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Application Type	BLA Supplement
STN	125701/262
CBER Received Date	July 23, 2024
PDUFA Goal Date	May 23, 2025
Committee Chair	Joseph Temenak
Clinical Reviewer(s)	Gauri Raval, Robin Wisch
Project Manager(s)	Maria Bagh, Lynsay Ehui
Priority Review	No
Reviewer Name(s)	Trinetri Ghosh, Mathematical Statistician, VEB/DB/OBPV
Review Completion Date / Stamped Date	May 21, 2025
Supervisory Concurrence	Ye Yang, Lead Mathematical Statistician, VEB/DB/OBPV Tsai-Lien Lin, Branch Chief VEB/DB/OBPV
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	10 µg of each serogroups A, C, Y and W in meningococcal capsular polysaccharides and approximately 55 µg tetanus toxoid protein carrier
Dosage Form(s) and Route(s) of Administration	A single 0.5 mL dose for intramuscular use
Dosing Regimen	Primary vaccination: • Infants aged from 6 weeks: 4-dose series at 2, 4, 6, and between 12 and 18 months of age. • Infants aged 6 months through 23 months: 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose.

	• Individuals 2 years of age and older: A single dose. Booster vaccination: • A single dose may be administered to individuals 13 years of age and older who are at continued risk for meningococcal disease if at least 3 years have elapsed since a prior dose of meningococcal (groups A, C, W, Y) conjugate vaccine. Vaccination following prior dose of Meningococcal Polysaccharide vaccine: • A single dose may be administered if at least 3 years have elapsed since a prior dose of meningococcal polysaccharide vaccine.
Indication(s) and Intended Population(s)	For active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y in individuals 6 weeks of age and older.

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GLOSSARY

Ab	Antibody
ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AESI	Adverse events of special interest
AR	Adverse reaction
BLA	Biologics License Application
CBER	Center for Biologics and Research
CI	Confidence interval
CSR	Clinical study report
DTaP	Diphtheria, tetanus, acellular pertussis vaccine
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FHA	Filamentous hemagglutinin adhesin
FIM	Fimbriae types 2 and 3
GMC	Geometric mean concentrations
GMT	Geometric mean titers
HB	Hepatitis B
HepA	Hepatitis A
Hib	*Haemophilus influenza* type b
hSBA	Serum bactericidal assay using human complement
Ig	Immunoglobulin
IM	Intramuscular
IPV	Poliovirus [inactivated] vaccine
IRT	Interactive response technology
IU	International unit
LB	Lower-bound
LLOQ	Lower limit of quantitation
MAAE	Medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MMR	Measles, Mumps and Rubella
NI	Non-inferiority
PCV13	Pneumococcal 13-valent conjugate vaccine
PPAS	Per-protocol analysis et
PRN	Pertactin
PT	Pertussis toxoid / toxin
RCDC	Reverse cumulative distributions curves
SAE	Serious adverse event
SafAS	Safety analysis set
SAP	Statistical analysis plan
sd	Standard deviation
SOC	System organ class
ULOQ	Upper limit of quantitation

1. Executive Summary

The Sanofi Pasteur Inc. MenACYW Conjugate Vaccine (Meningococcal Polysaccharide [Serogroups A, C, W, and Y] Tetanus Toxoid Conjugate Vaccine), registered under the trade name MenQuadfi®, has been approved in the United States (US) since April 23, 2020 for active immunization to prevent invasive meningococcal disease (IMD) caused by *N. meningitidis* serogroups A, C, W, and Y in individuals 2 years of age and older as a single dose (0.5 mL) vaccine administered intramuscularly. The applicant submitted a Biologics License Application (BLA) supplement (sBLA; STN 125701/262) on July 23, 2024 to extend the current indication to individuals 6 weeks through 23 months of age according to the following dosing schedules as part of post-marketing requirements:

- For infants aged 6 weeks to less than 6 months: 4-dose series at 2, 4, 6, and 12 to 18 months of age (the first dose may be given as early as 6 weeks of age).
- For infants aged 6 months through 23 months: 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose.

This sBLA is supported by data from three pivotal Phase III active comparator-controlled studies (MET41, MET42, and MET61) in the proposed age expansion group. This statistical review focuses on the safety and immunogenicity data from participants 6 weeks to 23 months old.

MET41 was a Phase III, modified double-blind, randomized, parallel-group, active-controlled study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers 6 weeks of age and older. A total of 2797 healthy infants aged ≥42 to ≤89 days were randomized 3:1 to receive either a 4-dose series of MenACYW conjugate vaccine and routine pediatric vaccines (Group 1) or a 4-dose series of MENVEO® vaccine and routine pediatric vaccines (Group 2).

In the overall safety population (SafAS), the percentages of participants who reported at least one solicited reaction up to 7 days after any injection were comparable between groups. The percentages of participants who reported at least one solicited injection site and solicited systemic reaction were 84.9% and 87.1% in Group 1 and 84.6% and 88.2% in Group 2, respectively. The most frequently reported reactions in both groups were injection site pain, irritability, crying abnormal, and drowsiness. After vaccination with MenACYW or MENVEO, the percentage of participants who experienced at least 1 solicited injection site reaction was 79.0% in Group 1 and 77.7% in Group 2. Most reported reactions were mild or moderate in intensity. The percentage of participants reporting any SAE up to 6 months after the last injection was 5.2% in Group 1 and 3.0% in Group 2. In addition, there were 3 deaths reported in Group 1 and none in Group 2. None of the SAEs or deaths were considered related to the study intervention by the investigator.

MET42 was a Phase III, partially modified double-blinded (unblinding may occur due to different number of doses and timing of vaccines), randomized, parallel-group, active-controlled study to compare the safety and immunogenicity of the MenACYW conjugate vaccine with MENVEO when administered concomitantly with routine pediatric vaccines

(i.e. Pentacel®, PREVNAR 13®, RotaTeq®, ENGERIX-B®, M-M-R II®, VARIVAX®, and HAVRIX®) to healthy infants and toddlers. A total of 2627 healthy infants aged ≥42 to ≤89 days were randomized in 2:1 ratio to receive either MenACYW conjugate vaccine (Group 1) or MENVEO (Group 2) with routine pediatric vaccines. Each group was further randomized in a 2:1 ratio into two subgroups based on the time of analyses conducted in the second year of life:

- Group 1 (G1):
  - G1a: MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age,
  - G1b: MenACYW conjugate vaccine at 2, 4, 6, and 15 to 18 months of age and routine vaccines at 2, 4, 6, 12 to 15, and 15 to 18 months of age.
- Group 2 (G2):
  - G2a: MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age,
  - G2b: MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age (with different timing of blood draw from G2a).

The pre-specified noninferiority (NI) criteria for the differences in serum bactericidal assay using human complement (hSBA) vaccine seroresponse rates at 30 days after MenACYW vaccination at 12 to 15 months of age (G1a) compared to MENVEO at 12 months of age (G2a) were met (via a -10% NI margin) for each of the four meningococcal serogroups. The pre-specified NI criteria for the percentages of participants with hSBA antibody titers ≥1:8 at 30 days after vaccination with MenACYW (G1) or MENVEO (G2) at 6 months of age (via a -10% NI margin) were met for each of the four meningococcal serogroups.

In the SafAS, the percentages of participants who reported at least one solicited reaction after any injection were comparable between the two groups. The percentages of participants who experienced at least one solicited injection site reaction and solicited systemic reaction after any injection were 78.0% and 80.0% in Group 1 and 79.8% and 81.9% in Group 2, respectively. The most frequently reported reactions in both groups were injection site pain, irritability, crying abnormal, and drowsiness. After any vaccination with MenACYW conjugate vaccine or MENVEO, 71.7% and 71.0% of participants reported solicited injection site reactions, respectively. Most solicited reactions were mild or moderate. The percentages of participants reporting SAEs up to 6 months after the last vaccination were 5.7% in Group 1 and 4.4% in Group 2. Two SAEs were assessed as related to the study vaccine by the investigator: a case of febrile convulsion in Group 1 and a case of post-vaccination fever in Group 2. Both cases were reported within 30 days of vaccination. There was one death due to cardiac arrest reported in Group 1 and was considered unrelated to study intervention by the investigator. There were no deaths reported in Group 2.

MET61 was a Phase III, randomized, parallel-group, active-controlled, multi-center study to compare the safety and immunogenicity of MenACYW conjugate vaccine (Group 1) and MENVEO (Group 2) when administered in a two-dose schedule and concomitantly

with routine pediatric vaccines at 6 to 7 and 12 to 13 months of age in healthy infants and toddlers. This study also compared the safety and immunogenicity of MenACYW conjugate vaccine (Group 3) and Menactra (Group 4) when administered in a two-dose schedule to healthy toddlers at 17 to 19 and 20 to 23 months of age. Blinding was maintained between Group 1 and Group 2, and between Group 3 and Group 4. For the infant population, 380 participants were randomized to Group 1 and 370 to Group 2. For the toddler population, 96 participants were randomized to Group 3 and 104 to Group 4.

The pre-specified NI criteria for hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine compared to MENVEO at 12 to 13 months of age (via a -10% margin) were met for each of the four meningococcal serogroups.

The percentages of participants who reported any solicited reaction were comparable between Group 1 and Group 2, and between Group 3 and Group 4. The percentages of participants who experienced at least one solicited injection site reaction and solicited systemic reaction were 63.5% and 66.0% in Group 1, 61.7% and 62.9% in Group 2, 57.1% and 60.4% in Group 3, and 48.0% and 62.0% in Group 4, respectively. The most frequently reported solicited reactions in all groups were injection site pain, irritability, crying abnormal, and drowsiness. The percentage of participants who experienced any solicited injection site reaction after the administration of the meningococcal vaccine was 55.9% in Group 1, 52.6% in Group 2, 57.1% in Group 3, and 48.0% in Group 4. Most solicited reactions were mild or moderate in intensity. The percentages of participants with SAEs up to 6 months after the last vaccination were 1.6% in Group 1, 3.3% in Group 2, 1.0% in Group 3, and 3.9% in Group 4. One SAE of Grade 3 febrile convulsion in Group 4 on Day 1 after vaccination was assessed as related to the study vaccine by the investigator. No deaths were reported during the study.

Overall, the data support the effectiveness of the MenACYW conjugate vaccine in infants aged 6 weeks and older. I defer to the clinical reviewer on the safety conclusions.

2. Clinical and Regulatory Background

MenACYW conjugate vaccine (MenQuadfi®) was approved in the US on April 23, 2020 for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and Y in individuals 2 years of age and older. The applicant submitted a BLA supplement (STN 125701/262) on July 23, 2024 to extend the current indication to individuals 6 weeks through 23 months of age according to the following dosing schedules:

- For infants aged 6 weeks to less than 6 months: 4-dose series at 2, 4, 6, and 12 to 18 months of age (the first dose may be given as early as 6 weeks of age).
- For infants aged 6 months through 23 months: 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is complete and organized to facilitate a thorough review.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issue was found. Please refer to reviews of other review disciplines.

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

Please refer to reviews of other review disciplines.

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

5.1 Review Strategy

This statistical review focuses on the safety and immunogenicity data from three Phase III studies: MET41, MET42, and MET61.

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

The following documents submitted to the sBLA are reviewed.

STN 125701/262.0:

- Section 2.7.3 Summary of Clinical Efficacy
- Section 2.7.4 Summary of Clinical Safety
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - MET41
        - MET41 Final Clinical Study Report
        - 16.1.1 Protocol and/or Amendment
        - 16.1.9 Documentation of statistical methods and interim analysis plans
        - Analysis Datasets
        - Tabulation Datasets
        - Miscellaneous Datasets
    - MET42
        - MET42 Final Clinical Study Report
        - 16.1.1 Protocol and/or Amendment
        - 16.1.9 Documentation of statistical methods and interim analysis plans
        - Analysis Datasets
        - Tabulation Datasets
        - Miscellaneous Datasets
    - MET61
        - MET61 Final Clinical Study Report

        - 16.1.1 Protocol and/or Amendment
        - 16.1.9 Documentation of statistical methods and interim analysis plans
        - Analysis Datasets
        - Tabulation Datasets
        - Miscellaneous Datasets
- Section 5.3.5.3 Reports of Analyses of Data from More than One Study
    - ISS
        - Integrated Summary of Safety (ISS) – 6 weeks through 23 months – Tables
        - Integrated Analysis Plan (IAP) for Safety – Core Body for MET41, MET42, MET61
        - Analysis Datasets

STN 125701/262.3:

- Section 1.11.3 Clinical Information Amendment
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - MET42
        - Tabulation Datasets

STN 125701/262.8:

- Section 1.11.4 Multiple Module Information Amendment
- Section 1.14.1.2 Annotated Draft Labeling Text

STN 125701/262.14:

- Section 1.11.3 Clinical Information Amendment
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - MET42
        - Analysis Datasets

STN 125701/262.15:

- Section 1.11.3 Clinical Information Amendment
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
    - MET42
        - Datasets

STN 125701/262.16:

- Section 1.11.3 Clinical Information Amendment

STN 125701/262.17:

- Section 1.11.3 Clinical Information Amendment
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

- MET61
  - Datasets

STN 125701/262.18:

- Section 1.11.3 Clinical Information Amendment
- Section 5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
  - MET41
    - Datasets
  - MET42
    - Datasets
  - MET61
    - Datasets

STN 125701/262.19:

- Section 1.11.4 Multiple Module Information Amendment

STN 125701/262.21:

- Section 1.11.3 Clinical Information Amendment

STN 125701/262.22:

- Section 1.11.3 Clinical Information Amendment
  - Clinical information amendment – Response to Information Request13 dated 13Mar2025 – part 2

STN 125701/262.23:

- Section 1.11.3 Clinical Information Amendment

STN 125701/262.24:

- Section 1.11.3 Clinical Information Amendment

STN 125701/262.25:

- Section 1.11.3 Clinical Information Amendment

STN 125701/262.26:

- Section 1.11.3 Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Table 1 contains a summary of MET41, MET42 and MET61.

Table 1: Studies Submitted to STN 125814/262

Study	MET41	MET42	MET61
Number of centers (Locations)	75 centers in the US and Puerto Rico	69 centers in the US	47 centers in the US and Puerto Rico

Study	MET41	MET42	MET61
Design, vaccinations	Randomized, modified, double-blind, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US.	Randomized, partially modified double-blind, parallel-group, active controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Menveo when administered concomitantly with routine pediatric vaccines to healthy infants and toddlers in the US.	Randomized, parallel group, active controlled, multi-center trial to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and Menveo when administered in a 1 + 1 schedule concomitantly with routine pediatric vaccines in healthy infants and toddlers in the US.
Number of participants	Randomized: 2797	Randomized: 2627	Randomized: 950

Source: Table 1 in Section 2.7.4 Summary of Clinical Safety from sBLA 125701/262.0.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study MET41

Title: A randomized study to describe the safety of an investigational quadrivalent meningococcal conjugate vaccine administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.

Study initiation date: September 17, 2018 (first subject first visit)
Study completion date: March 16, 2023 (last subject last contact)

6.1.1 Objectives

Primary objective:

- To describe the safety profile of MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.

6.1.2 Design Overview

This study was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to describe the safety of MenACYW conjugate vaccine when administered concomitantly with routine pediatric vaccines given to healthy infants and toddlers in the US. Approximately 3080 healthy infants aged ≥ 42 to ≤ 89 days were planned to be randomized in a 3:1 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine + routine pediatric vaccines (N=2310),
- Group 2: MENVEO + routine pediatric vaccines (N=770).

All participants were to receive a dose of either MenACYW conjugate vaccine or MENVEO at 2, 4, 6, and 12 months of age with the following routine pediatric vaccines:

- Pentacel® (DtaP-IPV//Hib) at 2, 4, and 6 months of age,
- PREVNAR 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 2, 4, 6, and 12 months of age,
- RotaTeq® (rotavirus vaccine) at 2, 4, and 6 months of age,
- ENGERIX-B® (hepatitis B vaccine) at 2 and 6 months of age,
- M-M-R II® (measles, mumps, and rubella vaccine) and VARIVAX® (varicella vaccine) at 12 months of age.

All participants were to complete the last study visit at 13 to 14 months of age. A fourth dose of Pentacel was to be administered at 15 to 18 months of age. Safety data were planned to be collected as follows: immediate unsolicited systemic AEs within 30 minutes after each vaccination, solicited AEs from Day 0 to Day 7 after each vaccination, unsolicited AEs from Day 0 after each vaccination to the next study visit, and SAEs (including AESIs) and MAAEs until the end of the 6-month follow-up period after the last vaccination.

This trial was a modified double-blind trial, with the participant's parent/guardian, the investigator, the sponsor, and other study personnel blinded to the treatment assignment. An unblinded vaccine administrator administered the appropriate vaccine but was not involved in safety data collection.

6.1.3 Population

The study population included healthy male and female participants aged 42 to 89 days on the day of the first study visit.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Table 2 provides a summary of the administered vaccines.

Table 2: Dose and Route of the Administered Vaccines – MET41

Vaccine	Dose, route
MenACYW conjugate vaccine	0.5 mL solution intramuscular (IM) at 2, 4, 6 and 12 months of age
MENVEO	0.5 mL solution IM at 2, 4, 6 and 12 months of age
Pentacel	0.5 mL solution IM at 2, 4 and 6 months of age
Prevnar 13	0.5 mL suspension IM at 2, 4, 6 and 12 months of age
RotaTeq	2 mL oral solution at 2, 4 and 6 months of age
Engerix-B	0.5 mL suspension IM at 2 and 6 months of age
M-M-R II	0.5 mL subcutaneous at 12 months of age
Varivax	0.5 mL suspension subcutaneous at 12 months of age

Source: Summarized by the reviewer based on information presented in the Final CSR version 2.0 MET41.

6.1.6 Sites and Centers

The study was conducted at two sites in Puerto Rico and 73 sites in the US.

6.1.7 Surveillance/Monitoring

Please refer to the clinical review memo.

6.1.8 Endpoints and Criteria for Study Success

Primary safety endpoints:

- Occurrence, nature (MedDRA preferred term), duration, intensity, and relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions occurring up to Day 7 after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions occurring up to Day 7 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to Day 30 after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of MAAEs throughout the trial.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Descriptive statistics, including frequency, percentage, and 95% CI, were provided for the primary safety endpoints. The 95% CI for single proportion was calculated using the exact binomial method.

The following six SafAS were used in the analyses.

- *Overall SafAS for any dose*: defined as those who received at least one dose of the study vaccines and had any safety data available. All participants had their safety analyzed after any dose according to the vaccine received at the first dose. Safety data recorded for a vaccine received out of the protocol design were excluded from the analysis (and listed separately).
- *SafAS for vaccination at 2 months of age (SafAS1)*: defined as those who received the study vaccine around 2 months of age and had any safety data available. All participants had their safety analyzed according to the vaccine they actually received at Day 0. Safety data recorded for a vaccine received out of the protocol design at Day 0 were excluded from the analysis (and listed separately).
- *SafAS for vaccination at 4 months of age (SafAS2)*: defined as those who received the study vaccine at 4 months of age and had any safety data available. All participants had their safety analyzed according to the vaccine they actually received at that visit. Safety data recorded for a vaccine received out of the protocol design at the visit were excluded from the analysis (and listed separately).

- *SafAS for vaccination at 6 months of age (SafAS3)*: defined as those who received the study vaccine at 6 months of age and had any safety data available. All participants had their safety analyzed according to the vaccine they actually received at this visit. Safety data recorded for a vaccine received out of the protocol design at the visit were excluded from the analysis (and listed separately).
- *SafAS for vaccination at 12 months of age (SafAS4)*: defined as those who received the study vaccine at 12 months of age and had any safety data available. All participants had their safety analyzed according to the vaccine they actually received at this visit. Safety data recorded for a vaccine received out of the protocol design at the visit were excluded from the analysis (and listed separately).
- *SafAS for all 4-dose vaccination (SafAS5)*: defined as those who received all four doses of the study vaccine and had any safety data available. Vaccinations received should be either all MenACYW conjugate vaccine or all MENVEO®.

Subgroup analyses by sex (male and female), race (White, Black, Asian, Other) and birth (pre-term and full-term) were performed.

6.1.10 Study Population and Disposition

Table 3 shows the disposition of participants. A total of 1797 (85.6%) participants in Group 1 and 618 (88.5%) participants in Group 2 completed 6 months of safety follow-up.

Table 3: Disposition by Randomized Group – All Randomized Participants in MET41

Age / Dose #/ Event	Group 1 (N=2099) n (%)	Group 2 (N=698) n (%)
2 months (Dose 1)	-	-
Randomized	2099 (100)	698 (100)
Received MenACYW	2080 (99.1)	0
Received Menveo	2 (<0.1)	695 (99.6)
Received Pentacel	2082 (99.2)	695 (99.6)
Received Prevnar 13	2082 (99.2)	695 (99.6)
Received RotaTeq	2082 (99.2)	695 (99.6)
Received Engerix-B	2082 (99.2)	695 (99.6)
4 months (Dose 2)	-	-
Present	2006 (95.6)	671 (96.1)
Received MenACYW	2005 (95.5)	1 (0.1)
Received Menveo	0	663 (95.0)
Received Pentacel	2004 (95.5)	664 (95.1)
Received Prevnar 13	2004 (95.5)	664 (95.1)
Received RotaTeq	2004 (95.5)	664 (95.1)
6 months (Dose 3)	-	-
Present	1953 (93.0)	650 (93.1)
Received MenACYW	1951 (92.9)	0
Received Menveo	0	648 (92.8)
Received Pentacel	1948 (92.8)	647 (92.7)

Age / Dose #/ Event	Group 1 (N=2099) n (%)	Group 2 (N=698) n (%)
Received Prevnar 13	1948 (92.8)	647 (92.7)
Received RotaTeq	1947 (92.8)	647 (92.7)
Received Engerix-B	1947 (92.8)	647 (92.7)
12 months (Dose 4)	-	-
Present	1843 (87.8)	623 (89.3)
Received MenACYW	1838 (87.6)	0
Received Menveo	0	623 (89.3)
Received M-M-R II	1827 (87.0)	618 (88.5)
Received Varivax	1830 (87.2)	618 (88.5)
Received Prevnar 13	1832 (87.3)	620 (88.8)

n: number of participants fulfilling the item listed.
N: total number of participants randomized in each study group.
Source: Table 2 in Final CSR version 2.0 MET41, p.74.

The numbers and percentages of participants included in each safety set are presented in Table 4. No notable difference in inclusion rate between groups was observed.

Table 4: Safety Analysis Sets by Vaccination Group in MET41

Safety analysis sets	Group 1 n (%)	Group 2 n (%)
Received vaccine*	2080 (100)	697 (100)
Overall SafAS for any dose	2080 (100)	697 (100)
SafAS1 (vaccination at 2 months of age)	2080 (100)	697 (100)
SafAS2 (vaccination at 4 months of age)	2006 (96.4)	663 (95.1)
SafAS3 (vaccination at 6 months of age)	1951 (93.8)	648 (93.0)
SafAS4 (vaccination at 12 months of age)	1838 (88.4)	623 (89.4)
SafAS5 (all 4-dose vaccination)	1836 (88.3)	622 (89.2)

**: participants who received at least 1 dose of study vaccines, including MenACYW conjugate vaccine, Menveo or the routine vaccines.*
n: number of participants fulfilling the item listed.
Source: Table 4 in Final CSR version 2.0 MET41, p.80.

Reviewer's comment: Two participants allocated to Group 1 received MENVEO at Day 0. Those two participants were included in Group 2 for SafAS1. Both participants received the remaining three doses of MenACYW conjugate vaccine at 4, 6, and 12 months of age and were therefore included in Group 1 for SafAS2, SafAS3, and SafAS4, respectively. In addition, there were 20 participants who were randomized but were not vaccinated.

The demographic characteristics are presented in Table 5 for the randomized participants, which were similar between groups.

Table 5: Baseline Demographics – All Randomized Participants in MET41

Demographic	Group 1 (N=2099)	Group 2 (N=698)	All (N=2797)
Sex: n (%)	-	-	-
Male	1101 (52.5)	362 (51.9)	1463 (52.3)

Demographic	Group 1 (N=2099)	Group 2 (N=698)	All (N=2797)
Female	998 (47.5)	336 (48.1)	1334 (47.7)
Sex ratio:Male/Female	1.10	1.08	1.10
Age: (Days)	-	-	-
M	2099	698	2797
Mean (sd)	64.7 (6.63)	64.9 (6.77)	64.7 (6.67)
Min; Max	42.0; 89.0	42.0; 89.0	42.0; 89.0
Median	63.0	63.0	63.0
Q1; Q3	61.0; 67.0	61.0; 67.0	61.0; 67.0
Racial origin: n (%)	-	-	-
White	1719 (81.9)	580 (83.1)	2299 (82.2)
Asian	28 (1.3)	12 (1.7)	40 (1.4)
Black or African American	210 (10.0)	67 (9.6)	277 (9.9)
American Indian or Alaska Native	8 (0.4)	0	8 (0.3)
Native Hawaiian or Other Pacific Islander	10 (0.5)	5 (0.7)	15 (0.5)
Mixed origin	102 (4.9)	31 (4.4)	133 (4.8)
Unknown	12 (0.6)	0	12 (0.4)
Not reported	10 (0.5)	3 (0.4)	13 (0.5)
Ethnicity: n (%)	-	-	-
Hispanic or Latino	566 (27.0)	197 (28.2)	763 (27.3)
Not Hispanic or Latino	1526 (72.7)	499 (71.5)	2025 (72.4)
Unknown	0	0	0
Not reported	7 (0.3)	2 (0.3)	9 (0.3)

Source: Table 5 in Final CSR version 2.0 MET41, p.82.

6.1.11 Efficacy Analyses

Efficacy and immunogenicity were not assessed in this study.

6.1.12 Safety Analyses

Solicited Adverse Reactions

Solicited local and systemic AEs within 7 days following any and each vaccination by maximum severity on the Overall SafAS, SafAS1, SafAS2, SafAS3, and SafAS4 are summarized in Table 6, Table **7**, Table 8, Table 9, and Table 10, respectively.

Overall, rates of solicited local and systemic reactions were generally similar between groups after each and any vaccination. The most frequently reported local and systemic reactions were injection site tenderness and irritability, respectively.

Table 6: Percentage of Participants Reporting Any Solicited AE within 7 Days Following Any Vaccination – Overall SafAS in MET41

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
One or more solicited local AE	1715/2021	84.9	572/676	84.6
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	1501/2021	74.3	499/676	73.8
Grade 1	820/2021	40.6	269/676	39.8
Grade 2	521/2021	25.8	177/676	26.2
Grade 3	160/2021	7.9	53/676	7.8
Injection site erythema*	-	-	-	-
Any	826/2021	40.9	257/676	38.0
Grade 1	793/2021	39.2	252/676	37.3
Grade 2	24/2021	1.2	4/676	0.6
Grade 3	9/2021	0.4	1/676	0.1
Injection site swelling*	-	-	-	-
Any	557/2019	27.6	170/676	25.1
Grade 1	536/2019	26.5	168/676	24.9
Grade 2	12/2019	0.6	1/676	0.1
Grade 3	9/2019	0.4	1/676	0.1
One or more solicited systemic AE	1759/2019	87.1	596/676	88.2
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	724/2002	36.2	219/671	32.6
Grade 1	402/2002	20.1	130/671	19.4
Grade 2	274/2002	13.7	77/671	11.5
Grade 3	48/2002	2.4	12/671	1.8
Vomiting	-	-	-	-
Any	542/2018	26.9	163/676	24.1
Grade 1	313/2018	15.5	91/676	13.5
Grade 2	206/2018	10.2	67/676	9.9
Grade 3	23/2018	1.1	5/676	0.7
Crying abnormal	-	-	-	-
Any	1437/2019	71.2	478/676	70.7
Grade 1	661/2019	32.7	228/676	33.7
Grade 2	618/2019	30.6	193/676	28.6
Grade 3	158/2019	7.8	57/676	8.4
Drowsiness	-	-	-	-
Any	1430/2017	70.9	475/676	70.3
Grade 1	846/2017	41.9	283/676	41.9
Grade 2	467/2017	23.2	147/676	21.7
Grade 3	117/2017	5.8	45/676	6.7
Appetite loss	-	-	-	-
Any	1014/2018	50.2	350/676	51.8
Grade 1	635/2018	31.5	233/676	34.5
Grade 2	314/2018	15.6	94/676	13.9

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
Grade 3	65/3.2	3.2	23/676	3.4
Irritability	-	-	-	-
Any	1604/2018	79.5	536/676	79.3
Grade 1	520/2018	25.8	174/676	25.7
Grade 2	852/2018	42.2	282/676	41.7
Grade 3	232/2018	11.5	80/676	11.8

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 10 and Table 12 in Final CSR version 2.0 MET41.

Table 7**:** Percentage of Participants Reporting Any Solicited AE within 7 Days Following 2-Month Vaccination – SafAS1 in MET41

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
One or more solicited local AE	1270/2008	63.2	429/674	63.6
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	997/2008	49.7	330/673	49.0
Grade 1	673/2008	33.5	224/673	33.3
Grade 2	251/2008	12.5	79/673	11.7
Grade 3	73/2008	3.6	27/673	4.0
Injection site erythema*	-	-	-	-
Any	319/2008	15.9	107/674	15.9
Grade 1	302/2008	15.0	107/674	15.9
Grade 2	16/2008	0.8	0/674	0
Grade 3	1/2008	<0.1	0/674	0
Injection site swelling*	-	-	-	-
Any	207/2007	10.3	57/674	8.5
Grade 1	196/2007	9.8	57/674	8.5
Grade 2	8/2007	0.4	0/674	0
Grade 3	3/2007	0.1	0/674	0
One or more solicited systemic AE	1510/2005	75.3	501/674	74.3
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	150/1972	7.6	53/663	8.0
Grade 1	122/1972	6.2	43/663	6.5
Grade 2	25/1972	1.3	9/663	1.4
Grade 3	3/1972	0.2	1/663	0.2
Vomiting	-	-	-	-
Any	296/2005	14.8	85/674	12.6
Grade 1	194/2005	9.7	51/674	7.6
Grade 2	93/2005	4.6	32/674	4.7

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
Grade 3	9/2005	0.4	2/674	0.3
Crying abnormal	-	-	-	-
Any	976/2005	48.7	326/674	48.4
Grade 1	638/2005	31.8	208/674	30.9
Grade 2	282/2005	14.1	98/674	14.5
Grade 3	56/2005	2.8	20/674	3.0
Drowsiness	-	-	-	-
Any	1074/2005	53.6	346/674	51.3
Grade 1	781/2005	39.0	242/674	35.9
Grade 2	246/2005	12.3	85/674	12.6
Grade 3	47/2005	2.3	19/674	2.8
Appetite loss	-	-	-	-
Any	510/2005	25.4	170/674	25.2
Grade 1	374/2005	18.7	127/674	18.8
Grade 2	124/2005	6.2	37/674	5.5
Grade 3	12/2005	0.6	6/674	0.9
Irritability	-	-	-	-
Any	1218/2005	60.7	409/674	60.7
Grade 1	615/2005	30.7	214/674	31.8
Grade 2	522/2005	26.0	168/674	24.9
Grade 3	81/2005	4.0	27/674	4.0

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 16 and Table 18 in Final CSR version 2.0 MET41.

Table 8: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 4-Month Vaccination – SafAS2 in MET41

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
One or more solicited local AE	1232/1927	63.9	526/638	82.4
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	922/1926	47.9	295/637	46.3
Grade 1	660/1926	34.3	209/637	32.8
Grade 2	206/1926	10.7	72/637	11.3
Grade 3	56/1926	2.9	14/637	2.2
Injection site erythema*	-	-	-	-
Any	407/1926	21.1	125/635	19.7
Grade 1	404/1926	21.0	123635	19.4
Grade 2	0/1926	0	2/635	0.3
Grade 3	3/1926	0.2	0/635	0
Injection site swelling*	-	-	-	-

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
Any	232/1926	12.0	68/636	10.7
Grade 1	226/1926	11.7	67/636	10.5
Grade 2	3/1926	0.2	1/636	0.2
Grade 3	3/1926	0.2	0/636	0
One or more solicited systemic AE	1378/1927	71.5	475/638	74.5
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	351/1899	18.5	113/629	18.0
Grade 1	219/1899	11.5	71/629	11.3
Grade 2	120/1899	6.3	39/629	6.2
Grade 3	12/1899	0.6	3/629	0.5
Vomiting	-	-	-	-
Any	208/1927	10.8	64/638	10.0
Grade 1	121/1927	6.3	41/638	6.4
Grade 2	78/1927	4.0	23/638	3.6
Grade 3	9/1927	0.5	0/638	0
Crying abnormal	-	-	-	-
Any	905/1926	47.0	314/638	49.2
Grade 1	540/1926	28.0	199/638	31.2
Grade 2	307/1926	15.9	97/638	15.2
Grade 3	58/1926	3.0	18/638	2.8
Drowsiness	-	-	-	-
Any	928/1926	48.2	310/638	48.6
Grade 1	686/1926	35.6	237/638	37.1
Grade 2	205/1926	10.6	54/638	8.5
Grade 3	37/1926	1.9	19/638	3.0
Appetite loss	-	-	-	-
Any	472/1926	24.5	149/638	23.4
Grade 1	345/1926	17.9	115/638	18.0
Grade 2	112/1926	5.8	29/638	4.5
Grade 3	15/1926	0.8	5/638	0.8
Irritability	-	-	-	-
Any	1128/1926	58.6	390/638	61.1
Grade 1	563/1926	29.2	210/638	32.9
Grade 2	486/1926	25.2	154/638	24.1
Grade 3	79/1926	4.1	26/638	4.1

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 22 and Table 24 in Final CSR version 2.0 MET41.

Table 9: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 6-Month Vaccination – SafAS3 in MET41

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
One or more solicited local AE	1135/1797	63.2	373/600	62.2
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	842/1796	46.9	270/599	45.1
Grade 1	641/1796	35.7	201/599	33.6
Grade 2	164/1796	9.1	57/599	9.5
Grade 3	37/1796	2.1	12/599	2.0
Injection site erythema*	-	-	-	-
Any	441/1795	24.6	140/598	23.4
Grade 1	436/1795	24.3	140/598	23.4
Grade 2	4/1795	0.2	0/598	0
Grade 3	1/1795	<0.1	0/598	0
Injection site swelling*	-	-	-	-
Any	231/1796	12.9	76/598	12.7
Grade 1	230/1796	12.8	76/598	12.7
Grade 2	1/1796	<0.1	0/598	0
Grade 3	0/1796	0	0/598	0
One or more solicited systemic AE	1178/1796	65.6	389/600	64.8
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	292/1742	16.8	78/583	13.4
Grade 1	194/1742	11.1	50/583	8.6
Grade 2	84/1742	4.8	22/583	3.8
Grade 3	14/1742	0.8	6/583	1.0
Vomiting	-	-	-	-
Any	141/1796	7.9	60/599	10.0
Grade 1	93/1796	5.2	42/599	7.0
Grade 2	47/1796	2.6	16/599	2.7
Grade 3	1/1796	<0.1	2/599	0.3
Crying abnormal	-	-	-	-
Any	705/1796	39.3	239/599	39.9
Grade 1	456/1796	25.4	160/599	26.7
Grade 2	214/1796	11.9	65/599	10.9
Grade 3	35/1796	1.9	14/599	2.3
Drowsiness	-	-	-	-
Any	749/1796	41.7	249/599	41.6
Grade 1	556/1796	31.0	189/599	31.6
Grade 2	171/1796	9.5	54/599	9.0
Grade 3	22/1796	1.2	6/599	1.0
Appetite loss	-	-	-	-
Any	410/1796	22.8	135/599	22.5
Grade 1	300/1796	16.7	103/599	17.2
Grade 2	99/1796	5.5	24/599	4.0

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
Grade 3	11/1796	0.6	8/599	1.3
Irritability	-	-	-	-
Any	964/1796	53.7	331/600	55.2
Grade 1	547/1796	30.5	193/600	32.2
Grade 2	360/1796	20.0	120/600	20.0
Grade 3	57/1796	3.2	18/600	3.0

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 28 and Table 30 in Final CSR version 2.0 MET41.

Table 10: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 12-Month Vaccination – SafAS4 in MET41

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
One or more solicited local AE	1133/1768	64.1	382/592	64.5
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	868/1765	49.2	288/592	48.6
Grade 1	632/1765	35.8	207/592	35.0
Grade 2	196/1765	11.1	71/592	12.0
Grade 3	40/1765	2.3	10/592	1.7
Injection site erythema*	-	-	-	-
Any	450/1765	25.5	145/592	24.5
Grade 1	441/1765	25.0	142/592	24.0
Grade 2	5/1765	0.3	2/592	0.3
Grade 3	4/1765	0.2	1/592	0.2
Injection site swelling*	-	-	-	-
Any	261/1764	14.8	82/591	13.9
Grade 1	256/1764	14.5	81/591	13.7
Grade 2	2/1764	0.1	0/591	0
Grade 3	3/1764	0.2	1/591	0.2
One or more solicited systemic AE	1160/1767	65.6	381/593	64.2
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	280/1733	16.2	61/583	10.5
Grade 1	157/1733	9.1	39/583	6.7
Grade 2	102/1733	5.9	18/583	3.1
Grade 3	21/1733	1.2	4/583	0.7
Vomiting	-	-	-	-
Any	113/1765	6.4	27/591	4.6
Grade 1	76/1765	4.3	18/591	3.0
Grade 2	32/1765	1.8	8/591	1.4

Solicited AE / Severity	Group 1 n/M	Group 1 %	Group 2 n/M	Group 2 %
Grade 3	5/1765	0.3	1/591	0.2
Crying abnormal	-	-	-	-
Any	740/1765	41.9	241/591	40.8
Grade 1	456/1765	25.8	153/591	25.9
Grade 2	234/1765	13.3	75/591	12.7
Grade 3	50/1765	2.8	13/591	2.2
Drowsiness	-	-	-	-
Any	712/1763	40.4	218/591	36.9
Grade 1	540/1763	30.6	166/591	28.1
Grade 2	134/1763	7.6	42/591	7.1
Grade 3	38/1763	2.2	10/591	1.7
Appetite loss	-	-	-	-
Any	460/1764	26.1	153/591	25.9
Grade 1	326/1764	18.5	113/591	19.1
Grade 2	104/1764	5.9	34/591	5.8
Grade 3	30/1764	1.7	6/591	1.0
Irritability	-	-	-	-
Any	993/1764	56.3	332.592	56.1
Grade 1	520/1764	29.5	172/592	29.1
Grade 2	396/1764	22.4	138/592	23.3
Grade 3	77/1764	4.4	22/592	3.7

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 34 and Table 36 in Final CSR version 2.0 MET41.

Unsolicited Adverse Events

In the overall SafAS, there were 7 participants (0.3%) in Group 1 and 2 participants (0.3%) in Group 2 who reported immediate unsolicited AE within 30 minutes of any vaccination, and there were three participants (0.1%) in Group 1 and one participant (0.1%) in Group 2 who reported immediate unsolicited AR within 30 minutes of any vaccination. The percentage of participants who reported any unsolicited AE within 30 days of any vaccination was 65.0% in Group 1 and 62.7% in Group 2. In general, the percentages of participants with unsolicited AEs reported within 30 days from each vaccination were comparable between Group 1 and Group 2.

Table 11 presents the percentage of participants who experienced at least one SAE, AESI, and MAAE within 30 days of any vaccination and during the study period by vaccination group. The percentages of participants reporting MAAEs were generally similar between groups. The percentages of participants reporting any SAE during the study were 5.2% in Group 1 and 3.0% in Group 2. Three participants in Group 1 (at 24 and 30 days after the first dose and four days after the third dose of MenACYW conjugate vaccine) and none in

Group 2 died during the study. None of the SAEs, including the three deaths in Group 1, were considered as related to the study vaccine by the investigator.

Table 11: Overview of SAEs, AESIs, and MAAEs in MET41

AEs / Safety Analysis Sets	Group 1 (within 30 days after vaccination) n/N (%)	Group 2 (within 30 days after vaccination) n/N (%)	Group 1 (during study) n/N (%)	Group 2 (during study) n/N (%)
SAE	-	-	-	-
Overall SafAS	44/2080 (2.1%)	9/697 (1.3%)	108/2080 (5.2%)	21/697 (3.0%)
SafAS1	23/2080 (1.1%)	4/697 (0.6%)	33/2080 (1.6%)	5/697 (0.7%)
SafAS2	4/2006 (0.2%)	0	11/2006 (0.5%)	2/663 (0.3%)
SafAS3	9/1951 (0.5%)	1/648 (0.2%)	35/1951 (1.8%)	4/648 (0.6%)
SafAS4	9/1838 (0.5%)	4/623 (0.6%)	33/1838 (1.8%)	12/623 (1.9%)
SafAS5	36/1836 (2.0%)	9/622 (1.4%)	93/1836 (5.1%)	21/622 (3.4%)
AESI	-	-	-	-
Overall SafAS	5/2080 (0.2%)	0	19/2080 (0.9%)	1/697 (0.1%)
SafAS1	2/2080 (0.1%)	0	3/2080 (0.1%)	0
SafAS2	0	0	0	0
SafAS3	1/1951 (<0.1%)	0	10/1951 (0.5%)	1/648 (0.2%)
SafAS4	3/1838 (0.2%)	0	8/1838 (0.4%)	1/623 (0.2%)
SafAS5	4/1836 (0.2%)	0	17/1836 (0.9%)	1/622 (0.2%)
MAAE	-	-	-	-
Overall SafAS	1060/2080 (51.0%)	339/697 (48.6%)	1581/2080 (76.0%)	526/697 (75.5%)
SafAS1	351/2080 (16.9%)	118/697 (16.9%)	715/2080 (34.4%)	236/697 (33.9%)
SafAS2	445/2006 (22.2%)	129/663 (19.5%)	811/2006 (40.4%)	256/663 (38.6%)
SafAS3	392/1951 (20.1%)	134/648 (20.7%)	1199/1951 (61.5%)	398/648 (61.4%)
SafAS4	447/1838 (24.3%)	129/623 (20.7%)	894/1838 (48.6%)	272/623 (43.7%)
SafAS5	1002/1836 (54.6%)	322/622 (51.8%)	1488/1836 (81.0%)	498/622 (80.1%)

n: number of participants experiencing the endpoints listed in first column.
N: number of participants in the analysis set. Percentages are based on N.
Source: Summarized by the reviewer based on information presented in Final CSR version 2.0 MET41.

Reviewer's comment: Safety analyses were also performed based on subgroups, i.e., sex, race, and gestational age at birth (pre-term and full-term). There were no notable differences from the primary analysis.

6.2 Study MET42 (Phase III)

Title: Immunogenicity and safety study of an investigational quadrivalent meningococcal conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.

Study initiation date: April 25, 2018 (first subject first visit)
Study completion date: September 22, 2023 (last subject last contact)

6.2.1 Objectives

Primary immunogenicity objectives:

1. To demonstrate the NI of the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a 4-dose series of MenACYW conjugate vaccine compared to a 4-dose series of MENVEO when given concomitantly with routine pediatric vaccines to infants and toddlers 6 weeks old to 15 months old (hSBA vaccine seroresponse for serogroups A, C, Y and W was defined as: for a participant with a pre-vaccination titer < 1:8, the post-vaccination titer should be ≥ 1:16 and for a participant with a pre-vaccination titer ≥ 1:8, the post-vaccination titer should be ≥ 4-fold greater than the pre-vaccination titer).
2. To demonstrate the NI of the hSBA antibody (Ab) response to meningococcal serogroups A, C, Y, and W following the administration of three doses in infancy of MenACYW conjugate vaccine compared to three doses in infancy of MENVEO when given concomitantly with routine pediatric vaccines to infants at 2, 4, and 6 months of age.

Secondary immunogenicity objectives:

1. To demonstrate the NI of immune responses of the routine pediatric vaccines administered concomitantly with MenACYW conjugate vaccine as compared with MENVEO in infants and toddlers 6 weeks old to 18 months old.
2. To assess the Ab responses against meningococcal serogroups A, C, Y, and W after the administration of the fourth dose of MenACYW conjugate vaccine or MENVEO when both were given concomitantly with routine pediatric vaccines at 12 months of age.
3. To assess the persistence of bactericidal Ab at 12 months of age in participants who previously received three doses of MenACYW conjugate vaccine or MENVEO in infancy concomitantly with routine pediatric vaccines at 2, 4, and 6 months of age.
4. To describe the Ab responses against the antigens of the routine pediatric vaccines (Pentacel, PREVNAR 13, M-M-R II, VARIVAX, RotaTeq, and ENGERIX-B) when administered concomitantly with either MenACYW conjugate vaccine or MENVEO.
5. To describe the Ab responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine vs MENVEO was administered concomitantly with routine pediatric vaccines.
6. To describe the Ab responses against meningococcal serogroups A, C, Y, and W when MenACYW conjugate vaccine was administered to children 12 to 15 months of age vs when MenACYW conjugate vaccine was administered to children 15 to

18 months of age, concomitantly with routine pediatric vaccines (Subgroup 1a vs Subgroup 1b), including the bactericidal antibodies persistence and the effect of fourth dose of MenACYW conjugate vaccine at 12 to 15 months of age or 15 to 18 months of age.

Safety objective:

- To describe the safety profile of MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.

6.2.2 Design Overview

This was a Phase III, partially modified double-blind, randomized, parallel-group, active controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine pediatric vaccines to healthy infants and toddlers in the US. Approximately 2628 healthy infants aged ≥ 42 to ≤ 89 days were planned to be randomized 2:1 to the following groups:

- Group 1 (G1): MenACYW conjugate vaccine and routine pediatric vaccines,
- Group 2 (G2): MENVEO and routine pediatric vaccines.

Each group was further randomized 2:1 to two subgroups based on the time of analyses conducted in the second year of life (30 days after the 12-month vaccinations or 30 days after the 15-month vaccinations):

- Group 1:
  - Subgroup 1a (G1a) (12 months): MenACYW conjugate vaccine and routine vaccines at 2, 4, 6, and 12 to 15 months of age,
  - Subgroup 1b (G1b) (15 months): MenACYW conjugate vaccine at 2, 4, 6, and 15 to 18 months of age and routine vaccines at 2, 4, 6, 12 to 15 months of age, and 15 to 18 months of age.
- Group 2:
  - Subgroup 2a (G2a) (12 months): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age,
  - Subgroup 2b (G2b) (15 months): MENVEO at 2, 4, 6, and 12 months of age and routine vaccines at 2, 4, 6, 12, and 15 to 18 months of age.

All participants received the following routine vaccines as per the Advisory Committee on Immunization Practices (ACIP) recommendations:

- Pentacel (diphtheria-tetanus-acellular pertussis [DTaP]-inactivated poliovirus vaccine [IPV]/Hib) at 2, 4, 6, and 15 to 18 months of age,
- PREVNAR 13 (PCV13) at 2, 4, 6, and 12 to 15 months of age,
- RotaTeq (pentavalent rotavirus vaccine [RV5]) at 2, 4, and 6 months of age,
- ENGERIX-B (HB vaccine) at 2 and 6 months of age,
- M-M-R II (measles, mumps, rubella [MMR] vaccine) at 12 to 15 months of age,
- VARIVAX (varicella vaccine) at 12 to 15 months of age.

In addition, participants in Subgroup 1b and Group 2 were provided the first dose of hepatitis A vaccine (HAVRIX) at 15 to 18 months of age as part of the study. For participants in Subgroup 1a, hepatitis A vaccine was provided after completion of the last study visit.

Safety data were collected as follows: immediate unsolicited systemic AEs were collected within 30 minutes after each vaccination. Solicited AEs were collected from Day 0 to Day 7 after each vaccination; unsolicited AEs were collected from Day 0 to Day 30 after each vaccination; SAEs (including AESIs) and MAAEs were collected until the end of the 6-month follow-up period after the last vaccination.

Blood samples for immunogenicity were collected pre-vaccination at 2 months of age and at 7 months of age for Group 1 and Group 2. For Subgroup 1a, blood samples were collected pre-vaccination at 12 to 15 months of age and at 13 to 16 months of age. For Subgroup 1b and Subgroup 2b, blood samples were collected pre-vaccination at 15 to 18 months of age and at 16 to 19 months of age. For Subgroup 2a, blood samples were collected pre-vaccination at 12 months of age and at 13 months of age.

During the infant part of the study, participants/parents, investigators, safety outcome assessors, and Sponsor were blinded to the meningococcal vaccine received, except for personnel administering the vaccine. However, during the toddler part of the study, individuals might be potentially unblinded due to the different timing of vaccination visits, and the number of vaccines received.

6.2.3 Population

The study population included healthy male and female infants aged 42 to 89 days on the day of the first visit, who had not been previously vaccinated against meningococcal disease with either mono- or polyvalent polysaccharide, or conjugate meningococcal vaccine containing serogroups A, C, Y, or W, or meningococcal B serogroup vaccine, or any pneumococcal, diphtheria, tetanus, pertussis, poliomyelitis, hepatitis A, measles, mumps, rubella, varicella, Hib, and/or rotavirus vaccines. Participants had to have received a first dose of hepatitis B vaccine at least 28 days prior to study enrollment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 12 summarizes the dose and route of the administered vaccines.

Table 12: Dose and Route of the Administered Vaccines in MET42

Vaccines	Dose, route
MenACYW conjugate vaccine	0.5 mL solution IM at 2, 4, and 6 months of age for Group 1; at 12 to 15 months of age for Subgroup 1a; and at 15 to 18 months of age for Subgroup 1b
MENVEO	0.5 mL solution IM at 2, 4, 6 and 12 months of age for Group 2
Pentacel	0.5 mL solution IM at 2, 4 and 6 and 15 to 18 months of age*
Prevnar 13	0.5 mL suspension IM at 2, 4, 6 and 12 to 15 months of age for Group 1; and at 2, 4, 6, and 12 months of age for Group 2
RotaTeq	2 mL oral solution at 2, 4 and 6 months of age

Vaccines	Dose, route
Engerix-B	0.5 mL suspension IM at 2 and 6 months of age
M-M-R II	0.5 mL subcutaneous at 12 to 15 months of age for Group 1 and at 12 months of age at Group 2
Varivax	0.5 mL suspension subcutaneous at 12 to 15 months of age for Group 1 and at 12 months of age at Group 2
HAVRIX	0.5 mL suspension IM at 15 to 18 months for Subgroups 1b, 2a and 2b

**: Participants in Subgroup 1a completed the last study visit at 13 to 16 months of age. For these participants, the fourth dose of Pentacel was administered at 15 to 18 months of age by the applicant for completion of the DTaP series with vaccine from the same manufacturer, as per ACIP recommendation.*
Source: Summarized by the reviewer based on information presented in the MET42 CSR.

6.2.6 Sites and Centers

The study was conducted at 69 sites in the US.

6.2.7 Surveillance/Monitoring

Please refer to the clinical reviewer's review.

6.2.8 Endpoints and Criteria for Study Success

Primary immunogenicity endpoints:

1. Meningococcal serogroups A, C, Y, and W Ab titers measured by hSBA before first study vaccination on Day 0 and 30 days after the fourth meningococcal vaccination (Subgroup 1a vs Subgroup 2a).
2. Ab titers ≥ 1:8 against meningococcal serogroups A, C, Y, and W measured by hSBA assessed 30 days after vaccination(s) at 6 months of age (Group 1 vs Group 2).

Secondary immunogenicity endpoints:

1. The following serological endpoints will be assessed:
   - Day 0 (before first vaccination) for Group 1 and Group 2:
     - Anti-rotavirus serum IgA Ab concentrations
   - 30 days after the 6-month vaccination for Group 1 and Group 2:
     - IgG Abs against hepatitis B surface antigen (anti-HB) concentrations ≥10 milli-international units (mIU)/mL
     - Anti PRP Ab concentrations ≥0.15 µg/mL
     - Anti PRP Ab concentrations ≥ 1.0 µg/mL
     - Anti-poliovirus types (1, 2 and 3) Ab titers ≥1:8
     - Anti-rotavirus serum IgA Ab concentrations with ≥3-fold rise over baseline
     - Anti-rotavirus serum IgA Ab GMCs
     - Anti-pertussis Ab GMCs (PT, FHA, PRN and FIM)
     - Anti-pneumococcal antibody GMCs (for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).
   - 30 days after the 12-month vaccinations for Subgroup 1a and Subgroup 2a:
     - Anti-measles Ab concentrations ≥ 255 mIU/mL
     - Anti-mumps Ab concentrations ≥ 10 mumps Ab units/mL

- Anti-rubella Ab concentrations ≥ 10 IU/mL
- Anti-varicella Ab concentrations ≥ 5 glycoprotein enzyme-linked immunosorbent assay (gpELISA) units/mL
- Anti-pneumococcal Ab GMCs (for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

- Before the 15-month vaccination for Subgroup 1b and Subgroup 2b:
  - Anti-pertussis antibody concentrations (PT, FHA, PRN and FIM).
- 30 days after the 15-month vaccinations for Subgroup 1b and Subgroup 2b:
  - Anti-PRP Ab concentrations ≥ 1.0 µg/mL
  - Anti-poliovirus types 1, 2, and 3 Ab titers ≥ 1:8
  - Anti-pertussis Ab vaccine response (PT, FHA, PRN, and FIM). Pertussis vaccine response is defined as:
    - Pre-vaccination < lower limit of quantitation (LLOQ), then post-vaccination should be ≥ 4x the LLOQ
    - Pre-vaccination > LLOQ but < 4x the LLOQ, then post-vaccination should achieve a 4-fold rise (post-vaccination/pre-vaccination ≥ 4)
    - Pre-vaccination ≥ 4x the LLOQ, then post-vaccination should achieve a 2-fold rise (post-vaccination/pre-vaccination ≥ 2)

2. The following serological endpoints will be assessed (effect of fourth dose of MenACYW or MENVEO):
   - Before the 12-month vaccination (pre-fourth dose) for Subgroups 1a and 2a:
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers.
   - 30 days after the 12-month vaccination for Subgroups 1a and 2a:
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-fourth dose (at 12 months of age).
3. The following serological endpoints will be assessed (persistence of bactericidal antibodies after infant vaccination with MenACYW or MENVEO):
   - 30 days after the 6-month vaccination and before the 12-month vaccination for Subgroup 1a and Subgroup 2a:
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥1:4 and ≥1:8.
4. The following serological endpoints will be assessed:
   - Day 0 (before first vaccination) for Groups 1 and 2
     - Anti-pertussis Ab concentrations (PT, FHA, PRN, FIM)
   - 30 days after the 6-month vaccination (after the third dose) for Group 1 and Group 2:
     - Anti-PRP Ab concentrations
     - Anti-diphtheria Ab concentrations
     - Anti-diphtheria Ab concentrations ≥ 0.01 IU/mL
     - Anti-diphtheria Ab concentrations ≥ 0.1 IU/mL
     - Anti-tetanus Ab concentrations
     - Anti-tetanus Ab concentrations ≥ 0.01 IU/mL
     - Anti-tetanus Ab concentrations ≥ 0.1 IU/mL
     - Anti-HBs Ab concentrations

- Anti-HBs concentrations ≥ 100 IU/mL
- Anti-polio (types 1, 2, and 3) Ab titers
- Anti-rotavirus serum IgA Ab concentrations
- Anti-rotavirus serum IgA Ab concentrations with ≥4-fold rise over baseline
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations (vaccine response)
- Anti-pneumococcal Ab concentrations (PCV13)
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 0.35 µg/mL
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 1 µg/mL

▪ 30 days after the 12-month vaccinations for Subgroup 1a and Subgroup 2a:
- Anti-measles Ab concentrations
- Anti-mumps Ab concentrations
- Anti-rubella Ab concentrations
- Anti-varicella Ab concentrations
- Anti-pneumococcal Ab concentrations (PCV13)
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 0.35 µg/mL
- Anti-pneumococcal Ab concentrations (PCV13) ≥ 1 µg/mL

▪ 30 days after the 6-month vaccination and before vaccination at the 15-month vaccinations for Subgroup 1b and Subgroup 2b to evaluate immune persistence after primary series vaccination with Hib and pertussis vaccines:
- Anti-PRP Ab concentration ≥ 0.15 µg/mL
- Anti-PRP Ab concentrations
- Anti-pertussis (PT, FHA, PRN, and FIM) Ab concentrations

▪ 30 days after the 15-month vaccinations for Subgroup 1b and Subgroup 2b:
- Anti-PRP Ab concentrations
- Anti-diphtheria Ab concentrations
- Anti-diphtheria Ab concentrations ≥ 0.1 IU/mL
- Anti-diphtheria Ab concentrations ≥ 1.0 IU/mL
- Anti-tetanus Ab concentrations
- Anti-tetanus Ab concentrations ≥ 0.1 IU/mL
- Anti-tetanus Ab concentrations ≥ 1.0 IU/mL
- Anti-polio (types 1, 2, and 3) antibody titers
- Anti-pertussis Ab (PT, FHA, PRN, and FIM) concentrations

5. The following serological endpoints will be assessed:

▪ Day 0 (before first vaccination) for Group 1 and Group 2:
- hSBA meningococcal serogroups A, C, Y and W Ab titers

▪ 30 days after the 6-month vaccination (after the third dose) for Group 1 and Group 2:
- hSBA meningococcal serogroups A, C, Y, and W Ab titers
- Titer distribution and reverse cumulative distribution curves (RCDCs)
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8
- hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (Day 0) to post-vaccination
- hSBA vaccine seroresponse

- Before the 12-month vaccination for Subgroups 1a and 2a and before the 15-month vaccination for Subgroup 1b:
  - hSBA meningococcal serogroups A, C, Y and W Ab titers
- 30 days after the 12-month vaccinations for Subgroup 1a and 2a and 30 days after the 15-month vaccination for Subgroup 1b:
  - hSBA meningococcal serogroups A, C, Y, and W Ab titers
  - Titer distribution and RCDCs
  - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8
  - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (Day 0) to post-dose 4 vaccination
  - hSBA vaccine seroresponse

6. The following serological endpoints will be assessed:
   - Day 0 (before first vaccination) for Subgroup 1a and Subgroup 1b:
     - hSBA meningococcal serogroups A, C, Y and W Ab titers
   - 30 days after the 6-month vaccination and before the 12-month vaccination for Subgroup 1a and before the 15-month vaccination for Subgroup 1b to evaluate the immune persistence after infant vaccination with MenACYW conjugate vaccine:
     - hSBA meningococcal serogroups A, C, Y and W Ab titers
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8
   - 30 days after the 12-month vaccinations for Subgroup 1a and 30 days after the 15-month vaccination for Subgroup 1b, including evaluation of the effect of the fourth dose of MenACYW conjugate vaccine:
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ratio (Subgroup 1b/Subgroup 1a)
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 1:4 and ≥ 1:8
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥1:8 difference (Subgroup 1b – Subgroup 1a)
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-vaccination (Day 0) to post-fourth dose vaccination
     - hSBA meningococcal serogroups A, C, Y, and W Ab titers ≥ 4-fold rise from pre-fourth dose vaccination to post-fourth dose vaccination
     - hSBA vaccine seroresponse
     - hSBA vaccine seroresponse difference (Subgroup 1b – Subgroup 1a).

Safety endpoints:

- Occurrence, nature (MedDRA preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions occurring up to seven days after each vaccination.

- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions occurring up to seven days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to 30 days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) up to the 6-month follow-up contact after the last vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of MAAEs up to the 6-month follow-up contact after the last vaccination.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The following analysis sets were defined.

Analysis sets:

- *FAS*: There were three FASs.
  - The *FAS1* was defined as the subset of all randomized participants who received at least one dose of the study vaccine in infancy (<12 months of age) and had a valid post-vaccination serology result in infancy.
  - The *FAS2* was defined as the subset of all randomized participants who received at least one dose of the study vaccine in infancy (< 12 months of age) and had a valid pre-vaccination serology result before the 12-month vaccination for Subgroups 1a and 2a or before the 15-month vaccination for Subgroups 1b and 2b.
  - The *FAS3* was defined as the subset of all randomized participants who received at least one dose of the study vaccine in the second year of life (≥12 months of age) and had a valid post-vaccination serology result in the second year of life.
- *PPAS*: There were three PPASs based on the three FASs.
  - *PPAS for infant vaccination (PPAS1)*: All participants in the FAS1 who correctly received the vaccine and had no important protocol deviations during infancy or other events leading to exclusions before locking the database.
  - *PPAS for immunogenicity persistence evaluation (PPAS2)*: All participants in the FAS2 who correctly received the vaccine and had no important protocol deviations or other events leading to exclusions before locking the database.
  - *PPAS for second year of life vaccination (PPAS3)*: All participants in the FAS3 who correctly received the vaccine and had no important protocol deviations during infancy and in the second year of life or other events leading to exclusions before locking the database.
- *SafAS*: The *Overall SafAS* was defined as those who received at least one dose of the study vaccines and had any safety data available. All participants had their safety data analyzed according to the vaccine received at the first dose. The *SafAS1*,

SafAS2, *SafAS3*, *SafAS4* and *SafAS5* were defined as those who have received the study vaccine at 2 months of age, 4 months of age, 6 months of age, 12-15 months of age, and 15-18 months of age, respectively. All participants had their safety data analyzed after each dose according to the respective vaccine they actually received. *SafAS6* was defined as those who received all four doses of the investigational vaccines and had any safety data available. All participants had their safety data analyzed according to the vaccine received at the first dose.

Primary immunogenicity analyses:
Primary immunogenicity analyses were conducted for each of the four serogroups on the PPAS. Analyses were also performed on the FAS as sensitivity analyses. The following primary hypotheses were tested:

- *Primary hypothesis 1*: H0: p(G1a) – p(G2a) ≤ -10% vs H1: p(G1a) – p(G2a) > -10%, where p(G1a) and p(G2a) were the percentages of participants who achieved hSBA vaccine seroresponse in Subgroup 1a and Subgroup 2a, respectively.
- *Primary hypothesis 2*: H0: p(G1) – p(G2) ≤ -10% vs H1: p(G1) – p(G2) > -10%, where p(G1) and p(G2) were the percentages of participants who achieved hSBA ≥1:8 in Group 1 and Group 2, respectively.

Each of serogroups A, C, Y and W was tested separately for the primary hypotheses. If the lower limit of the two-sided 95% CI of the difference between the two proportions was > -10% for each serogroup, the null hypothesis of inferiority was rejected. The overall non-inferiority of the primary hypotheses was demonstrated when all four individual null hypotheses were rejected. The CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

Secondary immunogenicity analyses:
Summary of NI hypotheses for secondary objective 1 is given in Table 13.

Table 13: Summary of Non-Inferiority Hypotheses in MET42

Antigen	Endpoint	NI margin	Hypothesis number
1st year: 30 days after the 6-month vaccination (G1 vs G2)	-	-	-
Hepatitis B	%≥10 mIU/mL	-10%	1
PRP	%≥0.15µg/mL	-5%	2
PRP	%≥1.0µg/mL	-10%	3
Polio†	%≥1:8	-5%	4
Rotavirus	%≥3-fold rise	-10%	5
Rotavirus	GMC (G1/G2)	0.67	6
Pertussis*	GMC (G1/G2)	0.67	7
Pneumococcal‡	GMC (G1/G2)	0.5	8
2nd year: 30 days after the 12-month vaccination (G1a vs G2a)	-	-	-
Measles	%≥255 mIU/mL	-10%	9
Mumps	%≥10 mumps Ab units/mL	-10%	10
Rubella	%≥ 10 IU/mL	-10%	11
Varicella	%≥5 gpELISA unis/mL	-10%	12
Pneumococcal‡	GMC (G1a/G2a)	0.5	13
2nd year: 30 days after the 15-month vaccination (G1b vs G2b)	-	-	-
PRP	%≥1.0µg/mL	-10%	14
Polio†	%≥1:8	-5%	15
Pertussis*	Response rate	-10%	16

** Pertussis: PT, FHA, PRN and FIM.*
† Polio: type 1, 2 and 3.
‡ Pneumococcal: 1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
Source: Table 5.2 in SAP MET42 version 3.0, p.69.

For each of the NI hypotheses (hypothesis 1 to 5, 9 to 12 and 14 to 16) using proportions, the 95% CI of the difference in proportions was computed using the Wilson Score method without continuity correction. For each of the NI hypotheses (hypothesis 6 to 8 and 13) using the GMC ratios, the statistical methodology was based on the use of the two-sided 95% CI of the difference in means of post-vaccination Log_{10} transformed concentrations with normal approximation.

Reviewer's Comment: *Multiple hypotheses were prespecified for the primary and secondary endpoints; however, no multiplicity adjustment was used.*

All immunogenicity analyses for the remaining secondary objectives were descriptive.

Safety analyses:
Safety endpoints were described. The main parameters for the safety endpoints were described by percentages and 95% CIs (based on the Clopper-Pearson method).

Missing data:
No missing data were imputed. The following rules for immunogenicity were applied:

- If a value was < LLOQ, then LLOQ/2 was used as the computed value.
- If a value was ≥ ULOQ, then the computed value was ULOQ.

Fold-rise was computed as follows for values < LLOQ:

- If the baseline value was < LLOQ and the post-baseline value was < LLOQ, then the fold-rise was 1.
- If the baseline value was ≥ LLOQ and the post-baseline value was < LLOQ, then the fold-rise was (LLOQ/2) / baseline value.
- If the baseline value was < LLOQ and the post-baseline value was ≥ LLOQ, then the fold-rise is post-baseline value / LLOQ.

Sample size and power for immunogenicity analysis:
Approximately 2628 participants were planned to be enrolled. An estimated non-evaluable rate of 34.1% resulted in approximately 1732 participants in the PPAS (1155 evaluable participants in Group 1 and 577 in Group 2). With 770 evaluable participants in Subgroup 1a and 385 evaluable participants in Subgroup 2a, the study had 98.4% power to reject primary hypothesis 1. With 1155 evaluable participants in Group 1 and 577 evaluable participants in Group 2, the study had 98.8% power to reject primary hypothesis 2. Similarly, the study had 94.2% power to reject secondary hypotheses 1 to 8, >99.9% power to reject secondary hypotheses 9 to 13, and 98.6% power to reject secondary hypotheses 14 to 16.

Subgroup analyses:
Subgroup analyses by sex (male and female), race (White, Black, Asian, Other) and gestational age at birth (pre-term and full-term) between Group 1 and Group 2, as well as between Subgroups 1a and 2a, were performed.

6.2.10 Study Population and Disposition

The disposition of participants is provided in Table 14. A total of 2627 participants were randomized.

Table 14: Disposition by Randomized Group – All Randomized Participants in MET42

Action/ Vaccine received	Group 1 (N=1746) n (%)	Group 2 (N=881) n (%)	Group 1a (N=1167) n (%)	Group 1b (N=579) n (%)	Group 2a (N=588) n (%)	Group 2b (N=293) n (%)
2 months (Dose 1)	-	-	-	-	-	-
Present	1746 (100)	881 (100)	-	-	-	-
BL performed	1432 (82.0)	726 (82.4)	-	-	-	-
MenACYW	1726 (98.9)	1 (0.1)	-	-	-	-
Menveo	0	867 (98.4)	-	-	-	-
Pentacel	1727 (98.9)	868 (98.5)	-	-	-	-
Prevnar 13	1727 (98.9)	868 (98.5)	-	-	-	-
RotaTeq	1726 (98.9)	869 (98.6)	-	-	-	-
Engerix-B	1727 (98.9)	868 (98.5)	-	-	-	-
4 months (Dose 2)	-	-	-	-	-	-
Present	1625 (93.1)	829 (94.1)	-	-	-	-

Action/ Vaccine received	Group 1 (N=1746) n (%)	Group 2 (N=881) n (%)	Group 1a (N=1167) n (%)	Group 1b (N=579) n (%)	Group 2a (N=588) n (%)	Group 2b (N=293) n (%)
MenACYW	1619 (92.7)	1 (0.1)	-	-	-	-
Menveo	0	827 (93.9)	-	-	-	-
Pentacel	1615 (92.5)	828 (94.0)	-	-	-	-
Prevnar 13	1615 (92.5)	828 (94.0)	-	-	-	-
RotaTeq	1615 (92.5)	828 (94.0)	-	-	-	-
6 months (Dose 3)	-	-	-	-	-	-
Present	1545 (88.5)	794 (90.1)	-	-	-	-
MenACYW	1542 (88.3)	0	-	-	-	-
Menveo	1 (<0.1)	793 (90.0)	-	-	-	-
Pentacel	1541 (88.3)	792 (89.9)	-	-	-	-
Prevnar 13	1541 (88.3)	792 (89.9)	-	-	-	-
RotaTeq	1538 (88.1)	790 (89.7)	-	-	-	-
Engerix-B	1541 (88.3)	791 (89.8)	-	-	-	-
7 months	-	-	-	-	-	-
Present	1481 (84.8)	764 (86.7)	-	-	-	-
BL performed	1359 (77.8)	684 (77.6)	-	-	-	-
12 months (Dose 4)	-	-	-	-	-	-
Present	-	-	942 (80.7)	472 (81.5)	479 (81.5)	232 (79.2)
BL performed	-	-	858 (73.5)	1 (0.2)	440 (74.8)	3 (1.0)
MenACYW	-	-	938 (80.4)	0	0	0
Menveo	-	-	0	0	477 (81.1)	231 (78.8)
M-M-R II	-	-	936 (80.2)	471 (81.3)	474 (80.6)	231 (78.8)
Varivax	-	-	934 (80.0)	471 (81.3)	474 (80.6)	231 (78.8)
Prevnar 13	-	-	938 (80.4)	471 (81.3)	476 (81.0)	231 (78.8)
13 months	-	-	-	-	-	-
Present	-	-	911 (78.1)	-	435 (74.0)	-
BL performed	-	-	831 (71.2)	-	400 (68.0)	-
15 months (Dose 4)	-	-	-	-	-	-
Present	-	-	0	445 (76.9)	426 (72.4)	222 (75.8)
BL performed	-	-	-	395 (68.2)	-	201 (68.6)
MenACYW	-	-	0	445 (76.9)	0	0
Pentacel	-	-	0	444 (76.7)	425 (72.3)	219 (74.7)
Havrix	-	-	0	444 (76.7)	424 (72.1)	219 (74.7)
16 months	-	-	-	-	-	-
Present	-	-	0	421 (72.7)	414 (70.4)	209 (71.3)
BL performed	-	-	0	385 (66.5)	-	194 (66.2)
Termination	-	-	-	-	-	-
Completed trial	1330 (76.2)	623 (70.7)	910 (78.0)	420 (72.5)	414 (70.4)	209 (71.3)
Did not completed	416 (23.8)	258 (29.3)	257 (22.0)	159 (27.5)	174 (29.6)	84 (28.7)
Early termination reason	-	-	-	-	-	-
AE	2 (0.1)	1 (0.1)	2 (0.2)	0	0	1 (0.3)
Protocol deviation	65 (3.7)	48 (5.4)	41 (3.5)	24 (4.1)	35 (6.0)	13 (4.4)
Lost to follow-up	86 (4.9)	60 (6.8)	47 (4.0)	39 (6.7)	43 (7.3)	17 (5.8)
Withdrawal by parent/guardian	263 (15.1)	149 (16.9)	167 (14.3)	96 (16.6)	96 (16.3)	53 (18.1)

Action/ Vaccine received	Group 1 (N=1746) n (%)	Group 2 (N=881) n (%)	Group 1a (N=1167) n (%)	Group 1b (N=579) n (%)	Group 2a (N=588) n (%)	Group 2b (N=293) n (%)
6-month safety follow-up	1381 (79.1)	658 (74.7)	943 (80.8)	438 (75.6)	440 (74.8)	218 (74.4)

BL: blood sampling.
n: number of participants fulfilling the item listed.
N: total number of participants randomized in each study group.
Source: Table 3 in Final CSR version 1.0 MET42, p116.

The numbers and percentages of participants included in the FAS1, FAS2, FAS3, PPAS1, PPAS2, PPAS3, Overall SafAS, SafAS1, SafAS2, SafAS3, SafAS4, SafAS5 and SafAS6 are presented in Table 15. Inclusions percentages were generally similar between groups.

Table 15: Analysis Set by Vaccination Group in MET42

Analysis sets	Group 1 n (%)	Group 2 n (%)	Group 1a n (%)	Group 1b n (%)	Group 2a n (%)	Group 2b n (%)
Immunogenicity assessments	-	-	-	-	-	-
N	1746	881	1167	579	558	293
FAS1	1339 (76.7)	663 (75.3)	-	-	-	-
PPAS1	928 (53.2)	460 (52.2)	-	-	-	-
FAS2	-	-	844 (72.3)	388 (67.0)	434 (73.8)	200 (68.3)
PPAS2	-	-	647 (55.4)	295 (50.9)	329 (56.0)	157 (53.6)
FAS3	-	-	816 (69.9)	378 (65.3)	398 (67.7)	193 (65.9)
PPAS3	-	-	675 (57.8)	308 (53.2)	308 (52.4)	126 (43.0)
Safety assessment	-	-	-	-	-	-
M	1727	867	938	472	480	228
Overall SafAS	1727 (100)	867 (100)	-	-	-	-
SafAS1	1727 (100)	867 (100)	-	-	-	-
SafAS2	1620 (93.8)	827 (95.4)	-	-	-	-
SafAS3	1542 (89.3)	794 (91.6)	-	-	-	-
SafAS4	-	-	938 (100)	472 (100)	480 (100)	228 (100)
SafAS5	-	-	-	444 (94.1)	425 (88.5)	219 (96.1)
SafAS6	1375 (79.6)	705 (81.3)	-	-	-	-

n: number of participants fulfilling the listed item.
N: number of participants randomized in each study group.
M: number of participants based on actual vaccination group.
Source: Adapted from Tables 5, 6, 7 and 8 in Final CSR version 1.0 MET42.

Demographic characteristics are presented in Table 16 for the randomized participants. There were no notable differences in demographic characteristics between groups.

Table 16: Baseline Demographics by Randomized Group in MET42

Demographic	Group 1 (N=1746)	Group 2 (N=881)	Group 1a (N=1167)	Group 1b (N=579)	Group 2a (N=588)	Group 2b (N=293)	All (N=2627)
Sex: n (%)	-	-	-	-	-	-	-
Male	918 (52.6)	466 (52.9)	618 (53.0)	300 (51.8)	324 (55.1)	142 (48.5)	1384 (52.7)

Demographic	Group 1 (N=1746)	Group 2 (N=881)	Group 1a (N=1167)	Group 1b (N=579)	Group 2a (N=588)	Group 2b (N=293)	All (N=2627)
Sex: n (%)	-	-	-	-	-	-	-
Female	828 (47.4)	415 (47.1)	549 (47.0)	279 (48.2)	264 (44.9)	151 (51.5)	1243 (47.3)
Age: (Days)	-	-	-	-	-	-	-
M	1746	881	1167	579	588	293	2627
Mean (sd)	65.3 (8.02)	65.3 (7.81)	65.3 (8.12)	65.3 (7.80)	65.4 (7.75)	65.0 (7.93)	65.3 (7.95)
Min; Max	42.0; 89.0	42.0; 89.0	42.0; 89.0	42.0; 89.0	42.0; 89.0	42.0; 89.0	42.0; 89.0
Median	64.0	64.0	64.0	64.0	64.0	64.0	64.0
Q1; Q3	61.0; 69.0	61.0; 69.0	61.0; 69.0	61.0; 69.0	61.0; 69.0	61.0; 69.0	61.0; 69.0
Race: n (%)	-	-	-	-	-	-	-
American Indian or Alaska Native	11 (0.6)	3 (0.3)	6 (0.5)	5 (0.9)	3 (0.5)	0	14 (0.5)
Asian	15 (0.9)	10 (1.1)	8 (0.7)	7 (1.2)	6 (1.0)	4 (1.4)	25 (1.0)
Black or African American	204 (11.7)	99 (11.2)	142 (12.2)	62 (10.7)	63 (10.7)	36 (12.3)	303 (11.5)
Native Hawaiian or Other Pacific Islander	7 (0.4)	6 (0.7)	5 (0.4)	2 (0.3)	4 (0.7)	2 (0.7)	13 (0.5)
White	1428 (81.8)	722 (82.0)	950 (81.4)	478 (82.6)	491 (83.5)	231 (78.8)	2150 (81.8)
Mixed origin	44 (2.5)	30 (3.4)	31 (2.7)	13 (2.2)	16 (2.7)	14 (4.8)	74 (2.8)
Unknown	19 (1.1)	6 (0.7)	14 (1.2)	5 (0.9)	3 (0.5)	3 (1.0)	25 (1.0)
Not reported	18 (1.0)	5 (0.6)	11 (0.9)	7 (1.2)	2 (0.3)	3 (1.0)	23 (0.9)
Ethnicity: n (%)	-	-	-	-	-	-	-
Hispanic or Latino	838 (48.0)	410 (46.5)	549 (47.0)	289 (49.9)	278 (47.3)	132 (45.1)	1248 (47.5)
Not Hispanic or Latino	897 (51.4)	465 (52.8)	611 (52.4)	286 (49.4)	305 (51.9)	160 (54.6)	1362 (51.8)
Unknown	3 (0.2)	4 (0.5)	2 (0.2)	1 (0.2)	3 (0.5)	1 (0.3)	7 (0.3)
Not reported	8 (0.5)	2 (0.2)	5 (0.4)	3 (0.5)	2 (0.3)	0	10 (0.4)

Source: Table 9 in Final CSR version 1.0 MET42, on p.132.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

Table 17 presents the results for primary hypothesis 1. NI of hSBA vaccine seroresponse rate at Day 30 after the fourth dose of MenACYW conjugate vaccine to MENVEO was demonstrated for each of the four serogroups in the PPAS3.

Table 17: Non-Inferiority of hSBA Vaccine Seroresponse Rate at Day 30 After the Fourth Dose – PPAS3 in MET42

Sero-group	Group 1a (N=675), n/M	Group 1a (N=675), %	Group 1a (N=675), 95% CI	Group 2a (N=308), n/M	Group 2a (N=308), %	Group 2a (N=308), 95% CI	G1a – G2a, Difference (%)	G1a – G2a, 95% CI
A	398/501	79.4	(75.6; 82.9)	173/223	77.6	(71.5; 82.9)	1.86	(-4.38; 8.64)
C	514/530	97.0	(95.1; 98.3)	210/238	88.2	(83.4; 92.0)	8.75	(4.80; 13.60)
Y	504/523	96.4	(94.4; 97.8)	215/233	92.3	(88.1; 95.4)	4.09	(0.68; 8.44)
W	527/540	97.6	(95.9; 98.7)	241/250	96.4	(93.3; 98.3)	1.19	(-1.18; 4.45)

n: Number of participants who achieved hSBA vaccine seroresponse.
N: Number of participants in PPAS3.
M: Number of participants with available data for the relevant endpoint.
Source: Table 10 in Final CSR version 1.0 MET42, on p.136.

Table 18 presents the results for primary hypothesis 2. NI for the percentage of participants with hSBA antibody titer ≥1:8 at Day 30 after the third dose of MenACYW conjugate vaccine to MENVEO was demonstrated for each of the four serogroups in the PPAS1.

Table 18: Non-Inferiority of the Percentage of Participants with hSBA Antibody Titer ≥1:8 at Day 30 After the Third dose – PPAS1 in MET42

Sero-group	Group 1 (N=928) n/M	Group 1 (N=928) %	Group 1 (N=928) 95% CI	Group 2 (N=460) n/M	Group 2 (N=460) %	Group 2 (N=460) 95% CI	G1 – G2 Difference (%)	G1 – G2 95% CI
A	664/852	77.9	(75.0; 80.7)	277/409	67.7	(63.0; 72.2)	10.21	(4.98; 15.59)
C	827/835	99.0	(98.1; 99.6)	386/421	91.2	(88.1; 93.7)	7.83	(5.31; 10.96)
Y	846/883	98.3	(97.1; 99.0)	388/423	91.7	(88.7; 94.2)	6.53	(4.01; 9.62)
W	871/883	98.6	(97.6; 99.3)	407/438	92.9	(90.1; 95.1)	5.72	(3.44;8. 57)

n: Number of participants with hSBA antibody titer ≥ 1:8.
N: Number of participants in PPAS1.
M: Number of participants with available data for the relevant endpoint.
Source: Table 11 in Final CSR version 1.0 MET42, on p.138.

Reviewer's comment: The primary immunogenicity analyses were also conducted on the relevant FAS and the results were consistent with those observed in PPAS.

6.2.11.2 Analyses of Secondary Endpoints

Table 19 presents the results of the NI analyses for the secondary endpoints. NI was met for all endpoints.

Table 19: Summary of Non-Inferiority Results for the Immune Responses to the Routine Pediatric Vaccines Administered Concomitantly with MenACYW compared to MENVEO

Antigen	Endpoint (Hypothesis #)	Type of estimate	Estimate and 95% CI	NI margin and conclusion
Day 30 after 6-month vaccinations (Group 1 vs Group 2 in PPAS1)	-	-	-	-
Hepatitis B	% ≥ 10 mIU/mL (1)	Difference in proportions	0.57% (95% CI: -0.95; 2.75)	-10%; NI is met
PRP	% ≥ 0.15 µg/mL (2)	Difference in proportions	2.55% (95% CI: 0.89; 4.84)	-5%; NI is met
PRP	% ≥ 1.0 µg/mL (3)	Difference in proportions	5.56% (95% CI: 1.90; 9.60)	-10%; NI is met
Polio Type 1	% ≥ 1:8 (4)	Difference in proportions	0% (95% CI: -0.46; 0.92)	-5%; NI is met
Polio Type 2	% ≥ 1:8 (4)	Difference in proportions	0% (95% CI: -0.46; 0.94)	-5%; NI is met
Polio Type 3	% ≥ 1:8 (4)	Difference in proportions	0% (95% CI: -0.45; 0.92)	-5%; NI is met
Rotavirus	% ≥ 3-fold rise (5)	Difference in proportions	-1.88% (95% CI: -5.26; 2.00)	-10%; NI is met
Rotavirus	GMC (G1/G2 ratio) (6)	GMC (G1/G2 ratio)	0.881 (95% CI: 0.728; 1.07)	0.67; NI is met
Pertussis: PT	GMC (G1/G2 ratio) (7)	GMC (G1/G2 ratio)	0.964 (95% CI: 0.880; 1.06)	0.67; NI is met
Pertussis: FHA	GMC (G1/G2 ratio) (7)	GMC (G1/G2 ratio)	0.970 (95% CI: 0.887; 1.06)	0.67; NI is met
Pertussis: PRN	GMC (G1/G2 ratio) (7)	GMC (G1/G2 ratio)	0.938 (95% CI: 0.830; 1.06)	0.67; NI is met
Pertussis: FIM	GMC (G1/G2 ratio) (7)	GMC (G1/G2 ratio)	0.996 (95% CI: 0.892; 1.11)	0.67; NI is met

Antigen	Endpoint (Hypothesis #)	Type of estimate	Estimate and 95% CI	NI margin and conclusion
Pneumococcal Serotype 1	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.17 (95% CI: 1.05; 1.30)	0.5; NI is met
Pneumococcal Serotype 3	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.12 (95% CI: 1.02; 1.22)	0.5; NI is met
Pneumococcal Serotype 4	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.10 (95% CI: 1.01; 1.19)	0.5; NI is met
Pneumococcal Serotype 5	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.23 (95% CI: 1.11; 1.36)	0.5; NI is met
Pneumococcal Serotype 6A	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.20 (95% CI: 1.09; 1.32)	0.5; NI is met
Pneumococcal Serotype 6B	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.26 (95% CI: 1.09; 1.44)	0.5; NI is met
Pneumococcal Serotype 7F	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.02 (95% CI: 0.946; 1.11)	0.5; NI is met
Pneumococcal Serotype 9V	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.17 (95% CI: 1.06; 1.29)	0.5; NI is met
Pneumococcal Serotype 14	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	0.970 (95% CI: 0.870; 1.08)	0.5; NI is met
Pneumococcal Serotype 18C	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.07 (95% CI: 0.983; 1.16)	0.5; NI is met
Pneumococcal Serotype 19A	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.10 (95% CI: 1.01; 1.20)	0.5; NI is met
Pneumococcal Serotype 19F	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.13 (95% CI: 1.03; 1.23)	0.5; NI is met
Pneumococcal Serotype 23F	GMC (G1/G2 ratio) (8)	GMC (G1/G2 ratio)	1.22 (95% CI: 1.09; 1.37)	0.5; NI is met
Day 30 after 12-month vaccinations (Group 1a vs Group 2a in PPAS3)	-	-	-	-

Antigen	Endpoint (Hypothesis #)	Type of estimate	Estimate and 95% CI	NI margin and conclusion
Measles	% ≥ 255 mIU/mL (9)	Difference in proportions	0.24% (95% CI: -1.73; 2.90)	-10%; NI is met
Mumps	% ≥10 mumps Ab units/mL (10)	Difference in proportions	-2.22% (95% CI: -4.44; 0.53)	-10%; NI is met
Rubella	% ≥ 10 IU/mL (11)	Difference in proportions	-0.12% (95% CI: -1.89; 2.32)	-10%; NI is met
Varicella	% ≥ 5 gpELISA units/ml (12)	Difference in proportions	1.69% (95% CI: -0.96; 5.05)	-10%; NI is met
Pneumococcal Serotype 1	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.11 (95% CI: 0.980; 1.25)	0.5; NI is met
Pneumococcal Serotype 3	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.03 (95% CI: 0.927; 1.14)	0.5; NI is met
Pneumococcal Serotype 4	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.04 (95% CI: 0.933; 1.16)	0.5; NI is met
Pneumococcal Serotype 5	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.10 (95% CI: 0.980; 1.23)	0.5; NI is met
Pneumococcal Serotype 6A	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.01 (95% CI: 0.912; 1.13)	0.5; NI is met
Pneumococcal Serotype 6B	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.16 (95% CI: 1.03; 1.31)	0.5; NI is met
Pneumococcal Serotype 7F	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	0.894 (95% CI: 0.806; 0.992)	0.5; NI is met
Pneumococcal Serotype 9V	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	0.976 (95% CI: 0.871; 1.09)	0.5; NI is met
Pneumococcal Serotype 14	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	0.847 (95% CI: 0.752; 0.954)	0.5; NI is met
Pneumococcal Serotype 18C	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	0.890 (95% CI: 0.799; 0.992)	0.5; NI is met
Pneumococcal Serotype 19A	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.06 (95% CI: 0.945; 1.18)	0.5; NI is met

Antigen	Endpoint (Hypothesis #)	Type of estimate	Estimate and 95% CI	NI margin and conclusion
Pneumococcal Serotype 19F	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.08 (95% CI: 0.967; 1.21)	0.5; NI is met
Pneumococcal Serotype 23F	GMC (G1a/G2a ratio) (13)	GMC (G1a/G2a ratio)	1.14 (95% CI: 0.999; 1.29)	0.5; NI is met
Day 30 after 15-month vaccinations (Group 1b vs Group 2b in PPAS3)	-	-	-	-
PRP	% ≥ 1.0 µg/mL (14)	Difference in proportions	-0.08% (95% CI: -2.57; 4.08)	-10%; NI is met
Polio Type 1	% ≥ 1:8 (15)	Difference in proportions	0% (95% CI: -1.33; 3.05)	-5%; NI is met
Polio Type 2	% ≥ 1:8 (15)	Difference in proportions	0% (95% CI: -1.30; 3.05)	-5%; NI is met
Polio Type 3	% ≥ 1:8 (15)	Difference in proportions	0% (95% CI: -1.31; 3.05)	-5%; NI is met
Pertussis: PT	% with vaccine response (16)	Difference in proportions	0.19% (95% CI: -2.35; 4.46)	-10%; NI is met
Pertussis: FHA	% with vaccine response (16)	Difference in proportions	0.01% (95% CI: -3.48; 5.14)	-10%; NI is met
Pertussis: PRN	% with vaccine response (16)	Difference in proportions	-1.18% (95% CI: -4.55; 3.67)	-10%; NI is met
Pertussis: FIM	% with vaccine response (16)	Difference in proportions	0.65% (95% CI: -2.24; 5.32)	-10%; NI is met

Source: Table 12 in Final CSR version 1.0 MET42, on p.142.

Reviewer's comments:

1. *Conclusions generally held for the relevant full analysis sets.*
2. *While no multiplicity adjustment was considered for testing of the primary and secondary endpoints, NI criteria were nonetheless met for all endpoints.*
3. *For the remaining secondary endpoints, descriptive statistics were calculated and summarized as follows:*
   a) *hSBA GMTs for serogroups A, C, Y and W at Day 0 before the fourth dose of MenACYW conjugate vaccine or MENVEO® appeared higher in Group 1a than in Group 2a in the PPAS3.*
   b) *hSBA GMTs at Day 30 after the fourth dose appeared higher in Group 1a than in Group 2a for serogroups C, Y, and W and similar for serogroup A in the PPAS3.*
   c) *hSBA GMTs for serogroups A, C, Y, and W at Day 30 after the third dose appeared higher in Group 1 than in Group 2 in the PPAS1.*
   d) *Percentages of participants with ≥ 4-fold rise in hSBA titer from pre-first dose to post-third dose appeared slightly higher in Group 1 than in Group 2 for all serogroups in the PPAS1.*

e) Percentages of participants with hSBA seroresponse at Day 30 post-fourth dose in the PPAS3 appeared higher in Groups 1a and 1b than in Group 2a for serogroup C, slightly higher in Group 1b than in Group 2a for serogroup Y, and were similar between the groups for serogroups A and W.

6.2.11.3 Subpopulation Analyses

Subgroup analyses were carried out based on gender, race, and gestational age at birth (pre- and full-term birth). No notable trends were observed.

6.2.12 Safety Analyses

Solicited Adverse Events

Solicited local and systemic AEs within 7 days following any and each vaccination, by maximum severity on Overall SafAS, SafAS1, SafAS2, SafAS3, SafAS4, and SafAS5 are summarized in Tables 20-25, respectively.

Overall, rates of solicited local and systemic reactions were generally similar between groups after each vaccination. The most frequently reported local and systemic reactions were injection site tenderness and irritability, respectively.

Table 20: Percentage of Participants Reporting Any Solicited AE within 7 Days Following Any Vaccination – Overall SafAS in MET42

Solicited AE / Severity	Group 1 (N=1727) n/M	Group 1 (N=1727) %	Group 2 (N=867) n/M	Group 2 (N=867) %
One or more solicited local AE	1280/1642	78.0	663/831	79.8
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	1102/1641	67.2	561/830	67.6
Grade 1	566/1641	34.5	293/830	35.3
Grade 2	387/1641	23.6	196/830	23.6
Grade 3	149/1641	9.1	72/830	8.7
Injection site erythema*	-	-	-	-
Any	545/1641	33.2	274/829	33.1
Grade 1	526/1641	32.1	256/829	30.9
Grade 2	16/1641	1.0	14/829	1.7
Grade 3	3/1641	0.2	4/829	0.5
Injection site swelling*	-	-	-	-
Any	402/1640	24.5	194/830	23.4
Grade 1	385/1640	23.5	181/830	21.8
Grade 2	14/1640	0.9	10/830	1.2
Grade 3	3/1640	0.2	3/830	0.4
One or more solicited systemic AE	1313/1642	80.0	681/831	81.9
Systemic AE / Severity	-	-	-	-

Solicited AE / Severity	Group 1 (N=1727) n/M	Group 1 (N=1727) %	Group 2 (N=867) n/M	Group 2 (N=867) %
Fever	-	-	-	-
Any	536/1605	33.4	287/815	35.2
Grade 1	315/1605	19.6	154/815	18.9
Grade 2	193/1605	12.0	116/815	14.2
Grade 3	28/1605	1.7	17/815	2.1
Vomiting	-	-	-	-
Any	396/1640	24.1	185/831	22.3
Grade 1	223/1640	13.6	113/831	13.6
Grade 2	155/1640	9.5	62/831	7.5
Grade 3	18/1640	1.1	10/831	1.2
Crying abnormal	-	-	-	-
Any	1023/1639	62.4	540/831	65.0
Grade 1	465/1639	28.4	248/831	29.8
Grade 2	418/1639	25.5	238/831	28.6
Grade 3	140/1639	8.5	54/831	6.5
Drowsiness	-	-	-	-
Any	974/1639	59.4	507/830	61.1
Grade 1	544/1639	33.2	288/830	34.7
Grade 2	331/1639	20.2	166/830	20.0
Grade 3	99/1639	6.0	53/830	6.4
Appetite loss	-	-	-	-
Any	703/16396.6	42.9	385/831	46.3
Grade 1	448/1639	27.3	250/831	30.1
Grade 2	208/1639	12.7	107/831	12.9
Grade 3	47/1639	2.9	28/831	3.4
Irritability	-	-	-	-
Any	1152/1639	70.3	597/831	71.8
Grade 1	395/1639	24.1	221/831	26.6
Grade 2	563/1639	34.4	281/831	33.8
Grade 3	194/1639	11.8	95/831	11.4

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 23 and Table 24 in Final CSR version 1.0 MET42.

Table 21: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 2-Month Vaccination – SafAS1 in MET42

Solicited AE / Severity	Group 1 (N=1727) n/M	Group 1 (N=1727) %	Group 2 (N=867) n/M	Group 2 (N=867) %
One or more solicited local AE	945/1627	58.1	456/825	55.3
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-

Solicited AE / Severity	Group 1 (N=1727) n/M	Group 1 (N=1727) %	Group 2 (N=867) n/M	Group 2 (N=867) %
Any	741/1625	45.6	356/823	43.3
Grade 1	463/1625	28.5	218/823	26.5
Grade 2	207/1625	12.7	110/823	13.4
Grade 3	71/1625	4.4	28/823	3.4
Injection site erythema*	-	-	-	-
Any	203/1624	12.5	94/823	11.4
Grade 1	195/1624	12.0	89/823	10.8
Grade 2	8/1624	0.5	4/823	0.5
Grade 3	0/1624	0	1/823	0.1
Injection site swelling*	-	-	-	-
Any	155/1623	9.6	74/823	9.0
Grade 1	146/1623	9.0	69/823	8.4
Grade 2	8/1623	0.5	5/823	0.6
Grade 3	1/1623	<0.1	0/823	0
One or more solicited systemic AE	1054/1627	64.8	522/824	63.3
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	121/1552	7.8	52/789	6.6
Grade 1	94/1552	6.1	39/789	4.9
Grade 2	26/1552	1.7	13/789	1.6
Grade 3	1/1552	<0.1	0/789	0
Vomiting	-	-	-	-
Any	214/1622	13.2	90/824	10.9
Grade 1	131/1622	8.1	58/824	7.0
Grade 2	75/1622	4.6	30/824	3.6
Grade 3	8/1622	0.5	2/824	0.2
Crying abnormal	-	-	-	-
Any	664/1622	40.9	325/824	39.4
Grade 1	407/1622	25.1	202/824	24.5
Grade 2	211/1622	13.0	104/824	12.6
Grade 3	46/1622	2.8	19/824	2.3
Drowsiness	-	-	-	-
Any	703/1621	43.4	348/823	42.3
Grade 1	516/1621	31.8	251/823	30.5
Grade 2	147/1621	9.1	75/823	9.1
Grade 3	40/1621	2.5	22/823	2.7
Appetite loss	-	-	-	-
Any	333/1622	20.5	168/824	20.4
Grade 1	245/1622	15.1	121/824	14.7
Grade 2	73/1622	4.5	41/824	5.0
Grade 3	15/1622	0.9	6/824	0.7
Irritability	-	-	-	-

Solicited AE / Severity	Group 1 (N=1727) n/M	Group 1 (N=1727) %	Group 2 (N=867) n/M	Group 2 (N=867) %
Any	842/1621	51.9	420/824	51.0
Grade 1	431/1621	26.6	232/824	28.2
Grade 2	348/1621	21.5	165/824	20.0
Grade 3	63/1621	3.9	23/824	2.8

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.166 and Table 8.208 in Final CSR version 1.0 MET42.

Table 22: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 4-Month Vaccination – SafAS2 in MET42

Solicited AE / Severity	Group 1 (N=1620) n/M	Group 1 (N=1620) %	Group 2 (N=827) n/M	Group 2 (N=827) %
One or more solicited local AE	875/1520	57.6	456/786	58.0
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	663/1519	43.6	345/786	43.9
Grade 1	440/1519	29.0	221/786	28.1
Grade 2	172/1519	11.3	98/786	12.5
Grade 3	51/1519	3.4	26/786	3.3
Injection site erythema*	-	-	-	-
Any	277/1517	18.3	128/784	16.3
Grade 1	276/1517	18.2	121/784	15.4
Grade 2	1/1517	<0.1	5/784	0.6
Grade 3	0/1517	0	2/784	0.3
Injection site swelling*	-	-	-	-
Any	186/1514	12.3	79/784	10.1
Grade 1	183/1514	12.1	72/784	9.2
Grade 2	2/1514	0.1	5/784	0.6
Grade 3	1/1514	<0.1	2/784	0.3
One or more solicited systemic AE	957/1521	62.9	499/786	63.5
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	256/1456	17.6	133/743	17.9
Grade 1	165/1456	11.3	88/743	11.8
Grade 2	82/1456	5.6	39/743	5.2
Grade 3	9/1456	0.6	6/743	0.8
Vomiting	-	-	-	-
Any	148/1518	9.7	67/786	8.5
Grade 1	93/1518	6.1	42/786	5.3
Grade 2	50/1518	3.3	21/786	2.7
Grade 3	5/1518	0.3	4/786	0.5

Solicited AE / Severity	Group 1 (N=1620) n/M	Group 1 (N=1620) %	Group 2 (N=827) n/M	Group 2 (N=827) %
Crying abnormal	-	-	-	-
Any	638/1517	42.1	326/786	41.5
Grade 1	401/1517	26.4	184/786	23.4
Grade 2	183/1517	12.1	120/786	15.3
Grade 3	54/1517	3.6	22/786	2.8
Drowsiness	-	-	-	-
Any	638/1517	38.2	305/786	38.8
Grade 1	406/1517	26.8	215/786	27.4
Grade 2	145/1517	9.6	71/786	9.0
Grade 3	29/1517	1.9	19/786	2.4
Appetite loss	-	-	-	-
Any	302/1517	19.9	180/786	22.9
Grade 1	215/1517	14.2	137/786	17.4
Grade 2	78/1517	5.1	36/786	4.6
Grade 3	9/1517	0.6	7/786	0.9
Irritability	-	-	-	-
Any	781/1518	51.4	400/786	50.9
Grade 1	400/1518	26.4	204/786	26.0
Grade 2	309/1518	20.4	155/786	19.7
Grade 3	72/1518	4.7	41/786	5.2

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.167 and Table 8.209 in Final CSR version 1.0 MET42.

Table 23: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 6-Month Vaccination – SafAS3 in MET42

Solicited AE / Severity	Group 1 (N=1542) n/M	Group 1 (N=1542) %	Group 2 (N=794) n/M	Group 2 (N=794) %
One or more solicited local AE	807/1458	55.3	403/749	53.8
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	618/1456	42.4	304/748	40.6
Grade 1	407/1456	28.0	208/748	27.8
Grade 2	165/1456	11.3	78/748	10.4
Grade 3	46/1456	3.2	18/748	2.4
Injection site erythema*	-	-	-	-
Any	283/1453	19.5	147/746	19.7
Grade 1	280/1453	19.3	142/746	19.0
Grade 2	3/1453	0.2	4/746	0.5
Grade 3	0/1453	0	1/746	0.1
Injection site swelling*	-	-	-	-

Solicited AE / Severity	Group 1 (N=1542) n/M	Group 1 (N=1542) %	Group 2 (N=794) n/M	Group 2 (N=794) %
Any	185/1453	12.7	97/746	13.0
Grade 1	180/1453	12.4	90/746	12.1
Grade 2	5/1453	0.3	6/746	0.8
Grade 3	0/1453	0	1/746	0.1
One or more solicited systemic AE	846/1460	57.9	433/748	57.9
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	212/1391	15.2	116/701	16.5
Grade 1	131/1391	9.4	74/701	10.6
Grade 2	71/1391	5.1	40/701	5.7
Grade 3	10/1391	0.7	2/701	0.3
Vomiting	-	-	-	-
Any	138/1458	9.5	50/748	6.7
Grade 1	92/1458	6.3	34/748	4.5
Grade 2	42/1458	2.9	12/748	1.6
Grade 3	4/1458	0.3	4/748	0.5
Crying abnormal	-	-	-	-
Any	548/1457	37.6	274/748	36.6
Grade 1	329/1457	22.6	168/748	22.5
Grade 2	176/1457	12.1	93/748	12.4
Grade 3	43/1457	3.0	13/748	1.7
Drowsiness	-	-	-	-
Any	515/1457	35.3	258/748	34.5
Grade 1	353/1457	24.2	179/748	23.9
Grade 2	133/1457	9.1	63/748	8.4
Grade 3	29/1457	2.0	16/748	2.1
Appetite loss	-	-	-	-
Any	276/1457	18.9	142/748	19.0
Grade 1	191/1457	13.1	105/748	14.0
Grade 2	71/1457	4.9	31/748	4.1
Grade 3	14/1457	1.0	6/748	0.8
Irritability	-	-	-	-
Any	691/1457	47.4	346/748	46.3
Grade 1	366/1457	25.1	188/748	25.1
Grade 2	262/1457	18.0	138/748	18.4
Grade 3	63/1457	4.3	20/748	2.7

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.168 and Table 8.210 in Final CSR version 1.0 MET42.

Table 24: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 12-Month Vaccination – SafAS4 in MET42

Solicited AE / Severity	Group 1a (N=938) n/M	Group 1a (N=938) %	Group 1b (N=472) n/M	Group 1b (N=472) %	Group 2a (N=480) n/M	Group 2a (N=480) %	Group 2b (N=228) n/M	Group 2b (N=228) %
One or more solicited local AE	453/864	52.4	222/416	53.4	247/438	56.4	112/208	53.8
Local AE / Severity	-	-	-	-	-	-	-	-
Injection site tender-ness*	-	-	-	-	-	-	-	-
Any	333/864	38.5	-	-	178/438	40.6	84/207	40.6
Grade 1	227/864	26.3	-	-	124/438	28.3	63/207	30.4
Grade 2	87/864	10.1	-	-	44/438	10.0	17/207	8.2
Grade 3	19/864	2.2	-	-	10/438	2.3	4/207	1.9
Injection site erythema*	-	-	-	-	-	-	-	-
Any	140/863	16.2	-	-	90/437	20.6	30/207	14.5
Grade 1	136/863	15.8	-	-	88/437	20.1	29/207	14.0
Grade 2	3/863	0.3	-	-	2/437	0.5	1/207	0.5
Grade 3	1/863	0.1	-	-	0/437	0	0/207	0
Injection site swe-lling*	-	-	-	-	-	-	-	-
Any	88/863	10.2	-	-	66/437	15.1	21/207	10.1
Grade 1	87/863	10.1	-	-	66/437	15.1	19/207	9.2
Grade 2	0/863	0	-	-	0/437	0	2/207	1.0
Grade 3	1/863	0.1	-	-	0/437	0	0/207	0
One or more solicited systemic AE	476/863	55.2	224/418	53.6	257/439	58.5	105/207	50.7
Systemic AE / Severity	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-
Any	118/798	14.8	53/3989	13.3	60/419	14.3	21/195	10.8
Grade 1	86/798	10.8	35/393	8.8	29/419	6.9	14/195	7.2
Grade 2	28/798	3.5	16/393	4.0	26/419	6.2	7/195	3.6
Grade 3	4/798	0.5	2/398	0.5	5/419	1.2	0/195	0

Solicited AE / Severity	Group 1a (N=938) n/M	Group 1a (N=938) %	Group 1b (N=472) n/M	Group 1b (N=472) %	Group 2a (N=480) n/M	Group 2a (N=480) %	Group 2b (N=228) n/M	Group 2b (N=228) %
Vomiting	-	-	-	-	-	-	-	-
Any	40/863	4.6	12/414	2.9	25/438	5.7	8/207	3.9
Grade 1	26/863	3.0	8/414	1.9	19/438	4.3	5/207	2.4
Grade 2	13/863	1.5	4/414	1.0	5/438	1.1	3/207	1.4
Grade 3	1/863	0.1	0/414	0	1/438	0.2	0/207	0
Crying abnormal	-	-	-	-	-	-	-	-
Any	277/862	32.1	128/414	30.9	154/438	35.2	67/207	32.4
Grade 1	178/862	20.6	91/414	22.0	102/438	23.3	44/207	21.3
Grade 2	74/862	8.6	28/414	6.8	41/438	9.4	18/207	8.7
Grade 3	25/862	2.9	9/414	2.2	11/438	2.5	5/207	2.4
Drowsiness	-	-	-	-	-	-	-	-
Any	290/863	33.6	127/414	30.7	150/438	34.2	60/207	29.0
Grade 1	213/863	24.7	98/414	23.7	114/438	26.0	51/207	24.6
Grade 2	58/863	6.7	24/414	5.8	31/438	7.1	7/207	3.4
Grade 3	19/863	2.2	5/414	1.2	5/438	1.1	2/207	1.0
Appetite loss	-	-	-	-	-	-	-	-
Any	188/863	21.8	70/414	16.9	94/438	21.5	43/207	20.8
Grade 1	144/863	16.7	59/414	14.3	74/438	16.9	33/207	15.9
Grade 2	36/863	4.2	7/414	1.7	11/438	2.5	8/207	3.9
Grade 3	8/863	0.9	4/414	1.0	9/438	2.1	2/207	1.0
Irritability	-	-	-	-	-	-	-	-
Any	405/863	46.9	181/414	43.7	206/438	47.0	88/207	42.5
Grade 1	231/863	26.8	17/414	25.8	113/438	25.8	51/207	24.6
Grade 2	138/863	16.0	61/414	14.7	80/438	18.3	33/207	15.9
Grade 3	36/863	4.2	13/414	3.1	13/438	3.0	4/207	1.9

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.169 and Table 8.211 in Final CSR version 1.0 MET42.

Table 25: Percentage of Participants Reporting Any Solicited AE within 7 Days Following 15-Month Vaccination – SafAS5 in MET42

Solicited AE / Severity	Group 1b (N=444) n/M	Group 1b (N=444) %	Group 2a (N=425) n/M	Group 2a (N=425) %	Group 2b (N=219) n/M	Group 2b (N=219) %
One or more solicited local AE	209/401	52.1	185/398	46.5	89/199	44.7

Solicited AE / Severity	Group 1b (N=444) n/M	Group 1b (N=444) %	Group 2a (N=425) n/M	Group 2a (N=425) %	Group 2b (N=219) n/M	Group 2b (N=219) %
Local AE / Severity	-	-	-	-	-	-
Injection site tenderness*	-	-	-	-	-	-
Any	163/400	40.8	-	-	-	-
Grade 1	118/400	29.5	-	-	-	-
Grade 2	38/400	9.5	-	-	-	-
Grade 3	7/400	1.8	-	-	-	-
Injection site erythema*	-	-	-	-	-	-
Any	75/401	18.7	-	-	-	-
Grade 1	71/401	17.7	-	-	-	-
Grade 2	2/401	0.5	-	-	-	-
Grade 3	2/401	0.5	-	-	-	-
Injection site swelling*	-	-	-	-	-	-
Any	49/400	12.3	-	-	-	-
Grade 1	49/400	12.3	-	-	-	-
Grade 2	0/400	0	-	-	-	-
Grade 3	0/400	0	-	-	-	-
One or more solicited systemic AE	201/401	50.1	187/398	47.0	92.199	46.2
Systemic AE / Severity	-	-	-	-	-	-
Fever	-	-	-	-	-	-
Any	42/383	11.0	47/373	12.6	15/184	8.2
Grade 1	29/383	7.6	31/373	8.3	11/184	6.0
Grade 2	9/383	2.3	13/373	3.5	3/184	1.6
Grade 3	4/383	1.0	3/373	0.8	1/184	0.5
Vomiting	-	-	-	-	-	-
Any	14/400	3.5	13/397	3.3	4/198	2.0
Grade 1	11/400	2.8	10/397	2.5	3/198	1.5
Grade 2	2/400	0.5	3/397	0.8	1/198	0.5
Grade 3	1/400	0.3	0/397	0	0/198	0
Crying abnormal	-	-	-	-	-	-
Any	109/399	27.3	102/397	25.7	54/198	27.3
Grade 1	75/399	18.8	75/397	18.9	39/198	19.7
Grade 2	29/399	7.3	21/397	5.3	11/198	5.6
Grade 3	5/399	1.3	6/397	1.5	4/198	2.0
Drowsiness	-	-	-	-	-	-
Any	100/399	25.1	104/397	26.2	50/198	25.3
Grade 1	78/399	19.5	83/397	20.9	39/198	19.7
Grade 2	18/399	4.5	17/397	4.3	7/198	3.5
Grade 3	4/399	1.0	4/397	1.0	4/198	2.0
Appetite loss	-	-	-	-	-	-

Solicited AE / Severity	Group 1b (N=444) n/M	Group 1b (N=444) %	Group 2a (N=425) n/M	Group 2a (N=425) %	Group 2b (N=219) n/M	Group 2b (N=219) %
Any	69/399	17.3	68/397	17.1	35/198	17.7
Grade 1	59/399	14.8	48/397	12.1	29/198	14.6
Grade 2	7/399	1.8	17/397	4.3	3/198	1.5
Grade 3	3/399	0.8	3/397	0.8	3/198	1.5
Irritability	-	-	-	-	-	-
Any	160/399	40.1	146/397	36.8	77/198	38.9
Grade 1	100/399	25.1	91/397	22.9	50/198	25.3
Grade 2	52/399	13.0	44/397	11.1	19/198	9.6
Grade 3	8/399	2.0	11/397	2.8	8/198	4.0

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.170 and Table 8.212 in Final CSR version 1.0 MET42.

Unsolicited Adverse Events

In the Overall SafAS, one participant (<0.1%) in each group reported immediate unsolicited AE within 30 minutes of any vaccination. The percentage of participants who reported any unsolicited AE within 30 days of any vaccination was 53.9% in Group 1 and 53.9% in Group 2. Similarly, percentages of participants reporting unsolicited AEs were comparable between groups within 30 days of each vaccination.

Table 26 presents the percentages of participants who reported any SAE, AESI, and MAAE within 30 days of any vaccination and during the study period by vaccination group. Overall, 5.7% and 4.4% of participants in Groups 1 and 2, respectively, reported any SAE during the study, of which two were assessed as related to the study vaccine by the investigator. One was a case of febrile convulsions in Group 1. The other was a case of post-vaccination fever in Group 2. Both cases occurred within 30 days of vaccination. One death due to cardiac arrest occurred in Group 1 six days after the 2-Month vaccinations. This event was assessed as unrelated to the study vaccine by the investigator.

Table 26: Overview of SAEs, AESIs, and MAAEs in MET42

SafAS / AE	Group 1	Group 2	Group 1a	Group 1b	Group 2a	Group 2b
30 days after vaccination	-	-	-	-	-	-
SAE	-	-	-	-	-	-
Overall SafAS	39/1727 (2.3%)	11/867 (1.3%)	-	-	-	-
SafAS1	10/1727 (0.6%)	5/867 (0.6%)	-	-	-	-
SafAS2	7/1620 (0.4%)	1/827 (0.1%)	-	-	-	-

SafAS / AE	Group 1	Group 2	Group 1a	Group 1b	Group 2a	Group 2b
SafAS3	17/1542 (1.1%)	3/794 (0.4%)	-	-	-	-
SafAS4	-	-	4/938 (0.4%)	1/472 (0.2%)	0	0
SafAS5	-	-	-	2/444 (0.5%)	1/425 (0.2%)	1/219 (0.5%)
SafAS6	33/1375 (2.4%)	8/705 (1.1%)	-	-	-	-
AESI	-	-	-	-	-	-
Overall SafAS	3/1727 (0.2%)	0	-	-	-	-
SafAS1	0	0	-	-	-	-
SafAS2	1/1620 (<0.1%)	0	-	-	-	-
SafAS3	0	0	-	-	-	-
SafAS4	-	-	1/938 (0.1%)	0	0	0
SafAS5	-	-	-	1/444 (0.2%)	0	0
SafAS6	3/1375 (0.2%)	0	-	-	-	-
MAAE	-	-	-	-	-	-
Overall SafAS	689/1727 (39.9%)	368/867 (42.4%)	-	-	-	-
SafAS1	236/1727 (13.7%)	134/867 (15.5%)	-	-	-	-
SafAS2	252/1620 (15.6%)	151/827 (18.3%)	-	-	-	-
SafAS3	306/1542 (19.8%)	153/794 (19.3%)	-	-	-	-
SafAS4	-	-	156/938 (16.6%)	62/472 (13.1%)	72/480 (15.0%)	36/228 (15.8%)
SafAS5	-	-	-	59/444 (13.3%)	53/425 (12.5%)	34/219 (15.5%)
SafAS6	606/1375 (44.1%)	326/705 (46.2%)	-	-	-	-
During the study	-	-	-	-	-	-
SAE	-	-	-	-	-	-
Overall SafAS	99/1727 (5.7%)	38/867 (4.4%)	-	-	-	-
SafAS1	30/1727 (1.7%)	11/867 (1.3%)	-	-	-	-

SafAS / AE	Group 1	Group 2	Group 1a	Group 1b	Group 2a	Group 2b
SafAS2	15/1620 (0.9%)	7/827 (0.8%)	-	-	-	-
SafAS3	41/1542 (2.7%)	13/794 (1.6%)	-	-	-	-
SafAS4	-	-	14/938 (1.5%)	6/472 (1.3%)	5/480 (1.0%)	1/228 (0.4%)
SafAS5	-	-	-	6/444 (1.4%)	3/425 (0.7%)	1/219 (0.5%)
SafAS6	79/1375 (5.7%)	30/705 (4.3%)	-	-	-	-
AESI	-	-	-	-	-	-
Overall SafAS	13/1727 (0.8%)	5/867 (0.6%)	-	-	-	-
SafAS1	2/1727 (0.1%)	0	-	-	-	-
SafAS2	1/1620 (<0.1%)	1/827 (0.1%)	-	-	-	-
SafAS3	4/1542 (0.3%)	1/794 (0.1%)	-	-	-	-
SafAS4	-	-	3/938 (0.3%)	2/472 (0.4%)	2/480 (0.4%)	0
SafAS5	-	-	-	2/444 (0.5%)	1/425 (0.2%)	0
SafAS6	12/1375 (0.9%)	4/705 (0.6%)	-	-	-	-
MAAE	-	-	-	-	-	-
Overall SafAS	1050/1727 (60.8%)	526/867 (60.7%)	-	-	-	-
SafAS1	468/1727 (27.1%)	250/867 (28.8%)	-	-	-	-
SafAS2	472/1620 (29.1%)	265/827 (32.0%)	-	-	-	-
SafAS3	754/1542 (48.9%)	365/794 (46.0%)	-	-	-	-
SafAS4	-	-	335/938 (35.7%)	159/472 (33.7%)	159/480 (33.1%)	70/228 (30.7%)
SafAS5	-	-	-	133/444 (30.0%)	140/425 (32.9%)	68/219 (31.1%)
SafAS6	918/1375 (66.8%)	464/705 (65.8%)	-	-	-	-

Source: Summarized by the reviewer based on information presented in the MET42 CSR.

Reviewer's comment: Safety analyses were also performed based on subgroups, i.e., sex, race, and gestational age at birth (Pre-term and Full-term). There did not appear to be notable differences from the primary analysis.

6.3 Study MET61 (Phase III)

Title: Immunogenicity and Safety Study of an Investigational Quadrivalent Meningococcal Conjugate Vaccine Administered Concomitantly With Routine Pediatric Vaccines in Healthy Infants and Toddlers

Study initiation date: October 4, 2018 (first subject first visit)
Study completion date: October 23, 2023 (last subject last contact)

6.3.1 Objectives

Primary objective:

1. To demonstrate the NI of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following administration of two doses of MenACYW conjugate vaccine compared to two doses of MENVEO® when given concomitantly with routine pediatric vaccines to infants and toddlers 6 to 7 months of age and 12 to 13 months of age (hSBA vaccine seroresponse for serogroups A, C, Y and W was defined as: for a participant with a pre-vaccination titer < 1:8, the post-vaccination titer should be ≥ 1:16 and for a participant with a pre-vaccination titer ≥ 1:8, the post-vaccination titer should be ≥ 4-fold greater than the pre-vaccination titer).

Secondary objectives:

1. To demonstrate the NI of the percentage of participants with hSBA titers to meningococcal serogroups A, C, Y, and W ≥ 1:8 following administration of two doses of MenACYW conjugate vaccine compared to two doses of MENVEO® when given concomitantly with pediatric routine vaccines to infants and toddlers at 6 to 7 months of age and 12 to 13 months of age.
2. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO.
3. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (in a subset of participants).
4. To describe the antibody response against meningococcal serogroups A, C, Y, and W 6 months after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (in a subset of participants).
5. To describe the antibody response against meningococcal serogroups A, C, Y, and W 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra.

Safety objectives:

1. To describe the safety profile of MenACYW conjugate vaccine and MENVEO when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers.
2. To describe the safety profile of MenACYW conjugate vaccine and Menactra administered in toddlers.

6.3.2 Design Overview

This was a Phase III, randomized, parallel group, active-controlled, multi-center study to compare the immunogenicity and describe the safety of MenACYW conjugate vaccine and MENVEO® when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in the US. This study also described the safety and immunogenicity of MenACYW conjugate vaccine and Menactra when administered to healthy toddlers. Approximately 870 healthy infants 6 to 7 months of age were planned to be randomized 1:1 to Groups 1 and 2, and 200 healthy toddlers 17 to 19 months of age were planned to be randomized 1:1 to Groups 3 and 4:

- Group 1: MenACYW conjugate vaccine + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age,
- Group 2: MENVEO + routine pediatric vaccines at 6 to 7 months of age and 12 to 13 months of age,
- Group 3: MenACYW conjugate vaccine at 17 to 19 months of age and 20 to 23 months of age,
- Group 4: Menactra at 17 to 19 months of age and 20 to 23 months of age.

Blinding was maintained between Group 1 and Group 2 and between Group 3 and Group 4. All participants in Group 1 and Group 2 were to receive a dose of either MenACYW conjugate vaccine or MENVEO with the following routine pediatric vaccines per ACIP recommendations:

- Diphtheria, tetanus and acellular pertussis (DTaP) at 6 months of age
- Inactivated poliovirus (IPV) at 6 months of age
- Haemophilus influenzae type b (Hib) at 6 months of age (in children immunized with PedvaxHIB® at 2 and 4 months of age, a third dose of Hib vaccine at 6 months of age was not required).
- Pneumococcal 13-valent conjugate vaccine (Prevnar 13®, PCV13) at 6 and 13 months of age
- Rotavirus (RotaTeq®) at 6 months of age
- Hepatitis B at 6 months of age
- Measles, mumps, and rubella (M-M-R II®) at 12 months of age
- Varicella (Varivax®) at 12 months of age.

Safety data were collected as follows: immediate unsolicited systemic AEs were collected within 30 minutes after each vaccination. Solicited AEs were collected from Day 0 to Day 7 after each vaccination; unsolicited AEs were collected from D0 to the next study visit; SAEs (including AESIs) and MAAEs were collected throughout the study until the end of the 6-month follow-up period after the last vaccination.

All participants in Group 1 and Group 2 were to provide three blood samples for immunogenicity assessment: before the first study vaccination, 30 days after the first dose of MenACYW conjugate vaccine or MENVEO (first 50% of participants in Groups 1 and 2), before the 12-month vaccination (remaining 50% of participants in Groups 1 and 2), and 30 days after the second dose of MenACYW conjugate vaccine or MENVEO. All participants in Groups 3 and 4 were to provide blood samples for immunogenicity assessment before the first

study vaccination and 30 days after the second dose of MenACYW conjugate vaccine or Menactra.

6.3.3 Population

The study enrolled healthy participants aged 6 to 7 months or 17 to 19 months. Infants had to have received two doses of DTaP, Hib, IPV, pneumococcal, hepatitis B (for children who received Pediarix® at 2 and 4 months of age, prior receipt of three doses of hepatitis B), and rotavirus vaccines. Participants aged 17 to 19 months had to have a documented history of having received all routine pediatric vaccines recommended by ACIP.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Table 27 provides the dose and route of the administered vaccines.

Table 27: Dose and Route of the Vaccines in MET61

Vaccines	Dose, route
MenACYW conjugate vaccine	0.5 mL solution IM at 6 to 7 months of age and 12 to 13 months of age in Groups 1 and 2; 0.5 mL solution IM at 17 to 19 months of age and at 20 to 23 months of age in Groups 3 and 4
MENVEO®	0.5 mL solution IM at 6 to 7 months of age and 12 to 13 months of age in Groups 1 and 2
Menactra	0.5 mL solution IM at 17 to 19 months of age and 20 to 23 months of age in Groups 3 and 4
Pentacel®	0.5 mL solution IM at 6 to 7 months of age in Groups 1 and 2
Pediarix	0.5mL suspension IM at 6 to 7 months of age in Groups 1 and 2
ActHIB*	0.5mL solution IM at 6 to 7 months of age and at 13 months of age in Groups 1 and 2
Hiberix®*	0.5mL solution IM at 6 to 7 months of age and at 13 months of age in Groups 1 and 2
PedvaxHIB*	0.5mL solution IM at 6 to 7 months of age and at 13 months of age in Groups 1 and 2
Prevnar 13®	0.5 mL suspension IM at 6 to 7 months of age and at 13 months of age in Groups 1 and 2
RotaTeq®	2 mL oral solution at 6 to 7 months of age in Groups 1 and 2
Engerix-B®$	0.5 mL suspension IM at 6 to 7 months of age in Groups 1 and 2
Recombivax HB$	0.5 mL suspension IM at 6 to 7 months of age in Groups 1 and 2
M-M-R II®	0.5 mL subcutaneous at 12 to 13 months of age in Groups 1 and 2
Varivax®	0.5 mL suspension subcutaneous at 12 to 13 months of age in Groups 1 and 2

**: Participant received either ActHib, Hiberix® or PedvaxHIB as Haemophilus b conjugate vaccine.*
$: Participant received either Engerix-B® or Recombivax HB as hepatitis B vaccines.
Source: Summarized by the reviewer based on information presented in the MET61 CSR.

6.3.6 Sites and Centers

The study was conducted at 45 sites in the US and two sites in Puerto Rico.

6.3.7 Surveillance/Monitoring

Please refer to the clinical review memo.

6.3.8 Endpoints and Criteria for Study Success

Primary immunogenicity endpoint:

1. Meningococcal serogroups A, C, Y, and W antibody titers measured by hSBA, before the first study vaccination and 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2).

Secondary immunogenicity endpoints:

1. Meningococcal serogroups A, C, Y, and W antibody titers ≥1:8 measured by hSBA 30 days after the second dose of MenACYW conjugate vaccine or MENVEO (Group 1 vs Group 2).
2. 30 days after the second vaccination at 12 to 13 months of age with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
    - hSBA meningococcal serogroups A, C, Y, and W antibody titers,
    - GMTs with 95% CI,
    - Titer distribution and RCDCs,
    - Percentage of participants with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI.
3. 30 days after the first vaccination at 6 to 7 months of age with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
    - hSBA meningococcal serogroups A, C, Y, and W antibody titers,
    - GMTs with 95% CI,
    - Titer distribution and RCDCs,
    - Percentage of participants with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI,
    - Percentage of participants with hSBA vaccine seroresponse and 95% CI.
4. 6 months after the first vaccination at 6 to 7 months of age (pre-vaccination 2) with MenACYW conjugate vaccine or MENVEO (Group 1 and Group 2):
    - hSBA meningococcal serogroups A, C, Y, and W antibody titers,
    - GMTs with 95% CI,
    - Titer distribution and RCDCs,
    - Percentage of participants with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI,
    - Percentage of participants with hSBA vaccine seroresponse and 95% CI.
5. 30 days after the second vaccination at 20 to 23 months of age with MenACYW conjugate vaccine or Menactra (Group 3 and Group 4):
    - hSBA meningococcal serogroups A, C, Y, and W antibody titers,
    - GMTs with 95% CI,
    - Titer distribution and RCDCs,
    - Percentage of participants with titer ≥ 4-fold rise from pre-vaccination to post-vaccination and 95% CI,
    - Percentage of participants with hSBA vaccine seroresponse and 95% CI.

Safety endpoints:

- Occurrence, nature (MedDRA preferred term), duration, intensity, relationship to vaccination, and whether the event led to early termination from the study, of any unsolicited systemic AEs reported in the 30 minutes after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited injection site reactions occurring up to 7 days after each vaccination.
- Occurrence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited systemic reactions occurring up to 7 days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of unsolicited AEs up to 30 days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs (including AESIs) throughout the trial up to the 6-month follow-up contact after the last vaccination.
- Occurrence, nature (MedDRA preferred term), time of onset, duration, intensity, action taken, relationship to vaccination, and whether the event led to early termination from the study, of MAAEs throughout the trial up to the 6-month follow-up contact after the last vaccination.

6.3.9 Statistical Considerations & Statistical Analysis Plan

The following analysis sets were defined for the analyses.

Analysis sets:

- *FAS*: There were three FASs.
  - *FAS1* was defined as the subset of all randomized participants who received ≥ 1 dose of the study vaccine in infancy (< 12 months of age) and had a valid post vaccination serology result in infancy. All participants were analyzed according to the vaccine group to which they were randomized.
  - *FAS2* was defined as the subset of all randomized participants who received ≥ 1 dose of the study vaccine in the second year of life (≥ 12 months of age) and had a valid post-vaccination serology result in the second year of life. All participants were analyzed according to the vaccine group to which they were randomized.
  - *FAS3* was defined as the subset of all randomized participants who received ≥ 1 dose of the study vaccine in infancy (< 12 months of age) and had a valid serology result at pre-vaccination 2. All participants were analyzed according to the vaccine group to which they were randomized.
- *PPAS*: There were three PPASs based on the three FASs.
  - *PPAS1* was defined as the subset of FAS1 with a valid serology obtained 30 days after vaccination at 6 to 7 months of age for all antigens and with no relevant protocol deviations.
  - *PPAS2* was defined as the subset of FAS2 with a valid serology obtained 30 days after vaccination during the second year of life and with no relevant protocol deviations.

  - *PPAS3* was defined as the subset of FAS3 with a valid serology obtained at pre-vaccination 2 for persistence 6 months after infant vaccination and with no relevant protocol deviations.
- *SafAS*: *Overall SafAS* was defined as those who received at least one dose of the study vaccines. Participants were analyzed according to the vaccine received at the first dose. *SafAS1, SafAS2, SafAS3, and SafAS4* were defined as those who received the study vaccine at 6-7 months of age, 12-13 months of age, 17-19 months of age, and 20-23 months of age, respectively. Participants were analyzed according to the vaccine received at that visit.

Primary immunogenicity analysis:
Primary immunogenicity analysis was conducted for each of the four serogroups on the PPAS, with sensitivity analysis performed on the FAS. The following primary hypothesis was tested for each serogroup:

- H0: p(G1) – p(G2) ≤ -10% vs H1: p(G1) – p(G2) > -10%, where p(G1) and p(G2) were the percentages of participants who achieved hSBA vaccine seroresponse at Day 30 after vaccination at 12 months of age in Groups 1 and 2, respectively.

Overall non-inferiority was demonstrated when all four individual null hypotheses were rejected. The CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

Secondary immunogenicity analyses:
The secondary NI hypothesis corresponding to secondary objective 1 was: H0: $p_s(G1) – p_s(G2) \leq -10\%$ vs H1: $p_s(G1) – p_s(G2) > -10\%$, where $p_s(G1)$ and $p_s(G2)$ were the percentages of participants who achieved hSBA Ab titers ≥ 1:8 in Group 1 and Group 2, respectively. Overall non-inferiority was demonstrated if all four individual null hypotheses were rejected. The CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

The remaining secondary immunogenicity endpoints were summarized descriptively. The 95% CIs of point estimates were calculated using the exact binomial distribution for proportions. For geometric means, 95% CIs of point estimates were calculated using normal approximation assuming they are log-normally distributed.

Safety analyses:
Safety endpoints were described by percentages and 95% CIs (based on the Clopper-Pearson method).

Missing data:
The following rules were applied for titers:

- If a value was < LLOQ, then LLOQ/2 was used as the computed value.
- If a value was ≥ ULOQ, then the computed value was ULOQ.

The following rules applied for calculations of fold-rise:

- If both baseline and post-baseline values were < LLOQ, then the fold-rise was 1.

- If the baseline value was ≥ LLOQ and the post-baseline value was < LLOQ, then the fold-rise was (LLOQ/2) / baseline value.
- If the baseline value was < LLOQ and the post-baseline value was ≥ LLOQ, then the fold-rise was post-baseline value / LLOQ.

Sample size and power for immunogenicity analysis:
Approximately 870 participants (435 per group) were planned to be enrolled. With a non-evaluable rate of 40%, 261 participants per group yielded approximately 90% and >99% power to demonstrate NI for the primary and secondary hypotheses, respectively.

Subgroup analyses:
Subgroup analyses by sex and race based on the PPAS were provided for the primary and secondary immunogenicity endpoints.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The disposition of participants is provided in Table 28. A total of 750 and 200 participants were randomized across the two age groups, respectively.

Table 28: Disposition by Randomized Group – All Randomized Participants in MET61

Action / vaccine received	Vaccination in infancy, Group 1 (N=380), n (%)	Vaccination in infancy, Group 2 (N=370), n (%)	Vaccination in second year of life, Group 3 (N=96), n (%)	Vaccination in second year of life, Group 4 (N=104), n (%)
Visit 1	6 – 7 months of age	6 – 7 months of age	17 – 19 months of age	17 – 19 months of age
Present at visit	380 (100)	370 (100)	96 (100)	104 (100)
Blood sample	314 (82.6)	300 (81.1)	92 (95.8)	97 (93.3)
MenACYW /Menveo / Menactra	370 (97.4)	361 (97.6)	96 (100)	103 (99.0)
Pentacel	218 (57.4)	215 (58.1)	-	-
Engerix-B / Recombivax HB	217 (57.4)	213 (57.6)	-	-
Pediarix	151 (39.7)	146 (39.5)	-	-
ActHib / Hiberix / PedvaxHIB	136 (35.8)	137 (37.0)	-	-
Prevnar 13	370 (97.4)	360 (97.3)	-	-
RotaTeq	370 (97.4)	358 (96.8)	-	-
Visit 2	7 – 8 months of age	7 – 8 months of age	20 – 23 months of age	20 – 23 months of age
Present at visit	357 (93.9)	340 (91.9)	87 (90.6)	97 (93.3)
Blood sample	175 (46.1)	171 (46.2)	-	-
MenACYW/Menactra	-	-	86 (89.6)	96 (92.3)

Action / vaccine received	Vaccination in infancy, Group 1 (N=380), n (%)	Vaccination in infancy, Group 2 (N=370), n (%)	Vaccination in second year of life, Group 3 (N=96), n (%)	Vaccination in second year of life, Group 4 (N=104), n (%)
Visit 3	12 – 13 months of age	12 – 13 months of age	21 – 24 months of age	21 – 24 months of age
Present at visit	310 (81.6)	306 (82.7)	85 (88.5)	96 (92.3)
Blood sample	123 (32.4)	125 (33.8)	78 (81.3)	91 (87.5)
MenACYW/Menveo	308 (81.1)	302 (81.6)	-	-
M-M-R II	306 (80.5)	298 (80.5)	-	-
Varivax	306 (80.5)	298 (80.5)	-	-
Visit 4	13 – 14 months of age	13 – 14 months of age	-	-
Present at visit	298 (78.4)	289 (78.1)	-	-
Blood sample	269 (70.8)	269 (72.7)	-	-
Termination	-	-	-	-
Completed trial	298 (78.4)	290 (78.4)	83 (86.5)	94 (90.4)
Did not complete	82 (21.6)	80 (21.6)	13 (13.5)	10 (9.6)
Early termination reason	-	-	-	-
AE	0	1 (0.3)	0	0
Protocol deviation	15 (3.9)	8 (2.2)	1 (1.0)	2 (1.9)
Lost to follow-up	20 (5.3)	11 (3.0)	5 (5.2)	2 (1.9)
Withdrawal by parent / guardian	47 (12.4)	60 (16.2)	7 (7.3)	6 (5.8)
Follow-up	-	-	-	-
6-month safety follow-up	312 (82.1)	306 (82.7)	83 (86.5)	96 (92.3)

n: number of participants fulfilling the item listed.
N: total number of participants randomized in each study group.
Source: Adapted from Tables 1 and 8.15 in Final CSR version 1.0 MET61.

The numbers and percentages of participants included in each analysis set are presented in Table 29. Overall, percentages of participants included in each analysis set were generally similar between vaccine groups within each age group.

Table 29: Analysis Set by Vaccination Group in MET61

Analysis sets	Group 1	Group 2	Group 3	Group 4
Immunogenicity	n/M (%)	n/M (%)	n/M (%)	n/M (%)
FAS1	165/214 (77.1)	165/206 (80.1)	-	-
PPAS1	135/214 (63.1)	138/206 (67.0)	-	-
FAS2	257/380 (67.6)	259/370 (70.0)	76/96 (79.2)	90/104 (86.5)
PPAS2	180/380 (47.4)	163/370 (44.1)	61/96 (63.5)	65/104 (62.5)
FAS3	122/166 (73.5)	120/164 (73.2)	-	-
PPAS3	108/166 (65.1)	96/164 (58.5)	-	-
Safety	n/N (%)	n/N (%)	n/N (%)	n/N (%)

Analysis sets	Group 1	Group 2	Group 3	Group 4
Overall SafAS	370/370 (100)	361/361 (100)	96/96 (100)	103/103 (100)
SafAS1	370/370 (100)	361/361 (100)	-	-
SafAS2	309/370 (83.5)	302/361 (83.7)	-	-
SafAS3	-	-	96/96 (100)	103/103 (100)
SafAS4	-	-	86/96 (89.6)	96/103 (93.2)

n: number of participants fulfilling the listed item.
N: number of participants based on actual vaccination group.
M: number of participants with planned blood sample for the respective analysis.
Source: Adapted from Tables 5, 6, 7 and 8 in Final CSR version 1.0 MET61.

The demographic characteristics are presented Table 30 for the randomized participants, which were similar between vaccine groups within each age group.

Table 30: Baseline Demographics – All Randomized Participants in MET61

Demographic	Group 1 (N=380)	Group 2 (N=370)	Group 3 (N=96)	Group 4 (N=104)
Sex: n (%)	-	-	-	-
Male	200 (52.6)	198 (53.5)	48 (50.0)	52 (50.0)
Female	180 (47.4)	172 (46.5)	48 (50.0)	52 (50.0)
Age: (months)	-	-	-	-
M	379	370	96	104
Mean (sd)	6.01 (0.700)	6.02 (0.396)	17.9 (0.632)	17.9 (0.673)
Min; Max	5.00; 18.0	5.00; 7.00	17.0l 19.0	17.0; 19.0
Median	6.00	6.00	18.0	18.0
Racial origin: n (%)	-	-	-	-
American Indian or Alaska Native	0	1 (0.3)	0	0
Asian	6 (1.6)	6 (1.6)	2 (2.1)	1 (1.0)
Black or African American	70 (18.4)	68 (18.4)	11 (11.5)	11 (10.6)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	277 (72.9)	264 (71.4)	79 (82.3)	87 (83.7)
Mixed origin	14 (3.7)	20 (5.4)	4 (4.2)	5 (4.8)
Not reported	10 (2.6)	4 (1.1)	0	0
Unknown	3 (0.8)	7 (1.9)	0	0
Ethnicity: n (%)	-	-	-	-
Hispanic or Latino	169 (44.5)	161 (43.5)	31 (32.3)	35 (33.7)
Not Hispanic or Latino	208 (54.7)	209 (56.5)	65 (67.7)	69 (66.3)
Not reported	2 (0.5)	0	0	0
Unknown	1 (0.3)	0	0	0

Source: Table 9 in Final CSR version 1.0 MET61.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoint

NI of hSBA vaccine seroresponse rate at Day 30 after the second dose of MenACYW conjugate vaccine administered at 12 to 13 months of age (Group 1) compared to that after the second dose of MENVEO (Group 2) was met for each of the four serogroups in the PPAS2 (Table 31).

Table 31: Non-Inferiority of hSBA Vaccine Seroresponse Rate 30 Days After the Second Dose of MenACYW Conjugate Vaccine or MENVEO (Group 1 vs Group 2) – PPAS2

Sero group	Group 1 (N=180), n/M	Group 1 (N=180), Sero-response rate (%)	Group 1 (N=180), 95% CI	Group 2 (N=163), n/M	Group 2 (N=163), Sero-response rate (%)	Group 2 (N=163), 95% CI	Group 1-Group 2, Differ-ence (%)	Group 1-Group 2, 95% CI
A	126/141	89.4	(83.1; 93.9)	102/123	82.9	(75.1; 89.1)	6.43	(-1.92; 15.08)
C	133/134	99.3	(95.9; 100)	123/126	97.6	(93.2; 99.5)	1.63	(-2.07; 6.06)
Y	138/140	98.6	(94.9; 99.8)	125/128	97.7	(93.3; 99.5)	0.92	(-3.03; 5.36)
W	142/143	99.3	(96.2; 100)	118/127	92.9	(87.0; 96.7)	6.39	(1.81; 12.25)

n: Number of participants who achieved hSBA vaccine seroresponse.
N: Number of participants in PPAS2.
M: Number of participants with available data for the relevant endpoint.
Source: Table 10 in Final CSR version 1.0 MET61.

Reviewer's comment: The primary immunogenicity analyses were also conducted on the FAS2, and the results were consistent with those observed in the PPAS2.

6.3.11.2 Analyses of Secondary Endpoints

At Day 30 after the second vaccination, NI of the percentage of participants with titer ≥ 1:8 comparing MenACYW conjugate vaccine (Group 1) to MENVEO (Group 2) was demonstrated in the PPAS2 (Table 32).

Table 32: Non-Inferiority of the Percentage of Participants with Titer ≥ 1:8 30 days After the Second Dose of MenACYW Conjugate Vaccine or MENVEO (Group 1 vs Group 2) – PPAS2

Sero group	Group 1 (N=180), n/M	Group 1 (N=180), %	Group 1 (N=180), 95% CI	Group 2 (N=163), n/M	Group 2 (N=163), %	Group 2 (N=163), 95% CI	Group 1-Group 2, Differ-ence (%)	Group 1-Group 2, 95% CI
A	162/170	95.3	(90.9; 97.9)	147/158	93.0	(87.9; 96.5)	2.26	(-3.01; 7.83)

Sero group	Group 1 (N=180), n/M	Group 1 (N=180), %	Group 1 (N=180), 95% CI	Group 2 (N=163), n/M	Group 2 (N=163), %	Group 2 (N=163), 95% CI	Group 1-Group 2, Differ-ence (%)	Group 1-Group 2, 95% CI
C	162/162	100	(97.7; 100)	157/160	98.1	(94.6; 99.6)	1.88	(-0.75; 5.37)
Y	170/170	100	(97.9; 99.8)	156/160	97.5	(93.7; 99.3)	2.50	(-0.18; 6.25)
W	171/171	100	(97.9; 100)	152/159	95.6	(91.1; 98.2)	4.40	(1.25; 8.81)

n: Number of participants who achieved hSBA Ab titer ≥ 1:8.
N: Number of participants in PPAS2.
M: Number of participants with available data for the relevant endpoint.
Source: Table 12 in Final CSR version 1.0 MET61.

Reviewer's comment:

1. *Results in FAS2 were consistent with those observed in PPAS2.*
2. *The remaining secondary endpoints were summarized descriptively. In general, hSBA GMTs, seroresponse rates, and percentages of participants with titer ≥ 1:4 and ≥ 1:8 were similar or numerically higher in Group 1 than in Group 2 at Day 30 after the first vaccination, pre-second vaccination, and Day 30 after the second vaccination for all serogroups, and were similar or numerically higher in Group 3 than in Group 4 at Day 30 after the second vaccination for all serogroups.*

6.3.11.3 Subpopulation Analyses

Subgroup analyses based on sex and race did not notably differ from the primary analyses.

6.3.12 Safety Analyses

Solicited Adverse Events

Solicited local and systemic AEs within 7 days following any and each vaccination, by maximum severity, on Overall SafAS, SafAS1, SafAS2, SafAS3, and SafAS4 are summarized in Tables 33-37, respectively. Rates of solicited local and systemic reactions were generally similar between Groups 1 and 2 and between Groups 3 and 4 after each vaccination. The most frequently reported local and systemic reactions were injection site tenderness and irritability, respectively.

Table 33: Percentage of Participants Reporting Any Solicited AE within 7 Days Following Any Vaccination – Overall SafAS in MET61

Solicited AE / Severity	Group 1 (N=370) n/M	Group 1 (N=370) %	Group 2 (N=361) n/M	Group 2 (N=361) %	Group 3 (N=96) n/M	Group 3 (N=96) %	Group 4 (N=103) n/M	Group 4 (N=103) %
One or more solicited local AE	226/356	63.5	211/342	61.7	52/91	57.1	48/100	48.0

Solicited AE / Severity	Group 1 (N=370) n/M	Group 1 (N=370) %	Group 2 (N=361) n/M	Group 2 (N=361) %	Group 3 (N=96) n/M	Group 3 (N=96) %	Group 4 (N=103) n/M	Group 4 (N=103) %
Local AE / Severity	-	-	-	-	-	-	-	-
Injection site tenderness*	-	-	-	-	-	-	-	-
Any	177/356	49.7	151/341	44.3	43/91	47.3	41/100	41.0
Grade 1	118/356	33.1	103/341	30.2	33/91	36.3	33/100	33.0
Grade 2	50/356	14.0	40/341	11.7	10.91	11.0	7/100	7.0
Grade 3	9/356	2.5	8/341	2.3	0/91	0	1/100	1.0
Injection site erythema*	-	-	-	-	-	-	-	-
Any	109/355	30.7	101/342	29.5	29/91	31.9	26/100	26.0
Grade 1	106/355	29.9	95/342	27.8	29/91	31.9	24/100	24.0
Grade 2	3/355	0.8	4/342	1.2	0/91	0	2/100	2.0
Grade 3	0/355	0	2/342	0.6	0/91	0	0/100	0
Injection site swelling*	-	-	-	-	-	-	-	-
Any	80/355	22.5	71/342	20.8	23/91	25.3	14/100	14.0
Grade 1	78/355	22.0	67/342	19.6	22/91	24.2	13/100	13.0
Grade 2	1/355	0.3	3/342	0.9	1/91	1.1	1/100	1.0
Grade 3	1/355	0.3	1/342	0.3	0/91	0	0/100	0
One or more solicited systemic AE	235/356	66.0	215/342	62.9	55/91	60.4	62/100	62.0
Systemic AE / Severity	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-
Any	58/347	16.7	56/330	17.0	13/90	14.4	18/100	18.0
Grade 1	38/347	11.0	34/330	10.3	6/90	6.7	11/100	11.0
Grade 2	17/347	4.9	18/330	5.5	6/90	6.7	6/100	6.0
Grade 3	3/347	0.9	4/330	1.2	1/90	1.1	1/100	1.0
Vomiting	-	-	-	-	-	-	-	-
Any	42/356	11.8	37/342	10.8	7/91	7.7	9/100	9.0
Grade 1	30/356	8.4	23/342	6.7	5/91	5.5	6/100	6.0
Grade 2	10/356	2.8	13/342	3.8	2/91	2.2	2/100	2.0
Grade 3	2/356	0.6	1/342	0.3	0/91	0	1/100	1.0
Crying abnormal	-	-	-	-	-	-	-	-
Any	160/356	44.9	138/342	40.4	35/91	38.5	34/100	34.0
Grade 1	94/356	26.4	92/342	26.9	24/91	26.6	22/100	22.0
Grade 2	59/356	16.6	40/342	11.7	10/91	11.0	9/100	9.0
Grade 3	7/356	2.0	6/342	1.8	1/91	1.1	3/100	3.0
Drowsiness	-	-	-	-	-	-	-	-

Solicited AE / Severity	Group 1 (N=370) n/M	Group 1 (N=370) %	Group 2 (N=361) n/M	Group 2 (N=361) %	Group 3 (N=96) n/M	Group 3 (N=96) %	Group 4 (N=103) n/M	Group 4 (N=103) %
Any	160/356	44.9	157/342	45.9	28/91	30.8	30/100	30.0
Grade 1	114/356	32.0	107/342	31.3	21/91	23.1	23/100	23.0
Grade 2	37/356	10.4	39/342	11.4	7/91	7.7	4/100	4.0
Grade 3	9/356	2.5	11/342	3.2	0/91	0	3/100	3.0
Appetite loss	-	-	-	-	-	-	-	-
Any	83/356	23.3	83/342	24.3	28/91	30.8	34/100	34.0
Grade 1	56/356	15.7	67/342	19.6	21/91	23.1	23/100	23.0
Grade 2	21/356	5.9	12/342	3.5	7/91	7.7	9/100	9.0
Grade 3	6/356	1.7	4/342	1.2	0/91	0	2/100	2.0
Irritability	-	-	-	-	-	-	-	-
Any	202/356	56.7	186/342	54.4	44/91	48.4	52/100	52.0
Grade 1	92/356	25.8	98/342	28.7	22/91	24.2	27/100	27.0
Grade 2	86/356	24.2	71/342	20.8	19/91	20.9	19/100	19.0
Grade 3	24/356	6.7	17/342	5.0	3/91	3.3	6/100	6.0

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 22 and Table 23 in Final CSR version 1.0 MET61.

Table 34: Percentage of Participants Reporting Any Solicited AE within 7 Days Following First Vaccination – SafAS1 in MET61

Solicited AE / Severity	Group 1 (N=370) n/M	Group 1 (N=370) %	Group 2 (N=361) n/M	Group 2 (N=361) %
One or more solicited local AE	197/351	56.1	184/339	54.3
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	150/351	42.7	117/337	34.7
Grade 1	111/351	31.6	80/337	23.7
Grade 2	31/351	8.8	30/337	8.9
Grade 3	8/351	2.3	7/337	2.1
Injection site erythema*	-	-	-	-
Any	74/350	21.1	73/338	21.6
Grade 1	72/350	20.6	71/338	21.0
Grade 2	2/350	0.6	2/338	0.6
Grade 3	0/350	0	0/338	0
Injection site swelling*	-	-	-	-
Any	56/350	16.0	53/338	15.7
Grade 1	55/350	15.7	50/338	14.8
Grade 2	1/350	0.3	3/338	0.9
Grade 3	0/350	0	0/338	0
One or more solicited systemic AE	209/351	59.5	193/339	56.9

Solicited AE / Severity	Group 1 (N=370) n/M	Group 1 (N=370) %	Group 2 (N=361) n/M	Group 2 (N=361) %
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	44/341	12.9	40/325	12.3
Grade 1	30/341	8.8	27/325	8.3
Grade 2	13/341	3.8	11/325	3.4
Grade 3	1/341	0.3	2/325	0.6
Vomiting	-	-	-	-
Any	30/351	8.5	27/339	8.0
Grade 1	20/351	5.7	15/339	4.4
Grade 2	9/351	2.6	12/339	3.5
Grade 3	1/351	0.3	0/339	0
Crying abnormal	-	-	-	-
Any	123/351	35.0	110/339	32.4
Grade 1	76/351	21.7	77/339	22.7
Grade 2	41/351	11.7	29/339	8.6
Grade 3	6/351	1.7	4/339	1.2
Drowsiness	-	-	-	-
Any	128/351	36.5	132/339	38.9
Grade 1	95/351	27.1	97/339	28.6
Grade 2	25/351	7.1	27/339	8.0
Grade 3	8/351	2.3	8/339	2.4
Appetite loss	-	-	-	-
Any	60/351	17.1	55/339	16.2
Grade 1	44/351	12.5	48/339	14.2
Grade 2	11/351	3.1	5/339	1.5
Grade 3	5/351	1.4	2/339	0.6
Irritability	-	-	-	-
Any	172/351	49.0	153/339	45.1
Grade 1	85/351	24.2	83/339	24.5
Grade 2	70/351	19.9	58/339	17.1
Grade 3	17/351	4.8	12/339	3.5

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.60 and Table 8.90 in Final CSR version 1.0 MET61.

Table 35: Percentage of Participants Reporting Any Solicited AE within 7 Days Following Second Vaccination – SafAS2 in MET61

Solicited AE / Severity	Group 1 (N=309) n/M	Group 1 (N=309) %	Group 2 (N=302) n/M	Group 2 (N=302) %
One or more solicited local AE	124/289	42.9	127/272	46.7
Local AE / Severity	-	-	-	-

Solicited AE / Severity	Group 1 (N=309) n/M	Group 1 (N=309) %	Group 2 (N=302) n/M	Group 2 (N=302) %
Injection site tenderness*	-	-	-	-
Any	87/289	30.1	87/272	32.0
Grade 1	59/289	20.4	67/272	24.6
Grade 2	26/289	9.0	16/272	5.9
Grade 3	2/289	0.7	4/272	1.5
Injection site erythema*	-	-	-	-
Any	63/289	21.8	59/272	21.7
Grade 1	62/289	21.5	55/272	20.2
Grade 2	1/289	0.3	2/272	0.7
Grade 3	0/289	0	2/272	0.7
Injection site swelling*	-	-	-	-
Any	42/289	14.5	40/272	14.7
Grade 1	41/289	14.2	39/272	14.3
Grade 2	0/289	0	0/272	0
Grade 3	1/289	0.3	1/272	0.4
One or more solicited systemic AE	137/290	47.2	129/273	47.3
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	26/279	9.3	20/261	7.7
Grade 1	19/279	6.8	11/261	4.2
Grade 2	5/279	1.8	7/261	2.7
Grade 3	2/279	0.7	2/261	0.8
Vomiting	-	-	-	-
Any	16/289	5.5	10/273	3.7
Grade 1	14/289	4.8	8/273	2.9
Grade 2	1/289	0.3	1/273	0.4
Grade 3	1/289	0.3	1/273	0.4
Crying abnormal	-	-	-	-
Any	77/289	26.6	69/273	25.3
Grade 1	53/289	18.3	49/273	17.9
Grade 2	22/289	7.6	18/273	6.6
Grade 3	2/289	0.7	2/273	0.7
Drowsiness	-	-	-	-
Any	80/289	27.7	86/273	31.5
Grade 1	59/289	20.4	64/273	23.4
Grade 2	19/289	6.6	19/273	7.0
Grade 3	2/289	0.7	3/279	1.1
Appetite loss	-	-	-	-
Any	44/289	15.2	47/272	17.3
Grade 1	30/289	10.4	37/272	13.6
Grade 2	12/289	4.2	8/272	2.9
Grade 3	2/289	0.7	2/272	0.7

Solicited AE / Severity	Group 1 (N=309) n/M	Group 1 (N=309) %	Group 2 (N=302) n/M	Group 2 (N=302) %
Irritability	-	-	-	-
Any	116/290	40.0	110/272	40.4
Grade 1	66/290	22.8	74/272	27.2
Grade 2	41/290	14.1	31/272	11.4
Grade 3	9/290	3.1	5/272	1.8

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO®.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.61 and Table 8.91 in Final CSR version 1.0 MET61.

Table 36: Percentage of Participants Reporting Any Solicited AE within 7 Days Following First Vaccination – SafAS3 in MET61

Solicited AE / Severity	Group 3 (N=96) n/M	Group 3 (N=96) %	Group 4 (N=103) n/M	Group 4 (N=103) %
One or more solicited local AE	38/90	42.2	42/99	42.4
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	31/90	34.4	35/99	35.4
Grade 1	24/90	26.7	29/99	29.3
Grade 2	7/90	7.8	5/99	5.1
Grade 3	0/90	0	1/99	1.0
Injection site erythema*	-	-	-	-
Any	20/90	22.2	22/99	22.2
Grade 1	20/90	22.2	21/99	21.2
Grade 2	0/90	0	1/99	1.0
Grade 3	0/90	0	0/99	0
Injection site swelling*	-	-	-	-
Any	17/90	18.9	12/99	12.1
Grade 1	16/90	17.8	11/99	11.1
Grade 2	1/90	1.1	1/99	1.0
Grade 3	0/90	0	0/99	0
One or more solicited systemic AE	49/90	54.4	51/99	51.5
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	10/89	11.2	12/98	12.2
Grade 1	7/89	7.9	7/98	.1
Grade 2	2/89	2.2	4/98	4.1
Grade 3	1/89	1.1	1/98	1.0
Vomiting	-	-	-	-
Any	4/90	4.4	6/99	6.1
Grade 1	4/90	4.4	5/99	5.1
Grade 2	0/90	0	1/99	1.0

Solicited AE / Severity	Group 3 (N=96) n/M	Group 3 (N=96) %	Group 4 (N=103) n/M	Group 4 (N=103) %
Grade 3	0/90	0	0/99	0
Crying abnormal	-	-	-	-
Any	24/90	26.7	26/99	26.3
Grade 1	17/90	18.9	17/99	17.2
Grade 2	6/90	6.7	7/99	7.1
Grade 3	1/90	1.1	2/99	2.0
Drowsiness	-	-	-	-
Any	22/90	24.4	23/99	23.2
Grade 1	18/90	20.0	19/99	19.2
Grade 2	4/90	4.4	2/99	2.0
Grade 3	0/90	0	2/99	2.0
Appetite loss	-	-	-	-
Any	19/90	21.1	23/99	23.2
Grade 1	14/90	15.6	16/99	16.2
Grade 2	5/90	5.6	6/99	6.1
Grade 3	0/90	0	1/99	1.0
Irritability	-	-	-	-
Any	36/90	40.0	43/99	43.4
Grade 1	20/90	22.2	24/99	24.2
Grade 2	13/90	14.4	16/99	16.2
Grade 3	3/90	3.3	3/99	3.0

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.62 and Table 8.92 in Final CSR version 1.0 MET61.

Table 37: Percentage of Participants Reporting Any Solicited AE within 7 Days Following Second Vaccination – SafAS4 in MET61

Solicited AE / Severity	Group 3 (N=86) n/M	Group 3 (N=86) %	Group 4 (N=96) n/M	Group 4 (N=96) %
One or more solicited local AE	40/82	48.8	32/93	34.4
Local AE / Severity	-	-	-	-
Injection site tenderness*	-	-	-	-
Any	34/82	41.5	25/93	26.9
Grade 1	27/82	32.9	22/93	23.7
Grade 2	7/82	8.5	2/93	2.2
Grade 3	0/82	0	1/93	1.1
Injection site erythema*	-	-	-	-
Any	21/82	25.6	15/93	16.1
Grade 1	21/82	25.6	14/93	15.1
Grade 2	0/82	0	1/93	1.1
Grade 3	0/82	0	0/93	0

Injection site swelling*	-	-	-	-
Any	17/82	20.7	7/93	7.5
Grade 1	17/82	20.7	7/93	7.5
Grade 2	0/82	0	0/93	0
Grade 3	0/82	0	0/93	0
One or more solicited systemic AE	41/82	50.0	43/93	46.2
Systemic AE / Severity	-	-	-	-
Fever	-	-	-	-
Any	9/82	11.0	8/91	8.8
Grade 1	5/82	6.1	5/91	5.5
Grade 2	4/82	4.9	3/91	3.3
Grade 3	0/82	0	0/91	0
Vomiting	-	-	-	-
Any	3/82	3.7	3/93	3.2
Grade 1	1/82	1.2	1/93	1.1
Grade 2	2/82	2.4	1/93	1.1
Grade 3	0/82	0	1/93	1.1
Crying abnormal	-	-	-	-
Any	21/82	25.6	18/93	19.4
Grade 1	16/82	19.5	13/93	14.0
Grade 2	5/82	6.1	4/93	4.3
Grade 3	0.82	0	1/93	1.1
Drowsiness	-	-	-	-
Any	19/82	23.2	13/93	14.0
Grade 1	15/82	18.3	10/93	10.8
Grade 2	4/82	4.9	2/93	2.2
Grade 3	0/82	0	1/93	1.1
Appetite loss	-	-	-	-
Any	17/82	20.7	24/93	25.8
Grade 1	14/82	17.1	20/93	21.5
Grade 2	3/82	3.7	3/93	3.2
Grade 3	0/82	0	1/93	1.1
Irritability	-	-	-	-
Any	29/82	35.4	31/93	33.3
Grade 1	18/82	22.0	23/93	24.7
Grade 2	10/82	12.2	5/93	5.4
Grade 3	1/82	1.2	3/93	3.2

**: Solicited local AEs related to MenACYW conjugate vaccine or MENVEO.*
n: number of participants experiencing the endpoints listed in first column.
M: number of participants with available data for the relevant endpoint. Percentages are based on M.
Source: Adapted from Table 8.63 and Table 8.93 in Final CSR version 1.0 MET61.

Unsolicited Adverse Events

In the Overall SafAS, the percentages of participants who reported any unsolicited AE within 30 days of any vaccination were 49.2% in Group 1, 42.7% in Group 2, 37.5% in

Group 3, and 35.9% in Group 4. The percentages of participants with unsolicited AEs within 30 days were similarly comparable between Groups 1 and 2 and between Groups 3 and 4 after each vaccination.

Table 38 presents the percentages of participants who experienced any SAE, AESI, and MAAE within 30 days of any vaccination and during the study period. No notable differences in rates of SAEs, AESIs, and MAAEs were observed. One SAE of Grade 3 febrile convulsions was assessed as related to the study vaccine by the investigator in Group 4 that occurred on Day 1 after the first vaccination. This event was also reported as an AESI. No deaths were reported during the study.

Table 38: Overview of SAEs, AESIs, and MAAEs in MET61

SafAS	Group 1	Group 2	Group 3	Group 4
SAE within 30 days after vaccination	-	-	-	-
Overall SafAS	1/370 (0.3%)	2/361 (0.6%)	0	2/103 (1.9%)
SafAS1	0	1/361 (0.3%)	-	-
SafAS2	1/309 (0.3%)	1/302 (0.3%)	-	-
SafAS3	-	-	0	1/103 (1.0%)
SafAS4	-	-	0	1/96 (1.0%)
AESI within 30 days after vaccination	-	-	-	-
Overall SafAS	0	0	0	1/103 (1.0)
SafAS1	0	0	-	-
SafAS2	0	0	-	-
SafAS3	-	-	0	1/103 (1.0%)
SafAS4	-	-	0	0
MAAE within 30 days after vaccination	-	-	-	-
Overall SafAS	136/370 (36.8%)	117/361 (32.4%)	28/96 (29.2%)	28/103 (27.2%)
SafAS1	91/370 (24.6%)	78/361 (21.6%)	-	-
SafAS2	67/309 (21.7%)	60/302 (19.9%)	-	-
SafAS3	-	-	22/96 (22.9%)	17/103 (16.5%)
SafAS4	-	-	14/86 (16.3%)	14/96 (14.6%)
SAE during the study	-	-	-	-
Overall SafAS	6/370 (1.6%)	12/361 (3.3%)	1/96 (1.0%)	4/103 (3.9%)
SafAS1	4/370 (1.1%)	10/361 (2.8%)	-	-
SafAS2	2/309 (0.6%)	3/302 (1.0%)	-	-

SafAS	Group 1	Group 2	Group 3	Group 4
SafAS3	-	-	1/96 (1.0%)	2/103 (1.9%)
SafAS4	-	-	0	2/96 (2.1%)
AESI during the study				
Overall SafAS	1/370 (0.3%)	2/361 (0.6%)	0	2/103 (1.9%)
SafAS1	1/370 (0.3%)	1/361 (0.3%)	-	-
SafAS2	0	1/302 (0.3%)	-	-
SafAS3	-	-	0	2/103 (1.9%)
SafAS4	-	-	0	0
MAAE during the study	-	-	-	-
Overall SafAS	252/370 (68.1%)	249/361 (69.0%)	61/96 (63.5%)	64/103 (62.1%)
SafAS1	224/370 (60.5%)	230/361 (63.7%)	-	-
SafAS2	148/309 (47.9%)	141/302 (46.7%)	-	-
SafAS3	-	-	52/96 (54.2%)	50/103 (48.5%)
SafAS4	-	-	35/86 (40.7%)	42/96 (43.8%)

Source: Summarized by the reviewer based on information presented in the MET61 CSR version 1.0.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated analysis of efficacy was submitted.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Integrated analyses of safety were performed combining Studies MET41, MET42 and MET61. Two objectives were considered in the analyses:

- Objective 1: To present a descriptive comparison of the safety profile of MenACYW conjugate vaccine with the safety profile of comparator vaccine (MENEVO) when administered in a 4-dose schedule concomitantly with routine pediatric vaccines.
- Objective 2: To describe the safety profile of the MenACYW conjugate vaccine and comparators (MENVEO and Menactra) after any dose (at least one dose administrated from 6 weeks to 23 months).

Safety endpoints considered in the integrated analyses were:

- Immediate unsolicited AEs/ARs within 0-30 minutes after each and any dose by System Organ Class (SOC) and preferred term.
- Solicited injection site and systemic reactions within 7 days after vaccination by time of onset, number of days of occurrence, and maximum intensity.

- Unsolicited AEs/ARs within 30 days after vaccination by SOC and preferred term, time of onset, duration, and maximum intensity.
- Grade 3 unsolicited AEs/ARs within 30 days after vaccination by SOC and preferred term.
- SAEs (including AESIs) and MAAEs from Day 0 to Day 7, Day 0 to Day 30, during 6-month follow-up period, and during the whole study after vaccination by SOC and preferred term.
- AEs leading to discontinuation by SOC and preferred term.

Endpoints were described via point estimates and exact 95% CIs for single proportions.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The first objective was assessed based on pooled MET41 and MET42 data. The second objective was assessed based on pooled MET41, MET42, and MET61 data.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 39 shows the number of participants included in each analysis. Totals of 3807 and 4273 MenACYW recipients were included for the two objectives, respectively.

Table 39: Overall Extent of Exposure in the Integrated Summary of Safety

Study	SafAS	MenACYW + routine pediatric vaccines	Menveo + routine pediatric vaccines	Menactra
Pooled MET41 and MET42	SafAS post any dose	3807	1564	-
Pooled MET41, MET42 and MET61	Overall SafAS post any dose	4273	1925	103

Source: Table 2.1 in the Integrated Summary of Safety (ISS).

Table 40 presents a summary of baseline demographics in the SafAS post any dose combining Studies MET41 and MET42. Overall, demographic characteristics were similar between the two groups. Distributions of sex and race were also similar across the three groups after inclusion of MET61 (not shown in table).

Table 40: Summary of Participant Demographics – Safety Analysis Set Post Any Dose (Pooled MET41 and MET42)

Demographic	MenACYW + routine pediatric vaccines (N=3807)	MENVEO + routine pediatic vaccines (N=1564)
Sex: n (%)		
Male	1998 (52.5)	819 (52.4)

Demographic	MenACYW + routine pediatric vaccines (N=3807)	MENVEO + routine pediatic vaccines (N=1564)
Female	1809 (47.5)	745 (47.6)
Age (days)		
M	3807	1564
Mean (sd)	64.9 (7.30)	65.0 (7.37)
Min; Max	42.0; 89.0	42.0; 89.0
Median	63.0	64.0
Q1; Q3	61.0; 68.0	61.0; 68.0
Racial origin: n (%)		
American Indian or Alaska Native	19 (0.5)	3 (0.2)
Asian	41 (1.1)	22 (1.4)
Black or African American	414 (10.9)	161 (10.3)
Native Hawaiian or Other Pacific Islander	16 (0.4)	11 (0.7)
White	3117 (81.9)	1293 (82.7)
Mixed origin	143 (3.8)	60 (3.8)
Not reported	27 (0.7)	9 (0.6)
Unknown	30 (0.8)	5 (0.3)

Source: Table 3.1.1 in the Integrated Summary of Safety (ISS).

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

There are no caveats to be noted for the analyses.

8.4 Safety Results

Solicited Adverse Events

The percentages of participants who reported any solicited injection site reaction after any vaccination with MenACYW conjugate vaccine or MENVEO in a four-dose schedule (MET41 and MET42 combined) were 75.7% (2772/3662) in MenACYW conjugate vaccine recipients and 74.0% (1115/1507) in MENVEO recipients. Similarly, the percentages of participants who reported any injection site reaction after any vaccination with MenACYW conjugate vaccine, MENVEO, or Menactra (MET41, MET42, and MET61 combined) were 73.6% (3023/4109) in MenACYW conjugate vaccine recipients, 70.0% (1295/1849) in MENVEO recipients, and 48.0% (48/100) in Menactra recipients.

The percentages of participants who reported any solicited systemic reaction after any vaccination with MenACYW conjugate vaccine or MENVEO in a four-dose schedule (MET41 and MET42 combined) were 83.6% (3060/3661) in MenACYW conjugate vaccine recipients and 84.1% (1268/1507) in MENVEO recipients. Similarly, the percentages of participants who reported any solicited systemic reaction after any vaccination with MenACYW conjugate vaccine, MENVEO, or Menactra (MET41,

MET42, and MET61 combined) were 81.5% (3350/4108) in MenACYW conjugate vaccine recipients, 80.2% (1483/1849) in MENVEO recipients, and 62.0% (62/100) in Menactra recipients.

Reviewer's comment: The lower percentages of participants reporting solicited reactions after any vaccination with Menactra appears to be driven primarily by the lower number of injections in Study MET61.

Unsolicited Adverse Events

Combining MET41, MET42 and MET61, 0.2% (8/4273) of MenACYW conjugate vaccine recipients, 0.2% (3/1925) of MENVEO recipients, and 0% (0/103) of Menactra recipients reported immediate unsolicited AEs within 30 minutes of any vaccine injection. The percentages of participants who reported at least one unsolicited AE within 30 days of any vaccination were 58.0% (2480/4273) in the MenACYW conjugate vaccine group, 54.4% (1047/1925) in the MENVEO group, and 35.9% (37/103) in the Menactra group. There were no notable differences between groups in terms of the percentages of participants discontinuing the study due to AE during the study period. Similar observations were made after any vaccination with MenACYW conjugate vaccine or MENVEO in a four-dose schedule (MET41 and MET42 combined).

The percentages of participants reporting any SAE during the study period (MET41, MET42, and MET61 combined) were 4.9% (208/4273) among MenACYW conjugate vaccine recipients, 3.6% (69/1925) among MENVEO recipients, and 3.9% (4/103) among Menactra recipients. One SAE reported in each group was considered by the investigator to be related to study vaccination. Approximately 0.7% (31/4273) of MenACYW conjugate vaccine recipients, 0.4% (8/1925) of MENVEO recipients, and 1.9% (2/103) of Menactra recipients reported at least one AESI during the study, and 68.6% (2930/4273) of MenACYW conjugate vaccine recipients, 67.4% (1298/1925) of MENVEO recipients, and 62.1% (64/103) of Menactra recipients reported any MAAE. Similar observations were made for SAEs, AESIs, and MAAEs after vaccination with MenACYW conjugate vaccine or MENVEO in a four-dose schedule (MET41 and MET42 combined).

A total of four deaths (MET41, MET42, and MET61 combined) were reported during the studies, all in the MenACYW conjugate vaccine group (i.e. cardiac arrest, head injury, sudden infant death syndrome, and unresponsive to stimuli). All four events were considered unrelated to vaccination by the investigator.

8.5 Additional Safety Evaluations

Please refer to the clinical reviewer's memo.

8.6 Safety Conclusions

Overall, there did not appear to be notable differences between MenACYW conjugate vaccine and MENVEO or Menactra in terms of frequencies of solicited injection site and systemic reactions within 7 days of any vaccination, or frequencies of unsolicited AEs within 30 days of any vaccination. I defer to the clinical reviewer on the safety conclusions.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Two Phase III studies evaluated MenACYW conjugate vaccine when given to infants at 2, 4, 6, and 12 to 15 or 15 to 18 months of age (safety and immunogenicity study MET42), and at 2, 4, 6, and 12 months of age (safety study MET41) along with other licensed routine pediatric vaccines. One Phase III safety and immunogenicity study, MET61, evaluated MenACYW conjugate vaccine when given at 6 to 7 and 12 to 13 months of age, or at 17 to 19 and 12 to 23 months of age, along with other licensed routine pediatric vaccines.

For study MET41, the percentages of participants who reported at least one solicited reaction up to 7 days after any injection were comparable between groups. The percentages of participants who reported at least one solicited injection site and solicited systemic reaction were 84.9% and 87.1% in Group 1 and 84.6% and 88.2% in Group 2, respectively. The most frequently reported reactions in both groups were injection site pain, irritability, crying abnormal, and drowsiness. After vaccination with MenACYW or MENVEO, the percentage of participants who experienced any solicited injection site reaction was 79.0% in Group 1 and 77.7% in Group 2. Most reported reactions were mild or moderate in intensity. The percentages of participants reporting any SAE during the study were 5.2% in Group 1 and 3.0% in Group 2. In addition, there were 3 deaths reported in Group 1 and none in Group 2. None of the SAEs or deaths were considered related to the study intervention by the investigator.

For study MET42, the percentages of participants who reported at least one solicited reaction after any injection were comparable between the two groups. The percentages of participants who experienced any solicited injection site reaction and solicited systemic reaction after any injection were 78.0% and 80.0% in Group 1 and 79.8% and 81.9% in Group 2, respectively. The most frequently reported reactions in both groups were injection site tenderness, irritability, crying abnormal, and drowsiness. After any vaccination with MenACYW conjugate vaccine or MENVEO, 71.7% and 71.0% of participants reported solicited injection site reactions, respectively. Most solicited reactions were mild or moderate. The percentage of participants reporting SAEs was 5.7% in Group 1 and 4.4% in Group 2 during the study. Two SAEs were assessed as related to the study vaccine by the investigator: a case of febrile convulsion in Group 1 and a case of post-vaccination fever in Group 2. Both cases were reported within 30 days of vaccination. There was one death due to cardiac arrest reported in Group 1 which was considered unrelated to study intervention by the investigator. There were no deaths reported in Group 2.

For study MET61, the percentages of participants who reported any solicited reaction were comparable between Group 1 and Group 2, and between Group 3 and Group 4. The percentages of participants who experienced at least one solicited injection site reaction and solicited systemic reaction were 63.5% and 66.0% in Group 1, 61.7% and 62.9% in

Group 2, 57.1% and 60.4% in Group 3, and 48.0% and 62.0% in Group 4, respectively. The most frequently reported solicited reactions in all groups were injection site tenderness, irritability, crying abnormal, and drowsiness. The percentage of participants who experienced any solicited injection site reaction after administration of the meningococcal vaccine was 55.9% in Group 1, 52.6% in Group 2, 57.1% in Group 3, and 48.0% in Group 4. Most solicited reactions were mild or moderate in intensity. The percentage of participants with SAEs was 1.6% in Group 1, 3.3% in Group 2, 1.0% in Group 3, and 3.9% in Group 4 during the study. One SAE of Grade 3 febrile convulsion in Group 4 on Day 1 after vaccination was assessed as related to the study vaccine by the investigator. No deaths were reported during the study.

Assessments of non-inferiority of immune responses after vaccination with MenACYW conjugate vaccine to MENVEO were based on studies MET42 and MET61. In MET42, the pre-specified NI criteria for the differences in hSBA vaccine seroresponse rates at 30 days after MenACYW vaccination at 12 to 15 months of age (G1a) to MENVEO at 12 months of age (G2a) were met (via a -10% NI margin) for each of the four meningococcal serogroups. The pre-specified NI criteria for the percentages of participants with hSBA antibody titer ≥1:8 at 30 days after vaccination with MenACYW (G1) or MENVEO (G2) at 6 months of age (via a -10% NI margin) were met for each of the four meningococcal serogroups. In MET61, the pre-specified NI criteria for hSBA vaccine seroresponse rate 30 days after the second dose of MenACYW conjugate vaccine compared to MENVEO at 12 to 13 months of age (via a -10% margin) were met for each of the four meningococcal serogroups.

Results presented in this review related to the primary and secondary immunogenicity and safety endpoints for all three studies, including the integrated analysis of safety, were verified using R 4.4.0.

10.2 Conclusions and Recommendations

Considering the totality of the evidence, based on my review of the statistical analyses and results presented in this BLA supplement, the data support the effectiveness of the MenACYW conjugate vaccine in infants aged 6 weeks and older. I defer to the clinical reviewer on the safety conclusions.