99.7% [98.5, 100.0] n=360
  - Group 4: 99.6% [97.9, 100.0] n=360
  - % difference: 0.1 **[-1.2,** 1.9]

The lower limits of the 95% CI were greater than -10% for each antigen (in bold above), therefore the non-inferiority criteria were met for both tetanus and diphtheria antigens when Tdap and HPV vaccines are administered with MenQuadfi compared to when they are not.

Secondary Analyses #3
Secondary objective #3 evaluated the antibody responses to the antigens present in HPV vaccine after the 3-dose series, when the first dose of HPV vaccine is given concomitantly with MenQuadfi and Tdap vaccines, compared to the antibody responses when the first dose of HPV vaccine is given with Tdap vaccine only. The non-inferiority criteria for success for each HPV antigen was determined if the lower limit of the 2-sided 95% CI of the GMTs ratio (Group 3/Group 4) across groups was >2/3 (0.667) for each antigen. The following list provides the GMT ratio (Group 3/Group 4) with the [95% CI (lower bound in bold)] by HPV antigen for the PPAS2.

Table 47: Study MET50 – Comparison of GMTs of HPV at Day 210 for MenQuadfi +Tdap+HPV-Group 3 and Tdap+HPV-Group 4, and GMT Ratio Across Groups, PPAS2

HPV Type	Group 3 (N=242) GMT	Group 4 (N=164) GMT	GMT Ratio (Group 3/Group 4) [95% CI]
6	800	800	1.00 [0.758, 1.320]
11	1492	1402	1.06 [0.861, 1.316]
16	6002	6395	0.939 [0.727, 1.212]
18	1271	1118	1.14 [0.886, 1.458]

Source: Adapted from STN 125701.0, Study MET50 CSR, Table 5.5, PPAS: Per Protocol Analyses Set. N: #subjects in PPAS2

The lower limits of the 95% CI for the GMT ratios across groups were >0.667 for each antigen, therefore the non-inferiority criteria for the immune responses to HPV vaccine when co-administered with MenQuadfi were met.

6.5.11.3 Subpopulation Analyses

Subgroup analyses were not provided for this study, however the results of subgroup analyses for Study MET43, which also evaluated a single dose of MenQuadfi in adolescents are provided in Section 6.1.11.3. No differences were observed in the immunogenicity results for Study MET43 based on age, race, and gender.

Reviewer Comment:
The subgroup analyses for Study MET43 are considered sufficient to assess differences in MenQuadfi immune responses in adolescents based on age, sex, and gender. There were no observed differences based on these analyses.

6.5.11.4 Dropouts and/or Discontinuations

Missing immunogenicity and safety data were not replaced.

6.5.11.5 Exploratory and Post Hoc Analyses

The post-hoc analyses of the primary immunogenicity objectives included the CBER requested seroresponse definitions and are included in Section 6.5.11.1 above.

6.5.12 Safety Analyses

6.5.12.1 Methods

Safety Analyses Set (SafAS) and the duration of adverse event safety monitoring were previously defined in this memo (Section 6.1.12.1).

6.5.12.2 Overview of Adverse Events

Table 48: Study MET50-Safety Overview: Proportion of Subjects Reporting an Adverse Event Following Single Dose Vaccination, MenQuadfi-Group 1, Menveo-Group 2, MenQuadfi+Tdap+HPV-Group 3, Tdap+HPV-Group 4, SafAS

AE Type: Monitoring Period*	Group 1 (N=496-503) %	Group 2 (N=492-501) %	Group 3 (N=388-392) %	Group 4 (N=296) %
Immediate AE: 30 minutes	0.6%	0.2%	0.8%	1.0%
Solicited Local: 30 days @ MenQuadfi or Menveo injection site	46.6%	45.7%	N/A	N/A
Solicited Local: 30 days @Tdap injection site	N/A	N/A	74.2%	73.7%
Solicited Local: 30days @HPV injection site	N/A	N/A	74.2%	71.3%
Solicited Systemic: 30 days	52.0%	51.0%	70.6%	65.9%
Unsolicited AE: 30 days	23.9%	27.3%	27.6%	23.6%
AEs leading to w/d: 30 days	0	0	0	0
MAAEs-1st: 1st 30 days*	8.5%	8.6%	11.5%	6.4%
MAAEs-2nd: Next 5 months**	23.3%	27.7%	29.8%	24.3%
SAEs: 6 months	0.8%	0.8%	1.0%	1.4%
Deaths: 6 months	0	0	0	0

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Table 6.1. SafAS: Safety Analyses Set. *Monitoring period: time interval that the relevant type of AE was monitored for postvaccination. x subjects: #subjects who experienced the solicited event; n: #subjects with available data for relevant endpoint, N= #subjects in SafAS, AE: adverse event. AEs leading to w/d: adverse events leading to study withdrawal. MAAEs: Medically attended adverse events. *MAAEs-1st: collected for 1st 30 day postvaccination (Visit 1 to Visit 2). **MAAEs-2nd:collected from Visit 2 to the 6 month follow-up phone call (5 months total). SAEs: serious adverse events. N/A: data not applicable

For any type of AE, the rates were similar for Group 1 (MenQuadfi) and Group 2 (Menveo). When MenQuadfi was concomitantly administered with TdaP and HPV vaccines (Group 3), the rates of solicited systemic reactions were higher than when MenQuadfi was administered alone (Group 1), but comparable to the rates observed when TdaP and HPV were administered

together (Group 4). The rates of all other types of AEs were comparable across all 4 study groups.

Solicited Adverse Reactions: 7 days Post-Vaccination
The following tables includes the percentage of participants who reported any and grade 3 solicited reactions across each study group: Group 1 (MenQuadfi), Group 2 (Menveo), Group 3 (Tdap+HPV+MenQuadfi), and Group 4 (Tdap+HPV). The (local) injection site reactions are reported by vaccine administered.

Table 49: Study MET50- Percentage of Participants with Any & Grade 3 Solicited Reactions (Local and Systemic) 7 Days Postvaccination, MenQuadfi-Group 1, Menveo-Group 2, MenQuadfi+Tdap+HPV-Group 3, Tdap+HPV-Group 4, SafAS

AE Type: Monitoring Period*	Group 1 (N=496-503) %	Group 2 (N=492-501) %	Group 3 (N=388-392) %	Group 4 (N=296) %
Local (Injection Site)	--	--	--	--
MenQuadfi/Menveo	--	--	--	--
Pain:	--	--	--	--
Any	45.2%	42.5%	47.2%	N/A
Grade 3*	1.4%	1.0%	2.3%	N/A
Swelling	--	--	--	--
Any	5.4%	6.5%	4.4%	N/A
Grade 3(>100mm)	0.2%	0.4%	0.3%	N/A
Erythema:	--	--	--	--
Any	5.0%	7.5%	3.9%	N/A
Grade 3 (>100mm)	0.4%	1.2%	0.5%	N/A
Tdap	--	--	--	--
Pain:	--	--	--	--
Any	N/A	N/A	73.7%	73.0%
Grade 3*	N/A	N/A	6.2%	3.8%
Swelling	--	--	--	--
Any	N/A	N/A	6.2%	6.9%
Grade 3(>100mm)	N/A	N/A	0.3	1.4%
Erythema:	--	--	--	--
Any	N/A	N/A	7.2%	4.8%
Grade 3(>100mm)	N/A	N/A	0.8%	0.7%
HPV	--	--	--	--
Pain:	--	--	--	--
Any	N/A	N/A	74.2%	69.6%
Grade 3*	N/A	N/A	6.4%	4.5%
Swelling	--	--	--	--
Any	N/A	N/A	6.7%	8.0%
Grade 3(>100mm)	N/A	N/A	0.5%	1.4%
Erythema:	--	--	--	--
Any	N/A	N/A	8.0%	5.5%
Grade 3(>100mm)	N/A	N/A	1.0%	1.0%
Systemic	--	--	--	--
Myalgia:	--	--	--	--
Any	35.3%	35.2%	61.3%	55.4%
Grade 3*	1.6%	1.8%	4.6%	3.8%
Headache:	--	--	--	--
Any	30.2%	30.9%	33.8%	29.0%
Grade 3*	1.8%	1.8%	2.8%	1.7%
Malaise:	--	--	--	--
Any	26.0%	26.4%	29.1%	27.9%
Grade 3*	2.2%	2.8%	2.6%	1.7%
Fever:	--	--	--	--
Any (≥38.0C)	1.4%	1.2%	1.6%	0.7%
Grade 3 (≥ 39.0C)	0.4%	0.6%	0.5%	0.4%

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Tables 6.3, Table 9.19. SafAS: Safety Analyses Set. Injection site reactions are reported by vaccine administered: MenQuadfi or Menveo; Tdap, or HPV. x subjects: # subjects who experienced the solicited event. #n: #subjects with available data for relevant endpoint, N= #subjects in SafAS. *Grade 3 (pain, myalgia, headache, malaise): significant, prevents daily activity. N/A: data not applicable

When MenQuadfi was administered alone (Group 1) or with Tdap and HPV vaccines (Groups 3), the proportion of participants reporting local reactions at the MenQuadfi injection site were comparable. The rates of myalgia were higher when all 3 vaccines were co-administered (Group 3, 61.3%) compared to when MenQuadfi was administered alone (Group 1, 35.3%), but similar to when TdaP and HPV vaccines were co-administered together (Group 4, 55.4%)

> **Reviewer Comment:** *The rates of solicited systemic reaction were when MenQuadfi, TdaP and HPV vaccines were co-administered were generally similar to solicited systemic reaction rates when Tdap and HPV were co-administered.*

Immediate AEs within 30 minutes Postvaccination
In Group 3 (MenQuadfi, Tdap and HPV vaccines) there were 3 subjects who reported the following immediate unsolicited AE: syncope (Grade 3) resulting in a fall with head/neck injury, vertigo (Grade 2), and vasovagal syncope (Grade 1). All three subjects recovered, and the events were reported by the investigators as related to study vaccines (MenQuadfi, Tdap, and HPV vaccines). There were similar reports of immediate AEs in other study groups, including syncope and dizziness.

Reviewer Comment: *In the general population reports of syncope or fainting have been observed and well-documented in adolescents following the administration of vaccines. Based on the information provided, the reported immediate AEs (syncope, vertigo) are likely related to the administration of study vaccines.*

Unsolicited AEs (Non-Serious): 30 days Postvaccination
The rates of unsolicited, non-serious AEs within 30 days postvaccination were similar across all four study groups (~23.6% to 27.6%). Unsolicited AE were most frequently reported under the SOC Infections/Infestations (7.2% in Group 1, 8.2% in Group 3). The most frequently reported unsolicited AE was upper respiratory tract infection (1.2% in Group 1, 1.8% in Group 3). Most unsolicited AEs were reported as Grade 1 or Grade 2 in severity. The proportion of participants reporting Grade 3 unsolicited AEs were comparable across groups, 3.0% in Group 1, 4.2% in Group 2, 4.8% in Group 3 and 4.1% in Group 4. There were 19 MenQuadfi (Group 3) participants who reported 24 unsolicited AEs (Grade 3), most of which were classified under the SOC Infection/Infestation.

Medically Attended Adverse Events: Through 6 Months Postvaccination
MAAEs were previously defined in this memo (Section 6.1.12.2). The proportion of participants who reported MAAEs within 30 days postvaccination were 11.5% in Group 3, 8.5% in Group 1, 8.6% in Group 2, and 6.4% in Group 4. The MAAEs after the 2nd visit during the follow-up period were comparable across all 4 study groups. For Group 3 participants, the majority of MAAEs were reported under the SOC Infections/Infestations SOC and were Grade 1 or 2 in intensity.

6.5.12.3 Deaths

There were no deaths reported in this study.

6.5.12.4 Nonfatal Serious Adverse Events

There were 17 SAEs (16 participants) reported during the study including 4 SAEs (4 participants) during the first 30 days postvaccination. None of the SAEs were considered related to study vaccination by the investigator.

In Group 1 (MenQuadfi) there were 4 SAEs (4 participants) during the study, including 2 SAEs (2 participants) in the first 30 days postvaccination. The SAEs during the study for this group included Type 1 diabetes mellitus uncontrolled without complications, fecal impaction, mycoplasma mucositis, and seizure. All 4 SAEs were not considered related to study vaccines.

In Group 3 (MenQuadfi+Tdap+HPV) there were 5 SAEs (4 participants) who reported the following SAEs during the study:

Subject (b) (6) *: Acute Asthma Exacerbation*
10-year female was admitted to the hospital due to acute asthma exacerbation associated with a recent history of a viral infection 38 days following study vaccination (MenQuadfi +Tdap+HPV). She improved after medical management of her symptoms, was discharged the following day, and full recovered.

Subject (b) (6) *: Nonautoimmune Hypothyroidism*
12-year female with medical history significant for Down's Syndrome developed hypothyroidism ~7 ½ months after MenQuadfi+Tdap+HPV vaccinations and 1 ½ months after the 2nd HPV vaccine dose. Subsequent work-up to evaluate for autoimmune disorders showed that the hypothyroidism was non-autoimmune. The condition was ongoing and required treated with levothyroxine sodium.

Subject (b) (6) *: Suicidal Ideations*
12-years old female with medical history significant for depression, sexual assault, and self-harm behavior developed suicidal ideations 73 days following vaccination with MenQuadfi +Tdap+HPV and 17 days following the 2nd dose of HPV vaccine. After an evaluation in the Emergency Department, the participant discharged and managed outpatient.

Subject (b) (6) *: Seizure*
12-year old female with medical history significant for autism, Attention Deficit Hyperactivity Disorder (ADHD), and seizure disorder experienced a grand mal seizure 253 days after MenQuadfi+Tdap+HPV vaccinations and 42 days after the 3rd HPV vaccine dose. The participant was seen by her physician who adjusted her anti-epileptic medication dose, and fully recovered.

Reviewer Comment: *In the reviewer's opinion, none of the reported SAEs were related to study vaccines.*

6.5.12.5 Adverse Events of Special Interest (AESI)

Please see Section 8 for an overview of AESI across all studies.

6.5.12.6 Clinical Test Results

Not applicable

6.5.12.7 Dropouts and/or Discontinuations

Across all 4 study groups, there were a total of 1641 (95.7%) who completed the study and 74 subjects (4.3%) who did not complete the study. There were no reports of study discontinuations due to SAEs or other AEs. The subjects who prematurely withdrew from the study are listed below by group and by reason:

Table 50: Disposition-MenQuadfi-Group 1, Menveo-Group 2, MenQuadfi+Tdap+HPV-Group 3, Tdap+HPV-Group 4

Population	Group 1 (N=505) %	Group 2 (N=507) %	Group 3 (N=403) %	Group 4 (N=300) %
Enrolled	505 (100%)	507 (100%)	403 (100%)	300 (100%)
Vaccinated	499 (98.8%)	504 (99.4%)	392 (97.3%)	297 (99.0%)
Completed Study	495 (98.0%)	500 (98.6%)	376 (93.3%)	270 (90.0%)
Withdrawal due to	--	--	--	--
Voluntary W/d	5 (1.0%)	3 (0.6%)	12 (3.0%)	13 (4.3%)
Lost to F/up	2 (0.4%)	1 (0.2%)	9 (2.2%)	10 (3.3%)
Non-compliance	3 (0.6%)	3 (0.6%)	6 (1.5%)	7 (2.3%)
AE/SAE	0	0	0	0

Source: Adapted from STN 125701.0, MET50 Clinical Study Report, Tables 4.1

Reviewer Comment: *There were no reports of study discontinuations due to adverse events. In Group 3 (MenQuadfi+Tdap+HPV), the most common reasons for withdrawal were voluntary study withdrawal and lost-to-follow-up, which occurred at a similar rate as those observed in Group 4 (Tdap+HPV).*

6.5.13 Study Summary and Conclusions

Study MET50 demonstrated in adolescents 10 years through 17 years of age that, based on hSBA response rates, MenQuadfi was immunologically non-inferior to Menveo, a US-licensed meningococcal A, C, Y, W conjugate vaccine. The data generated from the study support both the effectiveness and safety of MenQuadfi in adolescents, for whom the ACIP recommends routine vaccination (primary dose at 11 to 12 years of age). MET50 also evaluated for immune non-interference when MenQuadfi was administered concomitantly with Tdap vaccine and HPV Quadrivalent vaccine in adolescents. When administered concomitantly, lack of immune interference was demonstrated for all 4 meningococcal serogroups included in MenQuadfi and for the diphtheria, tetanus, HPV (Types 6, 11, 16, 18) antigens included in Tdap and HPV vaccines. Anti-pertussis GMC responses were non-inferior for the PT antigen, but did not meet non-inferiority for the FHA, PRN, and FIM antigens. The clinical relevance of the diminished responses to the FHA, PRN, and FIM antigens is unknown. The reviewer recommends inclusion of data pertaining to the immune responses to pertussis analyses in the package insert.

6.6 Trial #6 (Study MET44)

NCT01732627
Phase II, randomized, open-label (the laboratory technicians were blinded to group assignment), multi-center study in adults ≥ 56 years of age in the US

Study Overview
Phase 2 Study MET44 was a randomized open-label trial[35] that described the immunogenicity and safety of MenQuadfi compared to Menomune in 301 meningococcal vaccine-naïve adults 56 years of age and older. The study participants were randomized 2:1 to MenQuadfi group (201) or Menomune group (100), and enrollment was stratified by age into two cohorts (56 through 64 years and ≥65 years). All participants received a single vaccination dose; immunogenicity

35 Open label design due to different routes of administration for each vaccine: MenQuadfi intramuscular, Menomune subcutaneous

assessments were at baseline Day 0 and Day 30 (+14 days) post-vaccination; and safety data were collected from Day 0 to Day 30 (+14 days) post-vaccination.

Reviewer Comment*: MET44 was the applicant's first study to describe the immunogenicity and safety of MenQuadfi in adults 56 years of age and older compared to a US-licensed quadrivalent meningococcal polysaccharide vaccine.*

Study Objectives:

- To describe the antibody responses to meningococcal serogroups A, C, Y, and W135, measured by serum bactericidal assay using human complement (hSBA) induced by a single dose of MenQuadfi or Menomune in participants 56 years of age and older[36]
    - *Endpoints*: hSBA seroresponse rates[37] for each serogroup at Day 30 (+14 days) postvaccination
- To describe the safety profile of a single dose of MenQuadfi or Menomune in participants 56 years of age and older

Study Results:

MenQuadfi recipients were between the age of 56.0 and 86.8 years; Menomune recipient were between the age of 56.2 and 88.9 years. The Per Protocol Analyses Set that was used to describe the primary analyses included 195 Menquadfi recipients and 94 Menomune recipients. The proportion of participants who achieved hSBA seroresponse at Day 30 across treatment groups were as follows by serogroup:

- A: MenQuadfi 65.1%, Menomune 46.8%
- C: MenQuadfi 70.8%, Menomune 59.6%
- Y: MenQuadfi 75.4%, Menomune 48.9%
- W: MenQuadfi 74.4%, Menomune 55.3%

As noted above, the hSBA seroresponse rates following MenQuadfi vaccination were numerically higher than those following Menomune vaccination. The hSBA seroresponse rates in the younger age cohorts (56 through 64 years) were higher than those observed in the older age cohort (≥65 years) in both treatment groups. The safety analyses set included 199 MenQuadfi recipients compared to 100 Menomune recipients. The rates of solicited reactions were 57.8% in the MenQuadfi group compared to 53.0% in the Menomune group, with comparable rates of injection site and systemic reactions across study groups. The rates of unsolicited AE were 20.6% in the MenQuadfi group compared to 17.0% in the Menomune group. There were no deaths, SAEs, or significant AEs reported in MET44.

Reviewer Comment*: The MET44 safety and immunogenicity data in ~200 MenQuadfi recipients (age range: 56.0 through 86.8 years) support the overall findings from the applicant's Phase 3 study in elderly adults (MET49), which included safety and immunogenicity data in 450 MenQuadfi recipients (age range: 56 through 97 years). Please see Section 6.3 of this clinical memo for a review of MET49 clinical data.*

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36 Antibody responses measured by serum bactericidal assay using (b) (4) were also evaluated in the primary analyses. (b) (4) data will not be presented in this review.

37 Seroresponse definition: if titer is < 1:8 at baseline, a post-vaccination titer ≥ 1:8; or if titer is ≥ 1:8 at baseline, a ≥ 4-fold increase at post-vaccination

6.7 Trial #7 (Study MET28)

Phase I Study[38] of the Safety and Immunogenicity of a Quadrivalent Meningococcal (A, C, Y and W-135) Polysaccharide Tetanus Protein Conjugate Vaccine in Adults, Toddlers, and Infants

Study Overview:
Phase 1 Study MET28 was a randomized study conducted in Canada that evaluated the safety and immunogenicity of different formulations of MenQuadfi in a stage-down approach first in healthy adults (≥18 years to <40 years), then in toddlers (≥12 months through <19 months), and last in infants (2 months of age). The adult portion of the study design was evaluated descriptively, and only the adult data are presented in this clinical review.

Study Groups: The study enrolled/vaccinated 30 adults (safety analyses set N); PPAS 28 subjects

- Group 1: (b) (4) formulation ((b) (4)) (N=15)
- Group 2: (b) (4) formulation (10 ug polysaccharide per serogroup) (N=15)

An active comparator was not included for the adult portion of the study

Observational Study Objectives:
To describe the safety and immunogenicity profile in adults following one injection of two different formulations

> ***Reviewer Comment:*** *The study was not conducted under IND and did not receive regulatory input from CBER about the study design prior to its conduct.*

Summary of Study Results:
Both formulations were well tolerated, no deaths or SAEs were reported, and no subjects discontinued the study due an adverse event. The primary immunogenicity analyses were based on SBA responses using a serum bactericidal assay using (b) (4) . In general, suboptimal serogroup-specific (b) (4) responses were observed for (b) (4) formulations. Immune responses with the (b) (4) formulation for each serogroup were not quantitatively higher than corresponding responses with the (b) (4) formulation. Consequently, *new* (b) (4) formulations were developed and subsequently evaluated in Phase 1/Phase 2 Study MET32.

> ***Reviewer Comment***: *Study MET28 provided data that supported further development of* (b) (4) *formulations, which were evaluated in Phase 1/Phase 2 Study MET32.*

38: NCT code is not available for this Phase 1 study, which was performed in Canada prior to the US IND being filed. The applicant has provided the Canadian study identifier (9427-S2754/2-22C).

6.8 Trial #8 (Study MET32)

NCT00631995
Safety and Immunogenicity of a Quadrivalent Meningococcal (A, C, Y, and W-135) Tetanus Protein Conjugate Vaccine in Toddlers.

Study Overview:
Phase 1/Phase 2 Study MET32 was a randomized, active-controlled study conducted in Australia that evaluated the safety and immunogenicity of different vaccine formulations compared to an active control in toddlers. Participants were randomized to the active control Meningococcal Group C-Tetanus Toxoid Conjugate Vaccine, Adsorbed (NeisVacC®, Baxter International Inc) or one of 5 investigational formulation study groups. Each of the different formulation groups included either tetanus protein formulation 1 or tetanus protein formulation 2 with different concentrations of (b) (4) .

Study Design:
Study Objectives:
To describe the safety and immunogenicity profile of a single dose of different formulations administered at 12 months of age compared to a control vaccine.

Study Groups: The study enrolled 373 subjects; vaccinated 368 subjects (safety analyses set: N); and included 305 subjects in the PPAS. The number of subjects in the study groups in adults included

- 5 investigational formulations (N= 61 to 63 per group)
- NeisVacC (N= 62)

Reviewer Comment:
*The study design was not conducted under IND and did not receive regulatory input from CBER prior to its conduct. The active comparator (*NeisVac-C*) is not a US licensed vaccine.*

Summary of Study Results:
Overall the rates of solicited reactions were comparable between the investigational formulations and the control vaccine (79.7% to 93.4%) and were mostly of Grade 1 intensity. The formulations with (b) (4) did not correlate with higher rates of solicited reactions nor greater intensity/duration of solicited reactions. There were 7 SAEs in the study; all SAEs were in an investigational formulation group; one SAE was considered related study vaccination (reactive arthritis in a 12-month-old female the day following vaccination); and all other SAEs were considered not related to study vaccination by the investigators.

The immunogenicity assessments included the proportion of subjects with a titer ≥1:8 for each serogroup at one-month post vaccination as determined by serum bactericidal assay using human complement (hSBA). Though no clear dose dependent trends in hSBA immune responses were observed across groups, subjects who received formulations with higher polysaccharide concentrations demonstrated slightly higher immune responses compared to subjects who received formulations with (b) (4) . The applicant did not evaluate the 5 study formulations in subsequent trials. However, based on the data from this study, the final vaccine formulation was developed that combined the tetanus protein formulation 1 for serogroups A and C with the tetanus protein formulation 2 for serogroups Y and W.

Reviewer Comment: *The final vaccine formulation selection, including antigen and protein conjugate content was based on data from MET32. CBER did not provide regulatory input on final formulation selection.*

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The applicant is seeking the following indication for MenQuadfi:

> *Active immunization for the prevention of invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W, and Y for use in individuals 2 years of age and older*

7.1.1 Methods of Integration

In the 5 main studies used to support the effectiveness of MenQuadfi as a primary dose in individuals 2 years of age and older or a booster dose in individuals 15 years of age and older, seroresponse for meningococcal A, C, Y and W was defined as post-vaccination titer ≥ 1:16 for participants with pre-vaccination titer < 1:8, or post-vaccination titer at least 4-fold greater than the pre-vaccination titer for participants with pre-vaccination titer ≥1:8. For each study, the primary objective was to demonstrate non-inferiority of serogroup-specific hSBA seroresponses following the administration of MenQuadfi compared to a comparator vaccine, as defined as a lower bound of the 95% CI of the difference in seroresponse rates across treatment groups > -10.

The primary objectives were met for all of the 5 studies.

7.1.2 Demographics and Baseline Characteristics

For all participants (N=4801) who received a dose of MenQuadfi (MET43, MET35, MET49, MET56, MET50, MET44), the demographic and baseline characteristics were as follows:[39]

- Sex: 55.9% female: 44.1% male
- Age:
  - Mean: 27.2 years (SD 20.80)
  - Range: 2 years, 89.8 years
  - Median 16.5 years
- Race:
  - White: 80.4%
  - Black or African American: 14.1%
  - Asian: 1.3%
  - American Indian or Alaska Native: 0.5%
  - Native Hawaiian or Other Pacific Islander: 0.4%
  - Mixed Origin: 3.2%
  - Missing: 0.1%
- Ethnicity:
  - Hispanic or Latino: 18.3%
  - Not Hispanic or Latino: 81.5%
  - Missing: 0.2%

7.1.3 Immunogenicity Results by Age, Sex, Race/Ethnic Group

In each study, the hSBA seroresponse rates across treatment groups were evaluated descriptively by the following age cohorts: 2 through 5 years, and 6 through 9 years for Study MET35; 10

39 Source: Adapted from STN 125701.0, ISI, Table 1.2.1. Characteristics provided for the Per Protocol Analyses Set for each study.

through 17 years, and 18 through 55 years in Study MET43; 56 through 64 years, 65 through 74 years, and ≥75 years for Study MET49.

For all serogroups, there was an age-dependent increase in MenQuadfi hSBA seroresponse rates from early childhood 2 through 5 years of age (A 52%, C 94%, Y 88%, W 74%) through adolescents10 through 17 years of age (A 74%, C 96%, Y 96%, W 85%), and age-dependent decrease thereafter to age 56 years of age or older (A 58%, C 77% Y 74%, W 63%). All adolescents 10 through 17 years of age were meningococcal vaccine-naïve.

Notably, the magnitude of the serogroup C hSBA responses were greater in the younger age cohorts than the older age cohorts. Specifically, the difference in seroresponse rates across treatment groups (MenQuadfi – comparator) for serogroup C were as follows by age cohort and respective study:

- MET35: MenQuadfi - Menveo
  - children 2 through 5 years: 51%
  - children 6 through 9 years: 44%
- MET43: MenQuadfi - Menactra
  - adolescents 10 through 17 years: 42%
  - adults 18-55 years: 41%
- MET49: MenQuadfi - Menomune
  - adults 56-64 years: 27%
  - adults 65 through 74 years: 25%
  - adults ≥75 years: 36%

In addition, similar differences were observed in hSBA GMTs across age cohorts following MenQuadfi vaccination. The table below provides the serogroup specific hSBA GMTs following MenQuadfi vaccination by age cohort and respective study.

Table 51: MenQuadfi hSBA GMTs by Age Cohort

MenQuadfi GMTs by age cohorts	**A**	**C**	**Y**	**W**
2-5 years (MET35)	22	208	50	29
6-9 years (MET 35)	28	272	95	49
10-17 years (MET43)	78	504	208	97
10-17 years (MET50)	44	387	76	87
18-55 years (MET43)	106	234	219	76
56-64 years (MET49)	65	130	99	36
65-74 years (MET49)	47	87	61	25
≥ 75 years (MET49)	52	75	35	18

Source: Adapted from STN 125701; Studies MET35, MET43, MET50, MET49.

The serogroup C hSBA GMTs following MenQuadfi vaccination were numerically higher in individuals 10 through17 years (GMT 504) compared to individuals 56 through 64 years (GMT 130), 65 through 74 years (GMT 86.6), ≥75 years (GMT 75).

These findings may address an ongoing public health need in the US, as the incidence rates of serogroup C meningococcal disease remains high despite the introduction of licensed meningococcal conjugate A, C, Y, W vaccines into the ACIP recommended routine vaccination schedule in 2005 and 2010. As discussed in Section 2.1 of this review memo, in 2018 the

incidence rate of serogroup C disease (0.03 cases/100,000) was the 2nd highest of all meningococcal serogroups after serogroup B disease (0.04 cases/100,000).

Subpopulation Analyses by Sex
For MenQuadfi recipients, the hSBA immune responses observed in male and in female participants separately were similar to those observed overall in all MenQuadfi recipients.

Subpopulation Analyses by Racial/Ethnic Group
No definitive conclusions could be made due to small number of subjects enrolled who were Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander or Mixed origin.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data included in this application and reviewed to characterize the safety profile of the final formulation of MenQuadfi were from the following sources:

- Main trials: MET43, MET35, MET49, MET50, MET56
- Supportive trials: MET44

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were 6 studies (MET43, MET35, MET49, MET50, MET56, MET44) that were reviewed in this application to describe the safety profile of MenQuadfi. The safety database across these 6 clinical trials included 5118 study participants 2 years of age and older; all subjects were enrolled at sites either in the US or Puerto Rico.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall MenQuadfi exposure in participants across the 6 studies in different age groups is described in the table below.

Table 52: MenQuadfi Exposure by Age Cohort

Population	Age Group	Studies	Number of Subjects
All	2 years and above	MET35, MET43, MET44, MET49, MET50, MET56	5118
Children	2 through 9 years	MET35	498
Adolescents	10 through 17 years	MET43, MET50, MET56	1897
Adults	18 through 55 years	MET43, MET56	1684
Older adults (≥ 56 years)	56 through 64 years	MET44, MET49, MET56*	298
	65 years and above	MET44, MET49	258

Source STN 125701, Section 2.7.4- Summary of Clinical Safety, adapted from Tables 1.1, 1.2. *MET56 included subjects aged ≥ 15 years through 55 years. One subject older than 55 years was erroneously included in the study and included in the database.

For each study, the demographic characteristics were reviewed individually. The AE rates across treatment groups for each study when stratified by age or sex followed similar trends as those observed in all participants for the corresponding AE rate for that study.

8.2.3 Categorization of Adverse Events

Safety data collected across the 5 main trials MET43, MET35, MET49, MET50, MET56 and supportive trial MET44 include the following:

- Immediate unsolicited AEs for 30 minutes postvaccination
- Solicited AEs (injection site and systemic predefined adverse reactions) for 7 days postvaccination
- Unsolicited AEs for 30 days postvaccination
- Medically attended AEs for 30 days postvaccination, and Day 30 through 6 months follow-up contact (MET44 MAAEs collected only for 30 days postvaccination)
- SAEs/Deaths/AEs leading to study withdrawal for 30 days postvaccination and Day 30 through 6 months follow-up contact.
- Adverse Events of Special Interest (pre-defined) were only collected in Study MET35 for the duration of the study (30 days postvaccination and Day 30 through 6 months follow-up contact.

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

Safety data were not pooled across studies.

8.4 Safety Results

8.4.1 Deaths

There were no deaths among MenQuadfi participants in the 5 main trials and supportive study MET44.

8.4.2 Nonfatal Serious Adverse Events

Case narratives for SAEs reported by MenQuadfi participants are described in the review of the individual study (Section 6). None of the reported SAEs were considered by this reviewer to be related to MenQuadfi vaccination.

8.4.3 Study Dropouts/Discontinuations

There were no MenQuadfi participants who withdrew from any of the reviewed studies due to an adverse event.

8.4.4 Common Adverse Events

The rates of common unsolicited adverse events in MenQuadfi recipients by age were 28.4% in children 2 through 5 years, 20.2% in children 6 through 9 years, 16.5% in adolescents 10 through 17 years, and 11% in adults 18 through 55 years. The type of unsolicited AEs that were reported commonly occurred in the general population for each respective age cohort. The rates of unsolicited AEs not related vaccination were similar to the rates observed in the active comparator group. The rates were likely higher in the younger age cohorts due to the nature of AEs observed in younger children, which were mostly upper respiratory tract infections.

8.4.5 Clinical Test Results

Not applicable.

8.4.6 Local and Systemic Adverse Event

The most frequently reported solicited adverse events following a primary dose of MenQuadfi (occurring in ≥10% of MenQuadfi participants) were as follows by age cohort:

- Children 2 through 9 years of age: injection site pain (38.6%), erythema (22.6%), malaise (21.1%), myalgia (20.1%), swelling (13.8%) and headache (12.5%)

- Adolescents aged 10 through 17 years of age: injection site pain (34.8%–45.2%), myalgia (27.4%–35.3%), headache (26.5%–30.2%), and malaise (19.4%–26.0%)
- Adults aged 18 through 55 years: injection site pain (41.9%), myalgia (35.6%), headache (29.0%), and malaise (22.9%)
- Adults 56 years of age and older: pain at the injection site (25.5%), myalgia (21.9%), headache (19.0%), and malaise (14.5%)

Comparable rates of solicited adverse reactions were observed in adolescents and adults following a booster dose.

8.4.8 Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) were assessed in Study MET35 only which evaluated the safety of MenQuadfi compared to Menveo in children 2 years through 9 years of age. The following AESI were pre-specified and assessed for during the study: Generalized seizures (febrile/non-febrile), Kawasaki Disease, Guillain Barre Syndrome (GBS), and Idiopathic Thrombocytopenic Purpura (ITP). There was one AESI reported during the study in the Menveo study group: Subject #(b) (6) experienced epilepsy event 43 days postvaccination that was considered not related to study vaccine. There were no AESI reported in the MenQuadfi group.

8.6 Safety Conclusions

In a total of 6 randomized clinical trials conducted in the US and Puerto Rico, 5118 MenQuadfi recipients received one dose of MenQuadfi and provided post-vaccination safety data. No safety concerns were identified when MenQuadfi when administered to children (≥2 years) and adults (≥18 years) as a primary dose, or as a booster dose.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

The package insert included the following information described in section 9.1.1 and section 9.1.2:

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to MenQuadfi during pregnancy.

Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

There are no clinical studies of MenQuadfi in pregnant women. Available human data on MenQuadfi administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

A developmental toxicity study in female rabbits administered a full human dose (0.5 mL) prior to mating and during gestation period revealed no evidence of harm to the fetus due to MenQuadfi (see *Animal Data*).

Animal Data
In a developmental toxicity study, female rabbits received a human dose of MenQuadfi by intramuscular injection on five occasions: 30 days and 10 days prior to mating, gestation days 6, 12, and 27. No adverse effects on pre-weaning development up to post-natal day 35 were observed. There was no vaccine related fetal malformations or variations observed.

9.1.2 Use During Lactation

Risk Summary

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

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MenQuadfi and any potential adverse effects on the breastfed child from MenQuadfi or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

9.1.3 Pediatric Use and PREA Considerations

The proposed indication is for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W for use in individuals 2 years of age and older. As specified by the Pediatric Research Equity Act (PREA), the submission of this original BLA required an assessment for individuals 2 years through 17 years of age was included in this BLA. The applicant requested that the assessment of MenQuadfi in pediatric individuals 6 weeks through 23 months of age (<2 years) be addressed as follows:

Partial Waiver
Pediatric age group to be waived: 0 to < 6 weeks of age.

- Statutory reason for waiving pediatric assessment requirements:
  Section 505B(a)(B)(iii): The product does not represent a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age and is not likely to be used.

- Justification for waiver:
  Due to limitations of the neonatal immune response, initiating vaccination at 0 to<6 weeks of age with MenQuadfi will not provide a meaningful therapeutic benefit over initiating vaccination at 6 weeks of age.

  With the exception of Hepatitis B vaccine, for which a birth dose is routinely recommended to prevent perinatal transmission of hepatitis B virus, infant immunizations in the US are generally not administered before 6 weeks of age.

Partial Deferral
Pediatric age group to be deferred: 6 weeks through23 months of age (<2 years).

- Statutory reason for deferring pediatric assessment requirements:
  Section 505B(a)(3)(A)(i): The biological product is ready for approval for use in individuals 2 years of age and older before all pediatric studies are complete.

Sanofi is conducting seven studies in children 6 weeks through 23 months of age as part of their global clinical development plan. The review team concurred with the applicant's proposal that

of these seven studies, the three studies listed below (MET41, MET42 and MET61) are sufficient to support a pediatric assessment in the U.S. for this age group. Please see section 11.6 of the clinical review for timelines for conducting studies MET41, MET42 and MET61.

The applicant's requests for partial waiver and partial deferral of the required pediatric assessment was presented to FDA's Pediatric Review Committee (PerC) on March 10, 2020. The committee agreed with the requests, including the partial waiver, partial deferral, and the proposed timelines for each study's completion and submission.

9.1.4 Immunocompromised Patients

MenQuadfi has not been evaluated in immunocompromised patients.

9.1.5 Geriatric Use

The safety and effectiveness of MenQuadfi was established in adults older than 65 years of age.

10. CONCLUSIONS

In study MET43, MenQuadfi clinical lot consistency and immunological non-inferiority of MenQuadfi to Menactra following a primary dose vaccination was demonstrated in meningococcal vaccine-naïve adolescents 10 through 17 years of age, the population for whom a primary meningococcal conjugate A, C, Y, W vaccine dose is recommended for use by the ACIP. Immune non-inferiority of a primary dose of MenQuadfi to Menveo was established in children (2 through 9 years of age) in MET35 and in adolescents in MET56; non-inferiority of MenQuadfi to Menactra and Menomune were established in adults 18 through 55 years in MET43, and older adults ≥56 years in MET49, respectively. In addition, MenQuadfi booster responses for each serogroup were non-inferior to corresponding responses following a Menactra booster dose in individuals ≥15 years of age with a history of meningococcal A, C, Y, W conjugate vaccination ≥4 years earlier.

The safety profile of MenQuadfi was comparable to that observed following a dose of Menveo or Menactra, but MenQuadfi was more reactogenic compared to Menomune.

Overall, except for antibody responses to 3 of 4 pertussis vaccine antigens, immunogenicity and safety data support concomitant administration of MenQuadfi with TdaP and quadrivalent HPV vaccines in adolescents. Non-inferiority criteria were not met for pertussis antigens FHA, PRN, and FIM; the clinical relevance of the diminished response to these pertussis antigens is unknown.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

TABLE 53: Risk-Benefit Assessment of Primary and Booster Dose Vaccinations with MenQuadfi, Meningococcal Conjugate ACWY Vaccine for Use in Individuals 2 years and older.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Invasive meningococcal disease (IMD) is associated with high morbidity/mortality, even with timely treatment. Long term sequelae occur in 11-19% of those who survive and include hearing loss, neurologic disability, loss of limbs, and/or other serious conditions, despite treatment. Case fatality rate is 10-15 %.	IMD due to serogroups A, C, W and Y is a serious and potentially life-threatening condition. Individuals 2 years of age and older are at 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 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 conjugate vaccines (MCV4) are licensed and available in the US. Menveo and Menactra are approved for use in individuals 2 months through 55 years of age and 9 months through 55 years of age, respectively, as primary, and both vaccines are approved for use as a booster dose in individuals 15 through 55 year of age at continued risk for meningococcal disease. Menomune is a polysaccharide A,C,Y, W vaccine is licensed for use in individuals ≥2 years, but it is not commercially available. ACIP recommends primary MCV4 dose at 11-12 years, then booster dose at 16 years. In 2005, ACIP initially recommended primary dose in children 11-12 years of age children. Subsequent CDC surveillance data demonstrated a persistence of meningococcal disease activity for serogroups C and Y at 18 years of age. As a result, in 2010 ACIP recommended a booster dose at 16 years of age. CDC's 2017 Enhanced Surveillance Report (US): # IMD cases (incidence rate per 100,000) by serogroup: B-134 cases (0.04); C-86 cases (0.03); W-26 (0.01); Y-31 cases (0.01), nongroupable-35 cases (0.01), overall (350 cases (0.11)	Another MCV4 for use in 2 years of age and older would reduce risk of possible shortage of MCV4 vaccines supply in the US. MenQuadfi would be the only available quadrivalent meningococcal vaccine for use in individuals 56 years of age and older.
Clinical Benefit	The immunogenicity (effectiveness) of MenQuadfi primary and booster dose vaccinations were evaluated in ~5000 study participants who received the final MenQuadfi formulation. In participants 2 years and older, functional immune responses (hSBA) to MenQuadfi were noninferior to the US licensed comparators	The study results provided in the BLA support the effectiveness of MenQuadfi for individuals 2 year of age and older.
Risk	The most frequently reported solicited reactions included injection site pain, myalgia, headache, and malaise. The rates observed were comparable to those observed following US-licensed vaccines Menveo and Menactra in the respective studies. In adults ≥ 56 years of age, the solicited reaction rates were higher in MenQuadfi (conjugate vaccine) group compared to Menomune (polysaccharide vaccine) group. No deaths or vaccine-related SAEs were reported in the prelicensure clinical studies (~5000 MenQuadfi recipients).	The safety profile of MenQuadfi as either a primary dose or booster dose were generally comparable to the observed safety profiles of Menveo and Menactra, meningococcal conjugate vaccines currently licensed in the US.
Risk Management	The most common risks of MenQuadfi primary or booster dose vaccinations were described above. The proposed USPI (following labeling negotiations) has adequately captured these risks. MenQuadfi does not prevent *N. meningitidis* serogroup B disease.	The risks are adequately characterized in the USPI. Routine pharmacovigilance to monitor adverse events in accordance with 21 CFR 600.80 is sufficient. 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 years and older is favorable compared to the risks associated with vaccination. Data submitted to this original BLA establish the safety and effectiveness (immunogenicity) of primary dose and booster dose vaccinations in individuals 2 years of age and older. The safety of MenQuadfi is adequately described in the USPI, and the Applicant's routine pharmacovigilance plan is adequate for monitoring AEs post-marketing.

11.3 Discussion of Regulatory Options

Given that 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 non-inferiority to US-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 such that other regulatory options need to be considered

The applicant is seeking the following indication:

> MenQuadfi™ is a vaccine indicated for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y. MenQuadfi is approved for use in individuals 2 years of age and older.

11.4 Recommendations on Regulatory Actions

According to my review of the submitted clinical data, the safety and effectiveness of MenQuadfi as a primary dose vaccination in individuals 2 years of age and older, and as booster dose vaccination in individuals 15 years and older who had received a primary meningococcal conjugate quadrivalent vaccine dose at least 4 years prior are supported.

11.5 Labeling Review and Recommendations

The proprietary name MenQuadfi was reviewed by the Advertising and Promotional Labeling Branch and found acceptable. The prescribing information was reviewed and specific comments on the labeling were provided by CBER to the applicant who made the requested revisions. All issues were satisfactorily resolved.

11.6 Recommendations on Postmarketing Actions

Studies that the applicant is required to conduct following licensure are listed below and include 3 PREA-required studies.

<u>Pediatric Research Equity Act Postmarketing Requirements:</u>

1. Deferred pediatric study (MET41) under PREA to evaluate the safety of MenQuadfi in infants and toddlers 6 weeks through 12 months of age.
   Final Protocol Submission: November 9, 2017
   Study Completion Date: August 10, 2022
   Final Report Submission: August 31, 2023

2. Deferred pediatric study (MET42) under PREA to evaluate the immunogenicity and safety of MenQuadfi in infants and toddlers 6 weeks through 18 months of age.
   Final Protocol Submission: November 9, 2017

Study Completion Date: December 15, 2022
Final Report Submission: July 13, 2024

3. Deferred pediatric study (MET61) under PREA to evaluate the immunogenicity and safety of MenQuadfi in infants and toddlers 6 through 23 months of age.
   Final Protocol Submission: June 22, 2018
   Study Completion Date: August 5, 2022
   Final Report Submission: February 28, 2023

In addition, the applicant has proposed to establish a pregnancy registry for MenQuadfi to collect and analyze the outcome of exposure to MenQuadfi during pregnancy and monitor for any potential safety signals that may arise in this population in routine public health settings. The following study was agreed upon as a post-marketing commitment and is subject to reporting requirements of 21 CFR 601.70.

Post-Marketing Commitment:

1. To establish a pregnancy registry (Study MEQ00070) for MenQuadfi in the United States to collect and analyze the outcome of exposure to MenQuadfi during pregnancy and monitor for potential safety signals that may arise in this population in routine public health settings.

   Final Protocol Submission: November 30, 2020
   Study Completion Date: June 30, 2028
   Final Report Submission: June 30, 2029