Application Type	Biologics License Application (BLA)
STN	125701/0
CBER Received Date	26 Apr 2019
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Division / Office	DVRPA/OVRR
Committee Chair	Joseph Temenak, PhD
Clinical Reviewer(s)	Anuja Rastogi, MD, MPH
Project Manager	Mike Smith, PhD, Ramachandra Naik, PhD and Nikunj Sharma, PhD
Priority Review	No
Reviewer Name(s)	Elizabeth Teeple, PhD
Review Completion Date / Stamped Date	Date: March 27, 2020
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Applicant	Sanofi Pasteur
Established Name	Meningococcal (Groups A, C, Y, W) Conjugate Vaccine
(Proposed) Trade Name	MENQUADFI™
Pharmacologic Class	Vaccine
Formulation	0.5 mL dose of MenACYW conjugate vaccine, formulated in sodium acetate buffered saline solution with 10 µg of each of the meningococcal PS serogroups A, C, W, and Y, conjugated to approximately 55 µg tetanus toxoid protein carrier
Dosage Form(s) and Route(s) of Administration	Liquid solution, administered by intramuscular injection
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	For individuals 2 years of age and older for the prevention of invasive meningococcal disease (IMD) caused by serogroups A, C, W, and Y of *Neisseria meningitidis*

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GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
BL	Blood sample
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
D	Day
FAS	Full Analysis Set
FHA	Filamentous Hemagglutinin
FIM	Fimbriae types 2 and 3
GMC/T	Geometric Mean Concentration/Titer
GMCR/GMTR	Geometric Mean Concentration/Titer Ratio
HPV	Human papillomavirus
hSBA	Serum bactericidal assay using human complement
IMD	Invasive meningococcal disease
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
IR	Information Request
MAAE	Medically Attended Adverse Event
MCV4	Quadrivalent Meningococcal Conjugate Vaccine
PPAS	Per-Protocol Analysis Set
PRN	Pertactin
PT	Pertussis Toxoid
(b) (4)	(b) (4)
SAE	Serious Adverse Event
SafAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard deviation
Tdap	Tetanus, diphtheria, acellular pertussis

1. Executive Summary

Sanofi Pasteur submitted this Biologics License Application (BLA) to support licensure of a MenACYW conjugate vaccine (Meningococcal (Groups A, C, Y, and W) Conjugate Vaccine, trade name MenQuadfi), with the indication for prevention of invasive meningococcal disease (IMD) in subjects 2 years of age and older. The application is supported by three main Phase 3 studies for the age groups 2-9 years old (study MET35), 10-55 years old (MET43), and 56 years old and older (MET49). Additional studies were submitted to support an indication for use of MenQuadfi as a booster dose after an initial vaccination with a conjugated quadrivalent meningococcal vaccine (MCV4) and to provide descriptive information on concomitant administration with licensed vaccines Adacel (Tetanus, diphtheria, acellular pertussis [Tdap] vaccine) and Gardasil (Human papillomavirus [HPV] vaccine).

MET35: The primary immunogenicity objective of non-inferiority of MenQuadfi seroresponse compared to Menveo seroresponse was demonstrated in children aged 2-9 years old, with percent differences ranging from 7.6% for serogroup A (95% CI: 1.1%; 14.0%) to 47.4% for serogroup C (95% CI: 42.2%; 52.2%). Injection site reaction of pain was balanced across arms, while erythema and swelling were lower in MenQuadfi. Solicited systemic reactions (myalgia, malaise, headache, and fever) were balanced across vaccine arms.

MET43: For the first primary objective, the applicant demonstrated equivalence of hSBA GMTs across three lots and all four serogroups. In the second primary immunogenicity objective, MenQuadfi was shown to be non-inferior to Menactra in adolescents and adults aged 10-55 years old, with difference in percents ranging from 18.1% (95% CI: 14.5%; 21.9%) for serogroup Y to 40.9% (95% CI: 36.7%; 45.0%) for serogroup C. Solicited injection site and systemic reactions were balanced across the three lots of MenQuadfi and the Menactra arm.

MET50: In this open-label Phase 2 study, the primary objective was met supporting non-inferiority of MenQuadfi compared to Menveo in subjects 10-17 years of age. The sponsor tested non-inferiority of concomitant vaccines (Adacel and Gardasil) as secondary objectives, though did not power to meet these hypotheses. For the primary objective, non-inferiority criteria were successfully met for all four meningococcal serogroups. Solicited injection site and systemic reactions were balanced across the MCV4 arms, but higher in the concomitant vaccine arms.

MET49: The primary immunogenicity objective of non-inferiority of MenQuadfi seroresponse compared to Menomune seroresponse was demonstrated in older adults and the elderly aged at least 56 years old, with percent differences ranging from 15.7% for serogroup A (95% CI: 9.1%; 22.2%) to 31.0% for serogroup Y (95% CI: 24.6%; 37.0%). Injection site reaction of pain was higher in the MenQuadfi arm, and erythema and swelling were minimally higher in MenQuadfi. Solicited systemic reactions were slightly higher in MenQuadfi. However, this increase in AEs is expected when comparing a conjugated to an unconjugated vaccine.

MET56: The primary immunogenicity objective of demonstrating non-inferiority of MenQuadfi seroresponse compared to Menactra seroresponse was met in quadrivalent meningococcal conjugate vaccine (MCV4)-primed adolescents (≥ 15 to < 18 years) and adults (≥ 18 years), with percent differences ranging from 1.8% for serogroup Y (95% CI: -9.1%; 4.6%) to 7.4% for serogroup W (95% CI: 4.3%; 10.9%). The safety profiles were similar across the two vaccine arms.

In each of the three age groups, MenQuadfi was shown to be non-inferior to a currently licensed quadrivalent meningococcal vaccine when comparing seroresponse rates. The statistical methods used to support these conclusions are appropriate.

In conclusion, I recommend the approval of this application.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Meningococcal (Groups A, C, Y and W) Conjugate Vaccine (also referred to as MenACYW conjugate vaccine or MenQuadfi in this document) is an investigational vaccine that aims to provide broad coverage against invasive meningococcal disease (IMD) in infants and toddlers as well as children, adolescents, and adults, including those over 56 years of age.

Please see the clinical review for a full discussion.

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

Please refer to the clinical review.

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

Prior to initiating Phase 2 studies, the MenACYW conjugate vaccine formulation was finalized based on data provided by 2 studies: MET28, a Phase I study in infants, toddlers, and adults 18 through 40 years of age; and MET32, a Phase I/II study in toddlers, for a total of approximately 500 subjects. Please refer to the clinical review for a complete discussion.

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

N/A

2.6 Other Relevant Background Information

N/A

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the clinical and bioresearch and monitoring reviews.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to the appropriate discipline reviews for further discussion on Chemistry, Manufacturing, and Controls (CMC); assay validation; nonclinical pharmacology/toxicology; clinical pharmacology; clinical; and pharmacovigilance topics.

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

5.1 Review Strategy

The applicant submitted six studies to support the safety and immunogenicity of a single dose of MenQuadfi in ages 2 and older. Five of the six studies support licensure across age groups as indicated in the prescribing information; those studies are discussed in this review. All six studies are considered in the integrated/pooled analyses of immunogenicity and safety. Please see Section 5.3 for a further description.

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

The following sections in STN 125701/0.0 were reviewed in detail:

- Module 1.14: Labeling
- Module 2.5, 2.7.3, and 2.7.4: Clinical Overview, Summary of Clinical Efficacy, and Summary of Clinical Safety
- Module 5.3.5.1: Clinical study reports (CSRs) and protocols: MET35, MET43, MET44, MET49, MET50, and MET56
- Module 5.3.5.3: Integrated Summary of Immunogenicity (ISI) and Integrated Summary of Safety (ISS)

There was one amendment submitted to STN 125701/0.17 in response to a CBER information request to align the definition of seroconversion in the analysis of MET50 with the other studies. This amendment is included in the review of MET50.

5.3 Table of Studies/Clinical Trials

The six studies included in this submission to support the licensure of MenQuadfi in ages 2 and older are listed in Table 1.

Table 1: Overview of clinical studies included to support licensure

Study	Age group	Country	Description	Study Design	Treatment groups	Total Sample Size (total on MenQuadfi)
MET35	2 – 9 years old	USA, Puerto Rico	Safety & Immunogenicity Non-Inferiority vs. Menveo	III	Group 1 - MenQuadfi Group 2 - Menveo	1000 (498)
MET43	10 - 55 years old	USA	Safety, Immunogenicity Lot Consistency, and Non-Inferiority vs Menactra	III	Group 1 - MenQuadfi (Lot 1) Group 2 - MenQuadfi (Lot 2) Group 3 - MenQuadfi (Lot 3) Group 4 - Menactra	3344 (2676)
MET44	≥ 56 years old	USA	Safety & Descriptive Immunogenicity vs Menomune	II	Group 1 - MenQuadfi Group 2 - Menomune − A/C/Y/W-135	301 (199)
MET49	≥ 56 years old	USA	Safety & Immunogenicity Non-Inferiority vs Menomune	III	Group 1 - MenQuadfi Group 2 - Menomune − A/C/Y/W-135	907 (448)
MET50	10 - 17 years old	USA	Safety, Immunogenicity Non-Inferiority vs Menveo, and vs Concomitant Use with Adacel and Gardasil	II	Group 1 - MenQuadfi Group 2 - Menveo Group 3 - MenQuadfi, Adacel, and Gardasil Group 4 - Adacel and Gardasil	1715 (895)
MET56	≥ 15 years old	USA, Puerto Rico	Safety, Immunogenicity Non-Inferiority vs Menactra in MCV4 Primed Subjects	III	Group 1 - MenQuadfi Group 2 - Menactra	810 (402)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 MET35

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

6.1.1 Objectives (Primary, Secondary, etc)

Primary Objective

To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi compared to that observed following the administration of a single dose of Menveo in children aged 2 to 9 years.

Secondary Objectives

1) To compare the serum bactericidal assay using human complement (hSBA) antibody geometric mean titers (GMTs) of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi to those observed following the administration of Menveo in children aged 2 to 9 years of age.

2) To evaluate the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi and those observed following the administration of Menveo in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively.
3) To evaluate the hSBA vaccine seroresponse to meningococcal serogroups A, C, Y, and W before and 30 days (+14 days) post-vaccination in children 2 to 5 years of age, and in children 6 to 9 years of age, respectively.

Additionally, there was an observational objective to describe the safety profile of MenQuadfi and that of the licensed Menveo.

6.1.2 Design Overview

This was a Phase III, modified double-blind, randomized, parallel-group, active controlled, multicenter trial to evaluate the immunogenicity and describe the safety of MenQuadfi compared to the Menveo vaccine in healthy children 2 to 9 years of age in the US and Puerto Rico.

Healthy, meningococcal-vaccine naïve children aged 2 to 9 years were to be randomized in a 1:1 ratio as follows:

- Group 1: MenACYW conjugate vaccine: N=500
  - Group 1a: 250 children 2 to 5 years of age
  - Group 1b: 250 children 6 to 9 years of age
- Group 2: Menveo: N=500
  - Group 2a: 250 children 2 to 5 years of age
  - Group 2b: 250 children 6 to 9 years of age

All subjects were to provide blood samples (BLs) for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days after vaccination.

Solicited adverse event (AE) information were collected for 7 days after vaccination; unsolicited AE information was collected from Visit (V) 01 (Day [D]0) to V02 (D30 [+14 days]) and serious adverse event (SAE) information (including adverse events of special interest [AESIs]) was collected throughout the study period from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) were collected throughout the study from V01 through V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).

6.1.3 Population

Children aged 2 to 9 years on day of inclusion, with parent/guardian able to sign consent and comply with all trial procedures.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Trial Product: MenACYW conjugate vaccine [Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine.] Lot UD18366

Each 0.5 mL dose is a liquid formulated in sodium acetate buffered solution, containing 10 μg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately (b) (4) μg of tetanus toxoid protein carrier. Tetanus toxoid protein quantity is approximate and dependent on the (b) (4) for the conjugates used in each formulation and was (b) (4) μg for this batch. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Control Product: MENVEO® [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Novartis Vaccines and Diagnostics S.r.1., Sovicille, Italy)] Lot M16005.

Each 0.5 mL dose is comprised of two vials, a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate component. Each dose contains 10 μg of MenA oligosaccharide and 5 μg each of MenC, MenY, and MenW-125 oligosaccharide, with 32.7 to 64.1 μg of CRM_{197} protein carrier and ≤ 0.30 μg of residual formaldehyde. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

6.1.6 Sites and Centers

This was a multi-center trial involving 36 Investigators in 36 trial centers in the United States (US) and Puerto Rico.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint for the evaluation of immunogenicity was:

- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination.

The secondary endpoints for immunogenicity were:

- GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenQuadfi or Menveo
- Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days (+14 days) after vaccination with MenQuadfi or Menveo

6.1.9 Statistical Considerations & Statistical Analysis Plan

Primary Objective/Hypothesis

To demonstrate non-inferiority of vaccine seroresponse 30 days after the administration of MenQuadfi (Group 1) or Menveo (Group 2), the applicant proposed to test the following hypothesis.

- Null hypothesis (H0): $p_{(G1)} - p_{(G2)} \leq -10\%$
- Alternative hypothesis (H1): $p_{(G1)} - p_{(G2)} > -10\%$,

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively. Vaccine seroresponse was defined as post-vaccination titer ≥ 1:16 for subjects with a pre-vaccination titer < 1:8 and post-vaccination titer at least 4-fold greater than the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8.

Each of the serogroups A, C, Y, and W was tested separately. The study was successful if the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10% for all four serotypes.

Secondary Objectives

For secondary objective 1, the estimate and 95% CI for hSBA GMTR between Group 1 and Group 2 was descriptively presented. This analysis was repeated separately for age groups 2 to 5 years of age and 6 to 9 years of age for secondary objective 2. For secondary objective 3, differences in seroresponse rates and 95% CIs were presented separately for age groups 2 to 5 years of age and 6 to 9 years of age.

Analysis Set definitions

- Full Analysis Set (FAS)
  The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination blood sample result (at least one serogroup with a reportable, non-missing result). All subjects were analyzed according to the treatment group to which they were randomized.

- Safety Analysis Set (SafAS)
  The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they received.

- Per-Protocol Analysis Set (PPAS)
  The PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:
  - Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
  - Subject did not receive vaccine
  - Subject received a vaccine other than the one that he/she was randomized to receive
  - Preparation and/or administration of vaccine was not done as per-protocol
  - Subject did not receive vaccine in the proper time window (V01, which is D0)

- Subject did not provide post-dose serology sample in the proper time window (V02, which is 30 to 44 days after the vaccination at V01) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
- Subject's serology sample did not produce a valid test result
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

All immunogenicity analyses were performed on the PPAS, and some immunogenicity analyses were performed for exploratory purposes on the FAS. All safety analyses were performed on the SafAS.

Sample size calculations

A total of 1000 subjects were planned to be enrolled, with an expected 800 evaluable subjects, considering an estimated 20% drop-out rate. In the sample size calculations seroresponse estimates, as obtained from a previous Phase 2 study in adolescents who had receive one dose of the study product (NCT02199691), were assumed to be 77%, 98%, 86%, 96% for A, C, W, and Y antigens, respectively. Under the assumption of no difference between the two groups, and using an NI margin of 10%, power was calculated as 91.8%, >99%, 98%, >99%, for A, C, W, and Y antigens respectively, for an overall power of 90%.

Statistical Analyses

For the primary objective, the CI of the difference in proportions ($p_1 - p_2$) was computed using the Wilson Score method without continuity correction.

For secondary objective 1, the difference in log10(GMT) for Groups 1 and 2 was calculated and presented with the 95% CI based on a pooled sample variance. The 95% CI for the hSBA GMTR between Group 1 and Group 2 was formed by taking the antilogarithms of the lower and upper limits of the 95% CI for the difference in log10(GMT) between both vaccine groups. This analysis was repeated separately for age groups 2 to 5 years of age and 6 to 9 years of age for secondary objective 2. For secondary objective 3, differences in proportions and 95% CIs were estimated using the Wilson Score method without continuity correction.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Sample sizes for the FAS and PPAS are presented in Table 2. Of those subjects with at least one deviation, the most common reason for exclusion was lack of follow-up blood

sample or sample provided outside the time window (6.2% and 5.0% in Group 1 and 2, respectively, with 5.6% overall).

Table 2: Analysis sets by randomized group for all randomized subjects – Group 1 (MenQuadfi), Group 2 (Menveo)

Group	Group 1/ MenQuadfi	Group 2/ Menveo	All
Sample size (N)	**N=499**	**N=501**	**N=1000**
Analysis group size (%)	**n (%)**	**n (%)**	**n (%)**
FAS	480 (96.2)	482 (96.2)	962 (96.2)
PPAS	458 (91.8)	460 (91.8)	918 (91.8)
Subjects with at least one deviation	41 (8.2)	41 (8.2)	82 (8.2)

Notes: n: number of subjects fulfilling the item listed; N: number of subjects randomized
Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 4.2, p. 83.

6.1.10.1.1 Demographics

Baseline demographics are presented in Table 3. Main demographics are well balanced across vaccination groups.

Table 3: Baseline demographics by vaccination group – Group 1 (MenQuadfi), Group 2 (Menveo)

Group	Group 1/ MenQuadfi	Group 2/ Menveo	All
Sample size (N)	**N=499**	**N=501**	**N=1000**
Sex: n (%)			
Male	254 (51.0)	262 (53.0)	516 (52.0)
Female	244 (49.0)	232 (47.0)	476 (48.0)
Age (years)			
Mean (SD)	6.0 (2.3)	6.0 (2.4)	6.0 (2.3)
Racial origin: n (%)			
White	401 (80.5)	411 (83.2)	812 (81.9)
Asian	2 (0.4)	2 (0.4)	4 (0.4)
Black or African American	66 (13.3)	60 (12.1)	126 (12.7)
American Indian or Alaska Native	1 (0.2)	0 (0.0)	1 (0.1)
Native Hawaiian or Other Pacific Islander	4 (0.8)	0 (0.0)	4 (0.4)
Mixed origin	21 (4.2)	21 (4.3)	42 (4.2)
Ethnicity: n (%)			
Hispanic or Latino	114 (22.9)	115 (23.3)	229 (23.1)
Not Hispanic or Latino	383 (76.9)	379 (76.7)	762 (76.8)

Notes: n: number of subjects fulfilling the item listed in the first column; M: number of subjects with available data for the relevant endpoint; Percentages are based on M; Q1; Q3: first quartile; third quartile.
Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 4.4, pp. 85-86.

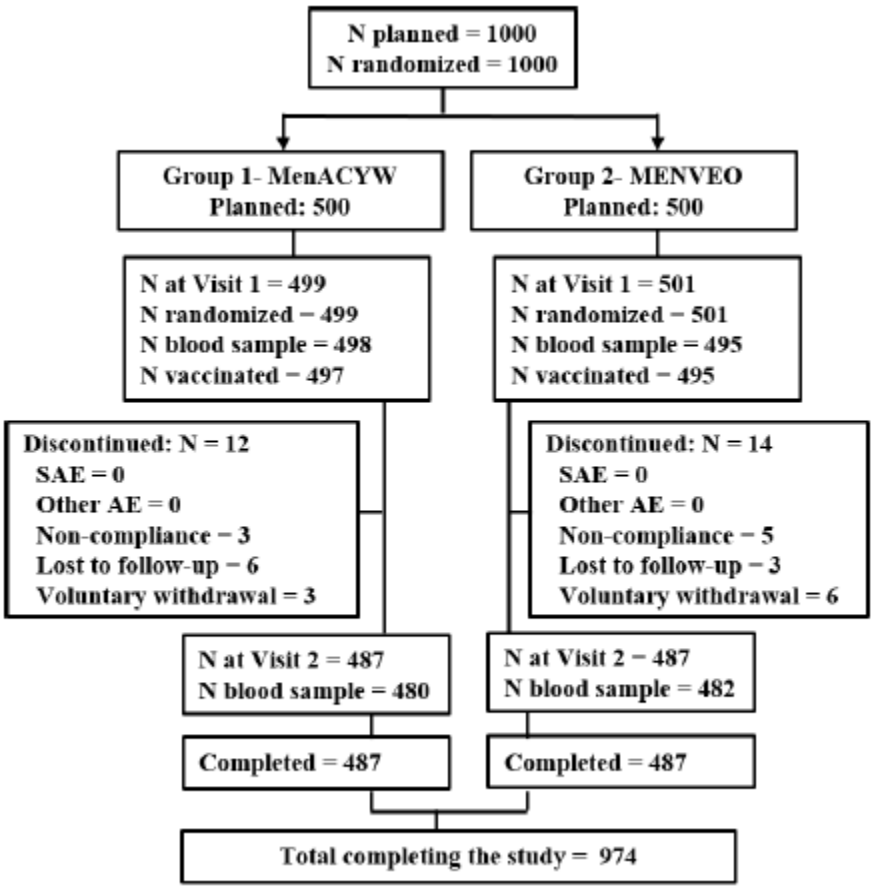
6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.1.10.1.3 Subject Disposition

Subject disposition is presented in Figure 1. There appear to be no differences across vaccination groups in loss to follow-up.

Figure 1: Subject disposition flow chart, MET35



Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Figure 4.1, p. 81.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Results of the primary analysis are presented in Table 4. All four serogroups demonstrated non-inferiority of MenQuadfi seroresponse to Menveo seroresponse in the overall population.

Table 4: Non-inferiority of the percentage of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; Menquadfi) versus Group 2 (G2; Menveo), presented as difference in percent of seroresponders - Per-Protocol Analysis Set

Serogroup	G1 n/M	G1 Seroresponse rate (%)	G1 (95% CI)	G2 n/M	G2 Seroresponse rate (%)	G2 (95% CI)	G1 - G2 Difference (%)	G1- G2 (95% CI)
A	252/455	55.4	(50.7; 60.0)	219/458	47.8	(43.2; 52.5)	7.6	(1.1, 14.0)
C	436/458	95.2	(92.8; 97.0)	219/458	47.8	(43.2; 52.5)	47.4	(42.2, 52.2)
Y	419/458	91.5	(88.5; 93.9)	364/459	79.3	(75.3; 82.9)	12.2	(7.7, 16.7)
W	361/458	78.8	(74.8; 82.5)	294/459	64.1	(59.5; 68.4)	14.8	(8.9, 20.5)

Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 5.1, p. 88.

6.1.11.2 Analyses of Secondary Endpoints

Results of the first secondary objective analysis are presented in Table 5, demonstrating a similar trend as in the primary analysis. Analyses of the remaining secondary hypotheses also demonstrated similar non-inferiority trends in difference of seroresponse and GMTR when stratified by groups 2-5 years of age and 6-9 years of age (Table 6 - Table 7).

Table 5: Comparison of the hSBA GMTs as GMT ratios against meningococcal serogroups A, C, Y, and W at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menveo) - Per-Protocol Analysis Set

Serogroup	G1 M	G1 GMT	G1 (95% CI)	G1 M	G1 GMT	G1 (95% CI)	G1/G2 GMTR	G1/G2 95% CI
A	456	24.8	(21.9; 27.9)	458	22.6	(19.7; 26.0)	1.09	(0.91; 1.32)
C	458	238	(209; 270)	459	17.0	(14.3; 20.2)	14.0	(11.3; 17.3)
Y	458	68.8	(61.3; 77.3)	459	43.5	(37.7; 50.4)	1.58	(1.31; 1.90)
W	458	37.5	(33.7; 41.8)	459	26.2	(23.0; 29.9)	1.43	(1.21; 1.69)

Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 5.2, p. 89.

Table 6: Comparison of the hSBA GMTs as GMT ratios at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menveo), by age group - Per-Protocol Analysis Set

Age Group	Serogroup	G1 M	G1 GMT	G1 (95% CI)	G1 M	G1 GMT	G1 (95% CI)	G1/G2 GMTR	G1/G2 95% CI
2 to 5 years	**A**	228	21.6	(18.2; 25.5)	221	18.9	(15.5; 23.0)	1.14	(0.883; 1.47)
2 to 5 years	**C**	229	208	(175; 246)	223	11.9	(9.79; 14.6)	17.4	(13.4; 22.6)
2 to 5 years	**Y**	229	49.8	(43.0; 57.6)	222	36.1	(29.2; 44.7)	1.38	(1.07; 1.78)
2 to 5 years	**W**	229	28.8	(24.6; 33.7)	222	20.1	(16.7; 24.2)	1.43	(1.12; 1.83)
6 to 9 years	**A**	228	28.4	(23.9; 33.8)	237	26.8	(22.0; 32.6)	1.06	(0.816; 1.38)
6 to 9 years	**C**	229	272	(224; 330)	236	23.7	(18.2; 31.0)	11.5	(8.24; 16.0)
6 to 9 years	**Y**	229	95.1	(80.2; 113)	237	51.8	(42.5; 63.2)	1.84	(1.41; 2.38)
6 to 9 years	**W**	229	48.9	(42.5; 56.3)	237	33.6	(28.2; 40.1)	1.45	(1.16; 1.82)

Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 5.3, p. 90.

Table 7: Comparison of the percentage of subjects achieving hSBA vaccine seroresponse as difference in percent seroresponders at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menveo), by age group - Per-Protocol Analysis Set

Age group	Sero-group	G1 n/M	G1 Seroresponse	G1 (95% CI)	G2 n/M	G2 Seroresponse	G2 (95% CI)	G1 - G2 Difference	G1- G2 (95% CI)
2 to 5 years	**A**	119/227	52.4	(45.7; 59.1)	99/221	44.8	(38.1;51.6)	7.6	(-1.6, 16.7)
2 to 5 years	**C**	216/229	94.3	(90.5; 96.9)	96/222	43.2	(36.6; 50.0)	51.1	(43.5, 57.8)
2 to 5 years	**Y**	202/229	88.2	(83.3; 92.1)	171/222	77.0	(70.9; 82.4)	11.2	(4.2, 18.1)
2 to 5 years	**W**	169/229	73.8	(67.6; 79.4)	136/222	61.3	(54.5; 67.7)	12.5	(3.9, 20.9)
6 to 9 years	**A**	133/228	58.3	(51.6; 64.8)	120/237	50.6	(44.1; 57.2)	7.7	(-1.3, 16.6)
6 to 9 years	**C**	220/229	96.1	(92.7; 98.2)	123/236	52.1	(45.5; 58.6)	44.0	(36.8, 50.6)
6 to 9 years	**Y**	217/229	94.8	(91.0; 97.3)	193/237	81.4	(75.9; 86.2)	13.3	(7.6, 19.2)
6 to 9 years	**W**	192/229	83.8	(78.4; 88.4)	158/237	66.7	(60.3; 72.6)	17.2	(9.4, 24.7)

Source: Original BLA 125701/0; Clinical Study Report MET35, version 2.0, 19 March 2019, Table 5.4, p. 91.

6.1.11.3 Subpopulation Analyses

In addition to the age group analyses above, primary objective analyses were repeated stratified by gender and by racial group. In all subgroups, MenQuadfi was demonstrated to be non-inferior to Menveo. Additionally, there were no differences in seroresponse rate across gender, and though sample sizes were small, there appear to be similar trends in seroresponse across race (see Table 8).

Table 8: Percentage of seroresponders stratified by racial group for Group 1 (G1; MenQuadfi) and Group 2 (G2; Menveo)

Racial group	Serogroup	G1 n/M	G1 Seroresponse rate (%)	G1 (95% CI)	G2 n/M	G2 Seroresponse rate (%)	G2 (95% CI)
Caucasian/White	**A**	212/369	57.5	(52.2; 62.6)	180/384	46.9	(41.8; 52.0)
Caucasian/White	**C**	358/371	96.5	(94.1; 98.1)	181/383	47.3	(42.2; 52.4)
Caucasian/White	**Y**	343/371	92.5	(89.3; 94.9)	307/384	79.9	(75.6; 83.8)
Caucasian/White	**W**	301/371	81.1	(76.8; 85.0)	252/384	65.6	(60.6; 70.4)
Black	**A**	27/58	46.6	(33.3; 60.1)	25/51	49.0	(34.8; 63.4)
Black	**C**	52/59	88.1	(77.1; 95.1)	28/52	53.8	(39.5; 67.8)
Black	**Y**	49/59	83.1	(71.0; 91.6)	40/52	76.9	(63.2; 87.5)
Black	**W**	41/59	69.5	(56.1; 80.8)	27/52	51.9	(37.6; 66.0)
Other	**A**	12/26	46.2	(26.6; 66.6)	12/21	57.1	(34.0; 78.2)
Other	**C**	24/26	92.3	(74.9; 99.1)	9/21	42.9	(21.8; 66.0)
Other	**Y**	25/26	96.2	(80.4; 99.9)	16/21	76.2	(52.8; 91.8)
Other	**W**	18/26	69.2	(48.2; 85.7)	14/21	66.7	(43.0; 85.4)

Source: Original BLA 125701/0; Clinical Study Report MET35 Appendix 15, version 2.0, 19 March 2019, Table 2, pp. 6-9.

6.1.11.4 Dropouts and/or Discontinuations

In both arms, less than 3% of the sample were lost to follow-up or discontinued, and none were considered related to vaccine administration. Thus, the complete case immunogenicity analyses presented are acceptable.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the parent/guardian recorded solicited events through day 7 and unsolicited adverse events through visit 2. Using a memory aid, the parent/guardian recorded possible serious adverse events and medically attended adverse events from visit 2 through the end of the study. Results were reported descriptively as percentages and 95% exact binomial/Clopper-Pearson confidence intervals.

6.1.12.3 Deaths

There were no deaths reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Ten subjects experienced a total of 12 SAEs during the study: 3 subjects within 30 days of vaccination, and 7 subjects reported SAEs after D30 through the 6-month follow-up period. None were considered as related to the vaccine, and none led to discontinuation from the study. Overall SAE rates were similar across study arms, with 1.4% (95% CI: 0.6, 2.9) in MenQuadfi and 0.6 (95% CI: 0.1, 1.8) in Menveo.

6.1.12.5 Adverse Events of Special Interest (AESI)

There was one AESI (temporal seizure) reported during the study, occurring in the Menveo arm during the 6-month follow-up period, and was assessed by the Investigator as not related to the vaccination.

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts due to adverse events.

6.2 Trial #2 MET43

Title: Immune Lot Consistency, Immunogenicity, and Safety of an Investigational Quadrivalent Meningococcal Conjugate Vaccine in Adolescents and Adults Aged 10 to 55 Years

6.2.1 Objectives (Primary, Secondary, etc)

Primary objectives

1) To demonstrate the immune lot consistency of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi with respect to serum bactericidal assay using human complement (hSBA) geometric mean titers (GMTs)
2) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra

Secondary objectives

1) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra in the adult population (18 to 55 years old)
2) To demonstrate the non-inferiority of the antibody responses to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi (pooled Lots 1 to 3) compared to those observed following the administration of a single dose of Menactra in the adolescent population (10 to 17 years old)
3) To compare the hSBA vaccine seroresponses of meningococcal serogroups A, C, Y, and W for each of 3 lots of MenQuadfi 30 days (+14 days) after vaccination
4) To compare the hSBA antibody GMTs of meningococcal serogroups A, C, Y, and W following the administration of MenQuadfi to those observed following the administration of Menactra

There was an additional observational objective to describe the safety profile of MenQuadfi and that of the licensed Menactra.

6.2.2 Design Overview

This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center study to evaluate immune lot consistency of MenACYW conjugate vaccine, evaluate the immune non-inferiority versus Menactra, and describe the safety and additional immunogenicity of study vaccines in adolescents and adults aged 10 to 55 years in the US.

Healthy, meningococcal-vaccine naïve adolescents and adults were randomized in a 3:3:3:2 ratio to the following groups:

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

All subjects were to receive a single dose of MenQuadfi (from 1 of the 3 lots [Lot 1, Lot 2, or Lot 3]) or Menactra on D0.

All subjects were to provide a pre-vaccination blood sample at Day 0 (D0) and a post-vaccination sample at V02 (30 to 44 days after the vaccination at V01). Antibodies to A, C, Y, and W antigens of MenQuadfi (Groups 1, 2, and 3) and Menactra (Group 4) were to be measured by hSBA for all subjects, and by (b) (4) for a subset of 100 subjects per treatment group.

Subjects were observed for 30 minutes after vaccination to capture all unsolicited systemic AEs. Solicited adverse event (AE) information was collected for 7 days after vaccination, unsolicited AE information was collected from Visit 1 (V01) (Day [D] 0) to V02 (D30 [+14 days]), and serious adverse event (SAE) information was collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAEEs) were collected throughout the study from V01 to V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).

6.2.3 Population

Subjects were aged 10 to 55 years old on the day of inclusion.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Trial Product: MenACYW conjugate vaccine [Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine.] Three lots (UD18368, UD18364, UD18365).

Each 0.5 mL dose is a liquid formulated in sodium acetate buffered solution, containing 10 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately (b) (4) µg of tetanus toxoid protein carrier. Tetanus toxoid protein quantity is approximate and dependent on the (b) (4) for the conjugates used in each formulation. Quantities for Lots 1, 2, and 3, were (b) (4)

µg, respectively. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Control Product: Menactra® [Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine.] Lot U5462AB.

Each 0.5 mL dose is a solution formulated in sodium phosphate buffered isotonic sodium chloride, containing 4 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately 48 µg of diphtheria toxoid protein carrier. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

6.2.6 Sites and Centers

There were approximately 90 sites throughout the United States.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoints

1) Geometric mean titer ratios (GMTRs) of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) after vaccination between lots for immune lot consistency

   The study was deemed successful if each of the pairwise 2-sided 95% confidence intervals (CI) of the ratio of the GMTs is > 1/2 and < 2, tested for all four antigens, with each hypothesis tested separately. As all 12 hypotheses needed to be successful (four antigens, each with 3 pairwise comparisons), no multiplicity adjustment was needed.

2) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenQuadfi and Menactra (Groups 1 - 3 pooled versus Group 4)

   Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption was rejected. Since all four hypotheses needed to succeed, and this group of hypotheses were to be tested only if equivalence was established across lots, no adjustment for multiplicity was needed.

Secondary Endpoints

1) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after

vaccination for immune non-inferiority between MenQuadfi and Menactra adult study participants (Groups 1b, 2b, and 3b pooled versus Group 4b)

2) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination for immune non-inferiority between MenQuadfi and Menactra adolescent study participants (Groups 1a, 2a, and 3a pooled versus Group 4a)
3) Vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA 30 days (+14 days) following the administration of MenQuadfi (Groups 1, 2, and 3) GMTRs of antibodies against meningococcal serogroups A, C, Y, and W measured by hSBA for the groups that received MenQuadfi (Groups 1 – 3 pooled) and Menactra (Group 4)

6.2.9 Statistical Considerations & Statistical Analysis Plan

Primary Objective 1

To demonstrate the equivalence of the three MenQuadfi lots in terms of GMTs, the applicant proposed the following hypotheses.

- Null hypothesis (H_0): $GMT_{(Gi)} / GMT_{(Gj)} \leq 1/2$ or $GMT_{(Gi)} / GMT_{(Gj)} \geq 2$ for any $i \neq j$
- Alternative hypothesis (H_1): $1/2 < GMT_{(Gi)} / GMT_{(Gj)} < 2$ for all $i \neq j$, where

$GMT_{(Gi)}$ and $GMT_{(Gj)}$ are the GMTs of antibodies at 30 days post-vaccination against the meningococcal serogroups A, C, Y, and W for the ith and jth lots, respectively.

Primary Objective 2

If equivalence was established, the three study vaccine arms were to be pooled to demonstrate non-inferiority of MenQuadfi compared to Menactra in terms of hSBA vaccine seroresponse. The following hypotheses were tested:

- Null hypothesis (H_0): $p_{(G123)} - p_{(G4)} \leq -10\%$
- Alternative hypothesis (H_1): $p_{(G123)} - p_{(G4)} > -10\%$, where

$p_{(G123)}$ and $p_{(G4)}$ are the percentages of subjects who achieve an hSBA vaccine seroresponse at 30 days post-vaccination in Groups 1 - 3 pooled and Group 4, respectively, and hSBA vaccine seroresponse for serogroups A, C, Y, and W was defined as:

- For a subject with a pre-vaccination titer < 1:8, the post-vaccination titer must have been ≥ 1:16.
- For a subject with a pre-vaccination titer ≥ 1:8, the post-vaccination titer must have been at least 4-fold greater than the pre-vaccination titer.

The definition of seroresponse was pre-specified in agreement with the FDA and reflects a lower limit of quantitation of 1:4.

Secondary Objective 1

To establish non-inferiority of MenQuadfi compared to Menactra in terms of hSBA vaccine seroresponse in the adult population (18 to 55 years old), the hypotheses and success criteria from Primary Objective 2 were repeated, restricting the sample to Groups 1b, 2b, and 3b pooled in the null hypotheses and Group 4b in the alternative hypotheses.

Secondary Objective 2

To establish non-inferiority of MenQuadfi compared to Menactra in terms of hSBA vaccine seroresponse in the adolescent population (10 to 17 years old), the hypotheses and success criteria from Primary Objective 2 were repeated, restricting the sample to Groups 1a, 2a and 3a pooled for the null hypotheses and Group 4b for the alternative hypotheses.

Secondary Objective 3

To compare the three MenQuadfi lots in terms of hSBA vaccine seroresponse, three pairwise differences in percentages of subjects who achieved an hSBA vaccine seroresponse at 30 days post vaccination of MenQuadfi were calculated for each meningococcal serogroup A, C, Y, and W across Groups 1, 2, and 3 were calculated, with estimate and 95% CI was provided descriptively.

Secondary Objective 4

To compare the MenQuadfi in terms of hSBA GMTs, for each meningococcal serogroup A, C, Y, and W, the ratio of GMTs between MenQuadfi Groups 1- 3 pooled (Lots 1, 2, and 3 combined) and the Menactra Group 4 was calculated and provided descriptively with the 95% CI.

Analysis Set definitions

- Full Analysis Set (FAS)
  The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination blood sample result (at least one serogroup with a reportable, non-missing result). All subjects were analyzed according to the treatment group to which they were randomized.

- Safety Analysis Set (SafAS)
  The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they received.

- Per-Protocol Analysis Set (PPAS)

The PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window (V01, which is D0)
- Subject did not provide post-dose serology sample in the proper time window (V02, which is 30 to 44 days after the vaccination at V01) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
- Subject's serology sample did not produce a valid test result
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

All immunogenicity analyses were performed on the PPAS, and some immunogenicity analyses were performed for exploratory purposes on the FAS. All safety analyses were performed on the SafAS.

When cleaning the data, it was noted that one site had mislabeled blood samples, and this error was corrected prior to database lock. The applicant created a PPAS2 and an FAS2, defined as the PPAS and FAS, respectively, that excluded the site with mislabeled samples. Some immunogenicity analyses were repeated to demonstrate the results were not affected by this correction of the data.

Sample size calculations

A total of 3300 subjects were planned to be enrolled, with an expected 2970 evaluable subjects, considering an estimated 10% drop-out rate. Groups 1, 2, and 3 were planned to have 810 evaluable subjects in each treatment group and Group 4 was planned to have 540 evaluable subjects. With this sample size, there was approximately 88% power to declare clinical equivalence of the 3 MenQuadfi lots and 99.9% power to declare NI of combined Groups 1-3 versus Group 4, for an overall estimated power around 88%.

Statistical Analyses

For Primary Objective 1, the three pairwise tests for each of the four serotypes were conducted using a two-sided 95% CI, estimated using a difference in means of the post-vaccination log10 titers with a pooled sample variance. For Primary Objective 2, each serotype was tested separately and was based on the 95% CI of the difference between proportions of seroresponders in the pooled Groups 1-3 and in Group 4 using the Wilson score method.

Secondary Objectives 1 and 2 repeated the analytical method of Primary Objective 1, restricting to the adult and adolescent populations, respectively. For Secondary Objective 3, pairwise differences for Groups 1-3 for the proportion of seroresponse 30 days after vaccine administration for each serotype were calculated and presented with the 95% CI computed using the Wilson score without a continuity correction. For Secondary Objective 4, the ratio of GMTs between Groups 1- 3 pooled Group 4, for each serotype, 30 days after vaccine administration was calculated on the log scale, with a 95% CI assuming a normal approximation.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Analysis population counts are reported in Table 9. Of those subjects with at least one deviation, the most common reason for exclusion was lack of follow-up blood sample or sample provided outside the time window (4.5%, 5.1%, and 5.3% in the MenQuadfi arms and 5.3% in the Menactra arm, with 5.1% overall).

Table 9: Population counts and percent of total for main analyses, by study arm (Groups 1-3, MenQuadfi Lots 1-3; Group 4, Menactra), MET 43.

Group	Group 1 MenQuadfi Lot 1	Group 2 MenQuadfi Lot 2	Group 3 MenQuadfi Lot 3	Group 4 Menactra	All
Sample size (N)	**902**	**895**	**906**	**641**	**3344**
FAS count (%)	874 (96.9)	861 (96.2)	875 (96.6)	615 (95.9)	3225 (96.4)
FAS 2 count (%)	869 (96.3)	856 (95.6)	870 (96.0)	612 (95.5)	3207 (95.9)
PPAS count (%)	843 (93.5)	820 (91.6)	845 (93.3)	593 (92.5)	3101 (92.7)
Subjects with at least one deviation count (%)	59 (6.5)	75 (8.4)	60 (6.6)	48 (7.5)	242 (7.2)
PPAS 2 count (%)	838 (92.9)	816 (91.2)	840 (92.7)	590 (92.0)	3084 (92.2)

"FAS 2" is defined the same as "FAS", but excludes subjects from Site 038
"PPAS 2" is defined the same as "PPAS", but excludes subjects from Site 038
Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Table 4.2, p. 87.

As part of the data cleaning process, it was discovered that sample labels for visits 1 and 2 were switched for Site 038. These data were corrected for the primary analysis. To verify this change did not affect study conclusions, additional analyses were also performed excluding Site 038, and the new data sets were labeled FAS 2 and PPAS 2.

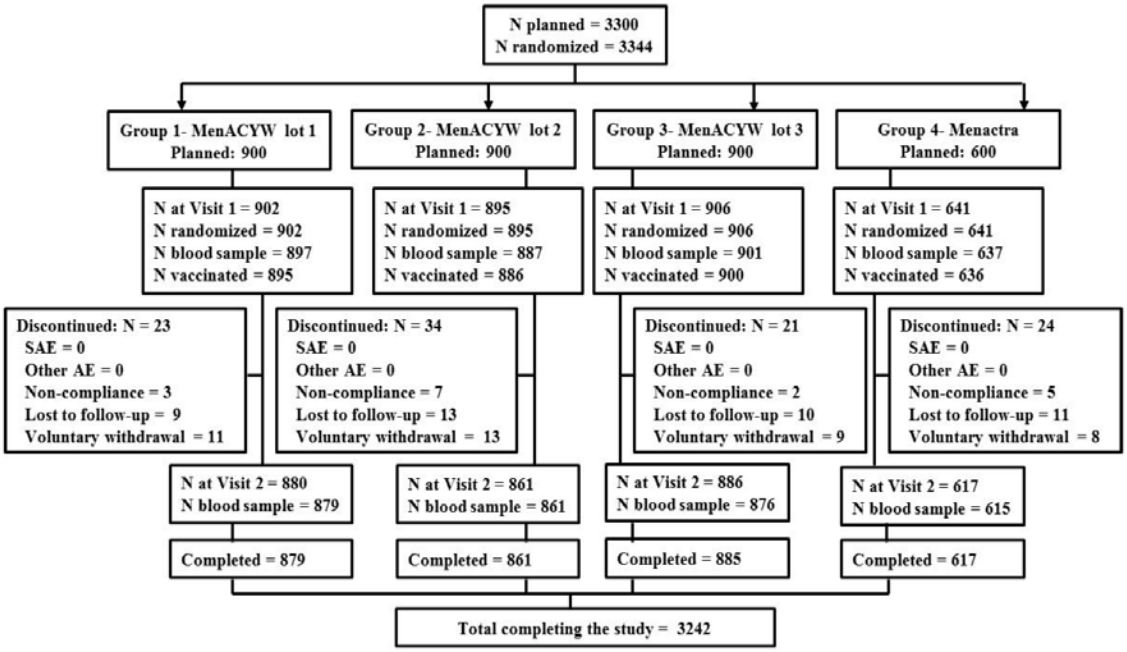
6.2.10.1.1 Demographics

There were slight differences in baseline demographics by randomized group. There were approximately 60% females in Groups 1 and 2, 55% females in Group 3, and 56% females in Group 4. The Menactra arm was slightly younger (mean = 26, median 17 years old), compared to the three MenQuadfi arms (mean = 27, median =25-26 years old across arms). Racial groups were fairly well balanced across the four arms (72%-75% White, 18%-21% Black/African American, 1%-2% Asian, and 3% Other across treatment arms).

6.2.10.1.3 Subject Disposition

Study disposition is outlined in Figure 2.

Figure 2: Disposition by study arm (Groups 1-3 are MenQuadfi Lots 1-3, Group 4 is Menactra), MET43.



Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Figure 4.1, p. 84.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

For each pair of lots and each antigen, the 2-sided 95% CI for the ratio of GMTs falls between 1/2 and 2 demonstrating overall lot consistency among the three lots (Table 10). For the second primary objective, hSBA seroresponse of the pooled MenQuadfi arms were shown to be non-inferior to the Menactra arm (Table 11).

Table 10: Equivalence of hSBA GMT against meningococcal serogroups A, C, Y, and W among 3 lots (Groups 1-3; G1, G2, G3, MenQuadfi Lots 1, 2, and 3, respectively) 30 days after vaccination, presented as GMT ratios and 95% CIs – PPAS

Serogroup	G1 M	G1 GMT	G2 M	G2 GMT	G3 M	G3 GMT	G1/G2 Ratio	G1/G2 (95% CI)	G2/G3 Ratio	G2/G3 (95% CI)	G1/G3 Ratio	G1/G3 (95% CI)
A	843	84.9	819	96.5	843	97.9	0.880	(0.751; 1.03)	0.985	(0.843; 1.15)	0.867	(0.740; 1.02)
C	841	326	820	305	845	352	1.07	(0.888; 1.29)	0.866	(0.714; 1.05)	0.927	(0.766; 1.12)
Y	843	213	820	210	844	218	1.02	(0.869; 1.19)	0.961	(0.816; 1.13)	0.975	(0.829; 1.15)
W	843	84.5	820	81.6	844	87.2	1.04	(0.878; 1.22)	0.936	(0.791; 1.11)	0.970	(0.818; 1.15)

Notes: M: Number of subjects with available data for the endpoint.
Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Table 5.1, p. 91.

Table 11: Non-inferiority of hSBA vaccine seroresponse rate for MenQuadfi (Groups 1-3 pooled; denoted G1-G3 pooled) versus Menactra (Group 4; G4), presented as difference in percent responders and 95% CI – PPAS

Serogroup	G1-G3 pooled n/M	G1-G3 pooled Rate (%)	G1-G3 pooled 95% CI	G4 n/M	G4 Rate (%)	G4 95% CI	G1-G3 pooled – G4 Difference (%)	G1-G3 pooled – G4 95% CI
A	1846/2503	73.8	(72.0; 75.5)	324/593	54.6	(50.5; 58.7)	19.1	(14.8; 23.5)
C	2222/2503	88.8	(87.5; 90.0)	284/593	47.9	(43.8; 52.0)	40.9	(36.7; 45.0)
Y	2290/2505	91.4	(90.3; 92.5)	435/593	73.4	(69.6; 76.9)	18.1	(14.5; 21.9)
W	2011/2505	80.3	(78.7; 81.8)	363/593	61.2	(57.2; 65.2)	19.1	(14.9; 23.3)

Notes: n: number of subjects who achieve an hSBA vaccine seroresponse; M: number of subjects with available data for the endpoint
Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Table 5.2, p. 92.

6.2.11.2 Analyses of Secondary Endpoints

For the second primary objective, hSBA seroresponses of the pooled MenQuadfi arms were shown to be non-inferior to the Menactra arm (Table 11).

Table 12: Non-inferiority of hSBA vaccine seroresponse rate for MenQuadfi (Groups 1b-3b pooled; denoted G1b-G3b pooled) versus Menactra (Group 4b; G4b), presented as difference in percent seroresponders and 95% CI - PPAS (18 to 55 Years Old)

Serogroup	G1b-G3b pooled n/M	G1b-G3b pooled Rate (%)	G1b-G3b pooled 95% CI	G4b n/M	G4b Rate (%)	G4b 95% CI	G1b-G3b pooled - G4b Difference (%)	G1b-G3b pooled - G4b 95% CI
A	1034/1406	73.5	(71.2; 75.8)	158/293	53.9	(48.0; 59.7)	19.6	(13.5; 25.8)
C	1173/1406	83.4	(81.4; 85.3)	124/293	42.3	(36.6; 48.2)	41.1	(35.0; 46.9)
Y	1241/1408	88.1	(86.3; 89.8)	178/293	60.8	(54.9; 66.4)	27.4	(21.7; 33.3)
W	1084/1408	77.0	(74.7; 79.2)	147/293	50.2	(44.3; 56.0)	26.8	(20.7; 32.9)

Notes: n: number of subjects who achieve an hSBA vaccine seroresponse; M: number of subjects with available data for the endpoint
Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Table 5.3, p. 93.

Table 13: Non-inferiority of hSBA vaccine seroresponse rate for MenQuadfi (Groups 1a-3a pooled; denoted G1a-G3a pooled) versus Menactra (Group 4a; G4a), presented as difference in percent seroresponders and 95% CI - PPAS (10 to 17 Years Old)

Serogroup	G1a-G3a pooled n/M	G1a-G3a pooled Rate (%)	G1a-G3a pooled 95% CI	G4a n/M	G4a Rate (%)	G4a 95% CI	G1a-G3a pooled - G4a Difference (%)	G1a-G3a pooled - G4a 95% CI
A	812/1097	74.0	(71.3; 76.6)	166/300	55.3	(49.5; 61.0)	18.7	(12.5; 24.9)
C	1049/1097	95.6	(94.2; 96.8)	160/300	53.3	(47.5; 59.1)	42.3	(36.6; 48.0)
Y	1049/1097	95.6	(94.2; 96.8)	257/300	85.7	(81.2; 89.4)	10.0	(6.18; 14.5)
W	927/1097	84.5	(82.2; 86.6)	216/300	72.0	(66.6; 77.0)	12.5	(7.22; 18.2)

Notes: n: number of subjects who achieve an hSBA vaccine seroresponse; M: number of subjects with available data for the endpoint
Source: Original BLA 125701/0; Clinical Study Report MET43, version 2.0, 22 March 2019, Table 5.4, p. 95.

For the comparison of the hSBA vaccine seroresponse rates at D30 in subjects who received Lot 1, Lot 2, or Lot 3 of MenACYW conjugate vaccine, the difference in the rate of subjects achieving hSBA vaccine seroresponse for

- Lot 1-Lot 2 was -5.4% for serogroup A, 1.3% for serogroup C, 0.5% for serogroup Y, and 0.8% for serogroup W;
- Lot 2-Lot 3 was 2.9% for serogroup A, 2.4% for serogroup C, 2.0% for serogroup Y, and 2.0% for serogroup W,
- Lot 1-Lot 3 was -2.5% for serogroup A, 3.7% for serogroup C, 2.5% for serogroup Y, and 2.8% for serogroup W.

In all lot-to-lot comparisons, for all serogroups, the lower limit of the 2-sided 95% CI of the difference was > -10%.

For the comparison of the hSBA GMTs at D30 between Groups 1-3 pooled and Group 4 at D30, the Groups 1-3 pooled / Group 4 GMTRs ranged from 1.90 to 8.05 for all serogroups (1.93 for serogroup A, 8.05 for serogroup C, 3.22 for serogroup Y, and 1.90 for serogroup W), and the lower limits of the 95% CIs of all serogroups were greater than 1.

6.2.11.3 Subpopulation Analyses

In addition to the stratification by age in the secondary endpoints, subgroup analyses were performed by sex and racial origin (White, Asian, African American/Black, American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander, Mixed Origin), for the primary immunogenicity GMT and seroresponse endpoints.

- By age comparisons: For serogroup C only, GMTs of the 10-17-year olds were approximately twice the GMTs of the 18-55-year olds. GMTs were similar across age groups for the other 3 serotypes. Seroresponse rates were higher in the 10-17 age group, compared to the 18-55 age group for the C, Y, W serogroups, but were similar across age groups for the A serotype.
- By sex: No differences were seen across gender for the GMTs or seroresponse rates for all serotypes.
- By racial origin: Only the White and African American racial subgroups were large enough to support meaningful comparisons. GMTs and seroresponse rates were similar for all four serotypes across these two subgroups.

6.2.11.4 Dropouts and/or Discontinuations

Discontinuation rates were similar at 2.3% - 3.8% across all four arms, and none were considered related to vaccine administration. Thus, the complete case immunogenicity analyses presented are acceptable.

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the subject or subject's parent/guardian recorded solicited events through day 7 and unsolicited adverse events and medically attended adverse events through visit 2. Using a memory aid, the subject or subject's parent/guardian recorded possible serious adverse events from visit 2 through the end of the study. Results were reported descriptively as percentages and 95% exact binomial/Clopper-Pearson confidence intervals.

After a monitoring site visit, it was determined that for Site 022 good clinical practice was not followed, the site coordinator was terminated, and the site's participation was wound down. While subject safety was determined to not have been affected, 6 subjects of Site 022 were excluded from the safety analysis, and an additional sensitivity analysis of safety was conducted including Site 022. Site 022 was included in all immunogenicity analyses.

There were no unsolicited non-serious AEs in the excluded six patients. Five (2 in MenQuadfi lot 2, 2 in MenQuadfi lot 3, and 1 in Menactra) of the six subjects had Grade 1 injection pain and all resolved by day 4. Given the small sample of the removed subjects, overall safety conclusions were unchanged.

6.2.12.3 Deaths

No deaths were reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events

During the study, 28 subjects in the pooled MenQuadfi arm experienced at least one SAE (1.0%, 95% CI: 0.7%, 1.5%) and 5 subjects in the Menactra arm experienced at least one SAE (0.8%, 95% CI: 0.3%, 1.8%).

Stratifying by age group, in the 10-17-year-old age group, 4 subjects in the pooled MenQuadfi arm experienced at least one SAE (0.3%, 95% CI: 0.1%, 0.9%) and 3 subjects in the Menactra arm experienced at least one SAE (0.9%, 95% CI: 0.2%, 2.7%). In the 18-55-year-old age group, 24 subjects in the pooled MenQuadfi arm experienced at least one SAE (1.6%, 95% CI: 1.0%, 2.4%) and 2 subjects in the Menactra arm experienced at least one SAE (0.6%, 95% CI: 0.1%, 2.3%).

None of the SAEs were considered related to the vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

There were no AESIs reported during the study.

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

There were no dropouts due to adverse events.

6.3 Trial #3 MET50

Title: A Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenQuadfi compared to that of the licensed vaccine Menveo, and when MenQuadfi is given with Adacel and Gardasil, in healthy adolescents 10 to 17 years of age in the US.

6.3.1 Objectives (Primary, Secondary, etc)

Primary Objective
To evaluate the antibody responses to the antigens present in MenQuadfi when MenQuadfi is given alone compared to those when Menveo is given alone.

Secondary Objectives

1) To evaluate the antibody responses to the antigens present in MenQuadfi, when MenQuadfi is given concomitantly with Adacel and Gardasil compared to those when it is given alone
2) To evaluate the antibody responses to the antigens present in Adacel, when Adacel is given concomitantly with MenQuadfi and Gardasil, compared to those when Adacel is given with Gardasil only
3) To evaluate the antibody responses to the antigens present in Gardasil after the 3-dose series, when the first dose of Gardasil is given concomitantly with MenQuadfi and Adacel, compared to those when the first dose of Gardasil is given with Adacel only

For safety, there was an observational objective to describe the safety profile of MenQuadfi, compared to that of the licensed vaccine Menveo, and when MenQuadfi is given with Tdap and HPV vaccines.

6.3.2 Design Overview

This was a Phase II, open-label (the laboratory technicians were blinded to group assignment), randomized, parallel-group, controlled, multi-center study to evaluate the immunogenicity and safety profile of a single dose of MenQuadfi when given alone compared to that of the licensed vaccine Menveo and when MenQuadfi was given concomitantly with Adacel® (Tetanus, diphtheria, acellular pertussis [Tdap] vaccine) and GARDASIL® (human papillomavirus [HPV] vaccine) in healthy, meningococcal vaccine-naïve adolescents 10 to 17 years of age in the US.

Subjects were randomized to one of 4 groups to receive:
Group 1 - MenQuadfi
Group 2 - Menveo
Group 3 - MenQuadfi, Adacel, and Gardasil
Group 4 - Adacel and Gardasil

6.3.3 Population

Healthy individuals aged 10 to 17 years of age on the day of inclusion, with either the subject or parent/legal guardian able to give informed consent and comply with all trial procedures.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Trial Product: MenACYW conjugate vaccine [Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine.] Lot UD16710

Each 0.5 mL dose is a liquid formulated in sodium acetate buffered solution, containing 10 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately [redacted] µg of tetanus toxoid protein carrier. Tetanus toxoid protein quantity is approximate and dependent on the [redacted] for the conjugates used in each formulation and was [redacted] µg for this batch. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Control Product: MENVEO® [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (Novartis Vaccines and Diagnostics S.r.1., Sovicille, Italy).] Commercial product was supplied by the sites.

Each 0.5 mL dose is comprised of two vials, a lyophilized MenA conjugate vaccine component to be reconstituted with the accompanying MenCYW-135 liquid conjugate component. Each dose contains 10 μg of MenA oligosaccharide and 5 μg each of MenC, MenY, and MenW-125 oligosaccharide, with 32.7 to 64.1 μg of CRM_{197} protein carrier and ≤ 0.30 μg of residual formaldehyde. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Two other products were administered as concomitant vaccines.
Adacel® (Tdap): Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Sanofi Pasteur Limited, Toronto Ontario Canada)
Form: Suspension
Composition: Each 0.5 mL dose of vaccine contains the following active ingredients:
Tetanus toxoid ..... 5 flocculation units (Lf)
Diphtheria toxoid ..... 2 Lf
Acellular pertussis antigens
Detoxified pertussis toxin (PT) ..... 2.5 μg
Filamentous hemagglutinin (FHA) ..... 5 μg
Pertactin (PRN) ..... 3 μg
Fimbriae types 2 and 3 (FIM) ..... 5 μg
Other ingredients per 0.5 mL dose include aluminum phosphate, formaldehyde, glutaraldehyde and 2-phenoxyethanol.
Route: IM
Batch Number: U4825AA

Vaccine 2: GARDASIL® (HPV): Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18)
Vaccine, Recombinant (Merck & Co., Inc., Whitehouse Station, NJ, USA)
Form: Suspension
Composition: Each 0.5 mL dose contains approximately:
HPV 6 L1 protein ..... 20 μg
HPV 11 L1 protein ..... 40 μg
HPV 16 L1 protein ..... 40 μg
HPV 18 L1 protein ..... 20 μg
Other ingredients per 0.5 mL dose include aluminum, sodium chloride, L-histidine, polysorbate 80, sodium borate, yeast protein, and Water for injection
Route: IM
Batch Number: Commercial product was supplied by the sites.

6.3.6 Sites and Centers

This was a multi-center trial involving 40 investigators in 40 trial centers in the US.

6.3.7 Surveillance/Monitoring

N/A

6.3.8 Endpoints and Criteria for Study Success

The primary endpoints for the evaluation of immunogenicity were:

- Antibody titers against meningococcal serogroups A, C, Y, and W measured by serum bactericidal assay using human complement (hSBA) for Group 1 and Group 2 at Day (D) 0 (before vaccination) and 30 days post vaccination.

The secondary endpoints for the evaluation of immunogenicity were:

- Antibody titers against meningococcal serogroups A, C, Y, and W measured by hSBA for Group 1 and Group 3 at D0 (before vaccination[s]) and 30 days post vaccination(s)
- Anti-pertussis antibody concentrations (pertussis toxoid [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae types 2 and 3 [FIM]) for Group 3 and Group 4 at 30 days post vaccinations
- Anti-tetanus and anti-diphtheria antibody concentrations for Group 3 and Group 4 at 30 days post vaccinations
- Anti-HPV antibody titers (types 6, 11, 16, and 18) for Group 3 and Group 4 at D0 and 30 days after the third dose of Gardasil

6.3.9 Statistical Considerations & Statistical Analysis Plan

Primary Objective

To demonstrate non-inferiority of vaccine seroresponse 30 days after the administration of MenQuadfi (Group 1) or Menveo (Group 2), the applicant proposed to test the following hypothesis.

- Null hypothesis (H_0): $p_{(G1)} - p_{(G2)} \leq -10\%$
- Alternative hypothesis (H_1): $p_{(G1)} - p_{(G2)} > -10\%$,

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively. Vaccine seroresponse was defined as post-vaccination titer ≥ 1:8 for subjects with a pre-vaccination titer < 1:8 and post-vaccination titer at least 4-fold greater than the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8.

Reviewer comment: To align results with the other studies in this application, CBER requested hSBA seroresponse analyses with the following definition for seroresponse: postvaccination hSBA titers ≥ 1:16 for subjects with pre-vaccination hSBA titers < 1:8 or at least a 4-fold increase in hSBA titers from pre- to post-vaccination for subjects with prevaccination hSBA titers ≥ 1:8. The applicant submitted analyses using the aligned definition to the BLA (Amendment 17, 22 November 2019). The revised definition results are presented in Section 6.3.11.5 Exploratory and Post Hoc Analyses.

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected. The difference in proportions was computed using the Wilson Score method without continuity correction.

Secondary Objectives

- Secondary Objective 1: To evaluate if thirty days after the administration of MenACYW conjugate vaccine, the percentages of subjects who achieve an hSBA vaccine seroresponse for meningococcal serogroups A, C, Y, and W in Group 3 are non-inferior to the corresponding percentages in Group 1, the following hypotheses were tested:

  Null hypothesis (H0): $p_{(men, G3)} - p_{(men, G1)} \leq -10\%$
  Alternative hypothesis (H1): $p_{(men, G3)} - p_{(men, G1)} > -10\%$

  where $p_{(men, G1)}$ and $p_{(men, G3)}$ are the percentages of subjects in Group 1 and Group 3, respectively, who achieve an hSBA vaccine seroresponse. Each of the serogroups A, C, Y, and W were tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10% for all four serogroups, the inferiority assumption was rejected.

- Secondary Objective 2:

  Non-inferiority of Pertussis Antigens
  To evaluate if geometric mean concentrations (GMCs) of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 3 are non-inferior to the GMCs in Group 4 at 30 days post Adacel, the following hypotheses were tested:

  Null hypothesis (H0): $GMC_{(pert, G3)} / GMC_{(pert, G4)} \leq 2/3$
  Alternative hypothesis (H1): $GMC_{(pert, G3)} / GMC_{(pert, G4)} > 2/3$,

  where $GMC_{(pert, G3)}$ and $GMC_{(pert, G4)}$ are the GMCs of antibodies against the pertussis antigens (PT, FHA, PRN, and FIM) in Group 3 and Group 4, respectively. Each of the antigens of PT, FHA, PRN, and FIM were tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMCs from the 2 groups was > 2/3 for each antigen, the inferiority assumption was rejected.

  Non-inferiority of Tetanus and Diphtheria Antigens
  To evaluate if percentages of subjects who achieve ≥ 1.0 IU/mL in anti-tetanus (or anti-diphtheria) antibody concentrations in Group 3 are non-inferior to those in Group 4 at 30 days post Adacel, the following hypotheses were tested:

  Null hypothesis (H0): $p_{(G3)} - p_{(G4)} \leq -10\%$
  Alternative hypothesis (H1): $p_{(G3)} - p_{(G4)} > -10\%$

where $p_{(G3)}$ and $p_{(G4)}$ are the percentages of subjects in Group 3 and Group 4, respectively, who achieve an anti-tetanus antibody concentration ≥ 1.0 IU/mL (or an anti-diphtheria antibody concentration ≥ 1.0 IU/mL). Tetanus and diphtheria were tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions was > -10%, the inferiority assumption was rejected.

- **For Secondary Objective 3:**

  Non-inferiority of HPV in terms of Geometric Mean Titers (GMTs)
  To evaluate if 30 days after receiving the third dose of Gardasil GMTs of antibodies against the HPV antigens (types 6, 11, 16, and 18) in Group 3 are non-inferior to the GMTs in Group 4, the following hypotheses were tested:

  Null hypothesis (H0): $GMT_{(hpv, G3)} / GMT_{(hpv, G4)} \leq 2/3$
  Alternative hypothesis (H1): $GMT_{(hpv, G3)} / GMT_{(hpv, G4)} > 2/3$
  where $GMT_{(hpv, G3)}$ and $GMT_{(hpv, G4)}$ are the GMTs of antibodies against the HPV antigens (types 6, 11, 16, and 18) in Group 3 and Group 4, respectively. Each of the antigens of HPV types 6, 11, 16 and 18 was tested separately. If the lower limit of the 2-sided 95% CI of the ratio of the GMTs from the 2 groups is > 2/3 for each antigen, the inferiority assumption was rejected.

  Non-inferiority of HPV in terms of percentage of subjects with seroconversion
  To evaluate if 30 days after receiving the third dose of Gardasil the percentages of subjects who achieve a HPV seroconversion for HPV types 6, 11, 16, and 18 in Group 3 are non-inferior to the corresponding percentages in Group 4, the following hypotheses were tested:

  Null hypothesis (H0): $p_{(hpv, G3)} - p_{(hpv, G4)} \leq -10\%$
  Alternative hypothesis (H1): $p_{(hpv, G3)} - p_{(hpv, G4)} > -10\%$

  where $p_{(hpv, G3)}$ and $p_{(hpv, G4)}$ are the percentages of subjects who achieve a HPV seroconversion in Group 3 and Group 4, respectively. Each of the HPV types 6, 11, 16, and 18 was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption was rejected. HPV seroconversion was defined as changing serostatus from seronegative to seropositive. Cutoff values for HPV seropositivity were ≥ 20 milli-Merck units/milliliter (mMU/mL) for types 6 and 16, ≥ 16 mMU/mL for type 11, and ≥ 24mMU/mL for type 18.

Analysis Set definitions

- Full Analysis Set (FAS)
  The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination blood sample result (at least one serogroup with a reportable, non-missing result). All subjects were analyzed according to the treatment group to which they were randomized.

- Safety Analysis Set (SafAS)
  The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they received.

- Per-Protocol Analysis Set (PPAS)
  Two PPAS were defined as subsets of the FAS. The first PPAS (PPAS1) was defined for assessing the ACYW and the Tdap immune response data for all subjects after they had received vaccination(s) at Visit 1 and completed blood draw 2 (BL2). The second PPAS (PPAS2) was defined for assessing the HPV immune response data for subjects in Group 3 and in Group 4 after they receive the third HPV vaccination at Visit 4 and completed blood draw 3 (BL3). The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:

  - Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
  - Subject did not receive vaccine
  - Subject received a vaccine other than the one that he/she was randomized to receive
  - Preparation and/or administration of vaccine was not done as per-protocol
  - Subject did not receive vaccine in the proper time window (V01, which is D0)
  - Subject did not provide post-dose serology sample in the proper time window (V02, which is 30 to 44 days after the vaccination at V01) or a post-dose serology sample was not drawn
  - Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
  - Subject's serology sample did not produce a valid test result
  - Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

All immunogenicity analyses were performed on the PPAS, and some immunogenicity analyses were performed for exploratory purposes on the FAS. All safety analyses were performed on the SafAS.

Sample size calculations

This study was powered to evaluate the primary hypothesis only. With 1700 subjects planned for enrollment, and 1445 evaluables after an estimated 15% dropout, the applicant calculated an overall 92.2% power to demonstrate non-inferiority with a margin of 10% for all four antigens. Assumptions were based on a previous Phase 2 study (MET44) and a previous Menveo vaccine study, V59P18, Group II (received MenACWY alone). See Table 14 for power calculations.

Table 14: Power of the study based on the primary objective only

Antigen	Endpoint	Non-inferiority margin	Estimates	Power (%)
A	Seroresponse	10%	**82%**	**96.5**
C	Seroresponse	10%	**84%**	**97.6**
W	Seroresponse	10%	**81%**	**95.9**
Y	Seroresponse	10%	**82%**	**96.5**
Overall				**87.1**

Source: Original BLA 125701/0; Clinical Study Report MET50, version 2.0, 12 July 2018, Table 3.6, p. 87.

Statistical Analyses

For the primary objective (comparing Group 1 to Group 2) and secondary objective 1 (comparing Group 3 to Group 1), each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the two-sided 95% CI of the difference between the 2 proportions is > -10%, the inferiority assumption was rejected, where the CI of the difference in proportions was computed using the Wilson Score method without continuity correction.

Regarding the remaining secondary objectives:

- For the non-inferiority hypotheses based on percentage rates (e.g. seroresponse), the CI of the difference in proportions was computed using the Wilson Score method without continuity.
- For the non-inferiority hypothesis using the GMTs or GMCs, the 2-sided 95% CI for the ratio of GMs were calculated using normal approximation of log-transformed titers or concentrations.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Analysis population counts are reported in Table 15. Of those subjects with at least one deviation leading to exclusion from PPAS1, the most common reason for exclusion was lack of follow-up blood sample or sample provided outside the time window (4.6%, 4.9%, 4.7%, and 7.7% in Groups 1-4, respectively, with 5.2% overall). Of those subjects with at least one deviation leading to exclusion from PPAS2, the most common reason for exclusion was lack of follow-up blood sample or sample provided outside the time window (25.6% and 28.3% in Groups 3-4, respectively, with 26.7% overall).

Table 15: Full Analysis Set and Per-Protocol Analysis Sets by randomized group - All Randomized Subjects

	Group 1 MenQuadfi	Group 2 Menveo	Group 3 MenQuadfi + Adacel + Gardasil	Group 4 Adacel + Gardasil	All
Total (N)	505	507	403	300	1715
FAS count (%)	492 (97.4)	499 (98.4)	388 (96.3)	286 (95.3)	1665 (97.1)
PPAS1 count (%)	463 (91.7)	464 (91.5)	360 (89.3)	263 (87.7)	1550 (90.4)
Subjects with at least one deviation count (%)	42 (8.3)	43 (8.5)	43 (10.7)	37 (12.3)	165 (9.6)
PPAS2 count (%)			242 (60.0)	164 (54.7)	406 (57.8)
Subjects with at least one deviation count (%)			161 (40.0)	136 (45.3)	297 (42.2)

Per-Protocol Analysis Set 2 was defined for assessing the HPV immune response for subjects in Group 3 and 4 after they completed the month 7 visit.
Source: Original BLA 125701/0; Clinical Study Report MET50, version 2.0, 12 July 2018, Tables 4.2 and 4.3, pp. 95-96.

6.3.10.1.1 Demographics

The distribution of sex was approximately even across all four arms, with males ranging from 48%-54% of the group sample size. Age was also similarly distributed across arm, with all four arms median approximately 11 years of age and 25th, 75th quartile approximately 10.5, 12 years of age, respectively. Racial groups ranged from 87% - 90% White, 4% - 6% Black, and 4% - 5% of mixed origin across groups, with nominal percentages in other racial groups.

Reviewer comment: Though the age distribution skews toward the younger end of the age range under study, this was balanced across treatment arms. Thus, comparisons across groups are valid.

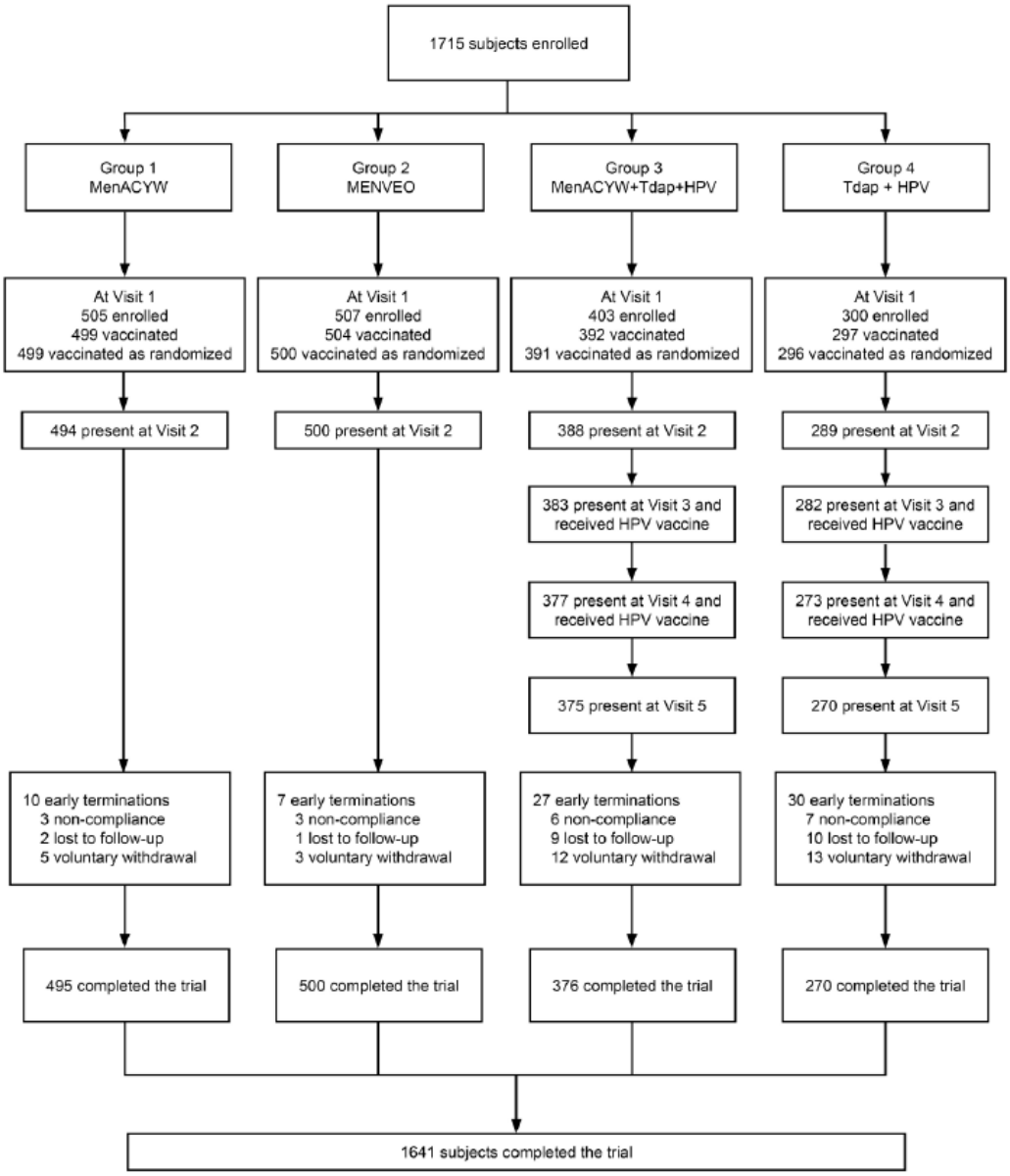
6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

N/A

6.3.10.1.3 Subject Disposition

Study disposition is outlined in Figure 3.

Figure 3: Subject disposition flow chart, MET50



Source: Original BLA 125701/0; Clinical Study Report MET50, version 2.0, 12 July 2018, Figure 4.1, p. 92.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The non-inferiority hypotheses comparing MenQuadfi to Menveo were met for all four serogroups. The two-sided 95% CIs for the differences of percentage of seroresponders in MenQuadfi – percentage of seroresponders in Menveo are:

- Serogroup A: Difference 9.2% (95% CI: 3.4, 15.0)
- Serogroup C: Difference 24.6% (95% CI: 20.3; 29.0)
- Serogroup Y: Difference 16.2% (95% CI: 12.3; 20.2)

- Serogroup W: Difference 19.6% (95% CI: 14.2; 24.8), where vaccine seroresponse is defined as post-vaccination titer ≥ 1:8 for baseline titer < 1:8 or ≥ 4-fold increase at post-vaccination for baseline titer ≥ 1:8.

Please see Section 6.3.11.5 for analysis results using the updated definition of seroresponse.

6.3.11.2 Analyses of Secondary Endpoints

Secondary Objective 1

The non-inferiority hypotheses comparing MenQuadfi, jointly administered with Adacel and Gardasil, to MenQuadfi administered alone were met for all four serogroups. The two-sided 95% CIs for the differences of percentage of seroresponders in Group 3 – percentage of seroresponders in Group 1 are:

- Serogroup A: Difference 5.0% (95% CI: -0.8, 10.5)
- Serogroup C: Difference 0.0% (95% CI: -2.5, 2.4)
- Serogroup Y: Difference -1.4% (95% CI: -4.3, 1.2)
- Serogroup W: Difference -2.3% (95% CI: -7.3, 2.6),

where vaccine seroresponse is defined as post-vaccination titer ≥ 1:8 for baseline titer < 1:8 or ≥ 4-fold increase at post-vaccination for baseline titer ≥ 1:8.

Please see Section 6.3.11.5 for analysis results using the updated definition of seroresponse.

Secondary Objective 2

Non-Inferiority of Pertussis Antigens

The non-inferiority of Adacel administered concomitantly with MenQuadfi and Gardasil compared to Adacel administered with Gardasil alone was met for the PT antigen but not the FHA, PRN, and FIM antigens, with GMCR Group 3/Group 4 estimates and confidence intervals as follows:

- PT: Ratio 0.85 (95% CI: 0.72, 0.99)
- FHA: Ratio 0.75 (95% CI: 0.66, 0.84)
- PRN: Ratio 0.75 (95% CI: 0.63, 0.90)
- FIM: Ratio 0.68 (95% CI: 0.53, 0.88).

At baseline, the GMCs for PT, FHA, PRN, and FIM were comparable in both study groups.

Reviewer comment: The study was not powered to ensure success of these secondary hypotheses. Additionally, without an established correlate of protection, it is not clear that the reduced concentrations of FHA, PRN, and FIM antigens in the concomitant arm result in reduced effectiveness of the Tdap vaccine when it is administered with MenQuadfi. In additional descriptive analyses of the pertussis antigens, the applicant compared two other endpoints – 4-fold rise and vaccine response. Vaccine response is defined as

- *For PT, PRN and FIM: baseline concentration is < 16 with post-vaccination concentration ≥ 4 x baseline, or baseline concentration is ≥ 16 with post-vaccination concentration ≥ 2 x baseline; and*
- *For FHA: baseline concentration is < 12 with post-vaccination concentration ≥ 4 x baseline, or baseline concentration is ≥ 12 with post-vaccination concentration ≥ 2 x baseline.*

Of the four antigens, PT was lower in 4-fold rise rates in the concomitant arm when compared to Adacel+Gardasil, with similar estimates across vaccine arms for the other three antigens. Vaccine response rates were similar across the two arms MenQuadfi+Adacel+Gardasil and Adacel+Gardasil for all four antigens. Please see the clinical review for further discussion.

Non-Inferiority of Tetanus and Diphtheria Antigens
The non-inferiority of Adacel administered concomitantly with MenQuadfi and Gardasil compared to Adacel administered with Gardasil alone were non-inferior as measured by the percentage of subjects who achieved ≥ 1.0 IU/mL anti-tetanus or anti-diphtheria antibody concentrations. For anti-tetanus, the difference in percent for Group 3-Group 4 was -1.1% (95% CI: -3.3, 1.3) and for anti-diphtheria, the difference was 0.1% (95% CI: -1.2, 1.9).

Secondary Objective 3
Non-inferiority of HPV Antigens
The non-inferiority of Gardasil 30 days after the 3-dose series when the first dose was administered concomitantly with MenQuadfi and Adacel compared to when the first dose of Gardasil was administered with Adacel alone was demonstrated for the PPAS2 in GMT ratio (GMTR) and in difference in percent achieving seroconversion (See Table 16).

Table 16: Comparison of HPV antigens 6, 11, 16, 18 in Group 3 (concomitant Gardasil with Adacel and MenQuadfi; G3) and Group 4 (Gardasil and Adacel alone; G4), presented as GMC ratios and 95% CIs and as difference in seroconversion rates and 95% CIs- Per-Protocol Analysis Set 2

HPV Type	G3/G4 Ratio	G3/G4 2-sided 95% CI for ratio	G3-G4 Difference (%)	G3-G4 2-sided 95% CI for Difference
6	1.00	(0.758; 1.320)	1.8	(-1.8; 6.3)
11	1.06	(0.861; 1.316)	0.8	(-1.3; 3.9)
16	0.939	(0.727; 1.212)	0.4	(-1.9; 3.6)
18	1.14	(0.886; 1.458)	0.4	(-1.9; 3.6)

Source: Original BLA 125701/0; Clinical Study Report MET50, version 2.0, 12 July 2018, Tables 5.5-5.6, pp. 105-106.

6.3.11.3 Subpopulation Analyses

N/A

6.3.11.4 Dropouts and/or Discontinuations

A total of 74 subjects (4.3%) did not complete the trial: 10 (2.0%) in Group 1, 7 (1.4%) in Group 2, 27 (6.7%) in Group 3, and 30 (10.0%) in Group 4. The most frequently reported reasons for discontinuation were: voluntary withdrawal not due to an adverse event, lost to follow-up, and non-compliance with the protocol. There were no early terminations due to an SAE or other AE. As dropouts in the primary analysis groups (Group 1 and 2) were minimal and unlikely related to the vaccine, the complete case immunogenicity analyses presented are acceptable.

6.3.11.5 Exploratory and Post Hoc Analyses

A preliminary analysis was conducted on the first 40% of all subjects enrolled in the study. Endpoints assessed included meningococcal hSBA, tetanus, diphtheria, and pertussis immunogenicity, as well as safety data for the period between Visit 1 and Visit 2. This analysis was descriptive in nature and did not contain any hypothesis testing; thus, no statistical adjustment was needed.

Analyses of the hSBA seroresponse objectives (primary and secondary 1) under the updated definition of seroresponse are reported in Table 17. Difference in hSBA seroresponse in the primary objective increased in serogroups C, Y, and W, primarily as a result of a decreased seroresponse in the Menveo arm.

Table 17: Reanalysis of Primary Objective and Secondary Objective 1: Difference in hSBA seroconversion in PPAS, presented as difference in seroconversion rates and 95% CI for MenQuadfi (G1) and Menveo (G2), denoted G1-G2, and difference in seroconversion rates and 95% CI for MenQuadfi + Adacel + Gardasil (G3) and MenQuadfi (G1), denoted G3-G1

Serogroup	G1 – G2 Difference (%)	G1 – G2 2-sided 95% CI for Difference	G3 – G1 Difference (%)	G3 – G1 2-sided 95% CI for Difference
A	9.8	(3.7; 15.9)	3.4	(-2.8; 9.5)
C	34.5	(29.7; 39.3)	0.3	(-2.6; 2.9)
Y	24.3	(19.2; 29.3)	-0.6	(-4.7; 3.4)
W	28.2	(22.5; 33.7)	-2.0	(-7.3; 3.1)

Notes: hSBA seroresponse is defined as either titer is < 1:8 at baseline with post-vaccination titer ≥ 1:16 or titer is ≥ 1:8 at baseline with a ≥ 4-fold increase at post-vaccination.
Source: BLA Amendment 125701/0.17; Clinical Study Report MET50, Appendix 15b, 6 Nov 2019, Tables 1 and 3, pp. 2,4.

6.3.12 Safety Analyses

6.3.12.1 Methods

All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the subject or subject's parent/guardian recorded solicited events through day 7 and unsolicited adverse events through visit 2. Using a memory aid, the subject or subject's parent/guardian recorded possible serious adverse events and medically attended adverse

events of special interest from visit 2 through the end of the study. Results were reported descriptively as percentages and 95% exact binomial/Clopper-Pearson confidence intervals.

6.3.12.3 Deaths

No deaths were reported during the study period.

6.3.12.4 Nonfatal Serious Adverse Events

Sixteen subjects reported SAEs during the trial period (4 in each arm); 4 subjects reported SAEs within 30 days of vaccination. SAE rates (95% CIs) are as follows:

- Group 1 (MenQuadfi): 0.8% (95% CI: 0.2%, 2.0%)
- Group 2 (Menveo): 0.8% (95% CI: 0.2%, 2.0%)
- Group 3 (MenQuadfi+Adacel+Gardasil): 1.0% (95% CI: 0.3%, 2.6%)
- Group 4 (Adacel+Gardasil): 1.4% (95% CI: 0.4%, 3.4%)

No SAE was considered related to the vaccine by the Investigator. All subjects recovered.

6.3.12.5 Adverse Events of Special Interest (AESI)

N/A

6.3.12.6 Clinical Test Results

N/A

6.3.12.7 Dropouts and/or Discontinuations

There were no early terminations due to an SAE or other AE.

6.4 Trial #4 MET49

Title: Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenQuadfi to Menomune - A/C/Y/W-135 in adults ≥ 56 years of age in the United States and Puerto Rico.

6.4.1 Objectives (Primary, Secondary, etc)

Primary Objective
To demonstrate the non-inferiority of the vaccine seroresponse to meningococcal serogroups A, C, Y, and W following the administration of a single dose of MenQuadfi compared to those observed following the administration of a single dose of Menomune - A/C/Y/W-135.

Secondary Objective
To compare the hSBA antibody geometric mean titers (GMTs) of meningococcal serogroups A, C, Y, and W following the administration of MenACYW vaccine to those observed following the administration of Menomune - A/C/Y/W-135.

For safety, there was an observational objective to describe the safety profile of MenQuadfi compared to that of the licensed Menomune – A/C/Y/W-135 after a single administration.

6.4.2 Design Overview

This was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and safety of MenQuadfi to Menomune - A/C/Y/W-135 in adults ≥ 56 years of age in the US and Puerto Rico.

Approximately 900 healthy adults were randomized in a 1:1 ratio to the following groups:

- Group 1: MenQuadfi
- Group 2: Menomune A/C/Y/W-135.

Enrollment was stratified by age. For subjects 56 to 64 years of age, 200 subjects were enrolled in both Group 1 and Group 2. For subjects 65 years of age and older, 250 subjects were enrolled in both Group 1 and Group 2. These subjects were further stratified into 2 sub-groups as 65 to 74 years of age and 75 years and older. At least 25% of the 250 subjects were enrolled in each of these age sub-groups.

A single dose was administered at baseline. All subjects provided pre-vaccination blood samples for immunogenicity assessment at baseline (Visit [V] 01) and at Day (D) 30 (+14-day window) post-vaccination (V02).

Solicited adverse event (AE) information was collected for 7 days after vaccination, unsolicited AE information was collected from V01 to D30 (V02), and serious adverse event (SAE) information was collected from D0 through D180 (+14 days) after vaccination. Medically-attended adverse events (MAAEs) collected from V01 through V02 (as part of the collection of unsolicited AE information) and from V02 through D180 (+14 days) (as MAAEs).

6.4.3 Population

Healthy individuals aged ≥ 56 years of age on the day of inclusion, able to give informed consent and comply with all trial procedures.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Trial Product: MenACYW conjugate vaccine [Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate vaccine (Sanofi Pasteur Inc., Swiftwater, PA, USA).] Lot UD18367.

Each 0.5 mL dose is a liquid formulated in sodium acetate buffered solution, containing 10 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately (b) (4) µg of tetanus toxoid protein carrier. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Control Product: Menomune® - A/C/Y/W-135 [Meningococcal Polysaccharide Vaccine, Groups A, C, Y, W-135 Combined (Sanofi Pasteur Inc., Swiftwater, PA, USA).] Lot UI041AA.

After reconstitution with diluent as indicated in the Prescribing Information, each 0.5 mL dose contains 50 µg of polysaccharide from each of serogroups A, C, Y, and W-135. Each dose of vaccine contains 2.5 milligrams (mg) to 5 mg of lactose added as a stabilizer. One dose (0.5 mL) was to be administered subcutaneously in the deltoid region of the arm.

6.4.6 Sites and Centers

There were 35 sites across the U.S. and Puerto Rico.

6.4.7 Surveillance/Monitoring

N/A

6.4.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint for the evaluation of immunogenicity was vaccine seroresponse of meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days after vaccination.

Each of the serogroups A, C, Y, and W was tested separately. The study was successful if the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10% for all four serotypes.

Secondary Endpoint
The secondary endpoint for immunogenicity was GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 30 days (+14 days) after vaccination with MenQuadfi and Menomune - A/C/Y/W-135.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Primary Objective Hypothesis
To demonstrate non-inferiority of vaccine seroresponse 30 days after the administration of MenQuadfi or Menomune- A/C/Y/W-135, the applicant proposed to test the following hypothesis.

- Null hypothesis (H_0): $p(G1) - p(G2) \leq -10\%$
- Alternative hypothesis (H_1): $p(G1) - p(G2) > -10\%$,

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively.

Analysis Set definitions

- Full Analysis Set (FAS)
  The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination serology result. All subjects were analyzed according to the treatment group to which they were randomized.

- Safety Analysis Set (SafAS)
  The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they received.

- Per-Protocol Analysis Set for D30 (PPAS)
  The PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:
  - Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
  - Subject did not receive vaccine
  - Subject received a vaccine other than the one that he/she was randomized to receive
  - Preparation and/or administration of vaccine was not done as per-protocol
  - Subject did not receive vaccine in the proper time window (V01, which is D0)
  - Subject did not provide post-dose serology sample in the proper time window (D30 to D44) or a post-dose serology sample was not drawn
  - Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
  - Subject's serology sample did not produce a valid test result
  - Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

All immunogenicity analyses were performed on the PPAS, and some immunogenicity analyses were performed for exploratory purposes on the FAS. All safety analyses were performed on the SafAS.

Sample size calculations

With 900 subjects planned for enrollment, and 765 evaluable after an estimated 15% dropout, the applicant calculated an overall 92.2% power to demonstrate non-inferiority with a margin of 10% for all four antigens. Assumptions were based on a previous Phase 2 study (MET44) as reported in Table 18.

Table 18: Power of the study based on the primary objective

Antigen	Endpoint	Non-inferiority margin	Investigation Estimates	Control Estimates	Power (%)
A	Seroresponse	10%	60%	**56%**	**97.6**
C	Seroresponse	10%	**65%**	**61%**	**98.0**
W	Seroresponse	10%	**63%**	**59%**	**97.8**
Y	Seroresponse	10%	**70%**	**66%**	**98.6**
Overall					**92.2**

Source: Original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 3.4, p. 65.

Statistical Analyses

For the primary objective, the CI of the difference in proportions ($p_1 - p_2$) was computed using the Wilson Score method without continuity correction. For secondary objective 2, the difference in log10(GMT) for Groups 1 and 2 was calculated and descriptively presented with the 95% CI based on a pooled sample variance.

Missing data were not imputed. Subgroup analyses were planned for age, race, and sex.

Reviewer comment: The final CSR reported that missing data were imputed, but with no follow-up information. However, I verified in the original SAP that missing data were not imputed.

Safety results were described for subjects in all study groups. The main parameters for the safety endpoints were described by 95% CIs (exact binomial/Clopper-Pearson method).

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

Analysis populations by study arm are presented in Table 19. Of those subjects with at least one deviation, the most common reason for exclusion was lack of follow-up blood sample or sample provided outside the time window (2.2% in the MenQuadfi arms and 4.4% in the Menomune arm, with 3.3% overall).

Table 19: Immunogenicity and safety analysis sets by randomized group MenQuadfi (Group 1) and Menomune (Group 2) - All Randomized Subjects

	Group 1 MenQuadfi	Group 2 Menomune	All
Total (N)	451	455	906
FAS count (%)	443 (98.2)	450 (98.9)	893 (98.6)
(b) (4) **subset count (%)**	98 (21.7)	98 (21.5)	196 (21.6)
PPAS count (%)	433 (96.0)	431 (94.7)	864 (95.4)
Subjects with at least one deviation count (%)	18 (4.0)	24 (5.3)	42 (4.6)

Source: Original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 4.2, p. 71.

Reviewer comment: A subset of 100 participants were randomized to draw an increased volume of serum to repeat meningococcal bactericidal activity using (b) (4) *. These results are considered exploratory and not discussed further.*

6.4.10.1.1 Demographics

The summary of demographic characteristics is presented in Table 20. Distributions were well-balanced across arms.

Table 20: Baseline demographics by injected group MenQuadfi (Group 1) and Menomune (Group 2)- All Randomized Subjects

	Group 1 MenQuadfi	Group 2 Menomune	All
Total (N)	451	455	906
Sex: n (%)			
Male	192 (42.6)	194 (42.6)	386 (42.6)
Female	259 (57.4)	261 (57.4)	520 (57.4)
Age (years)			
Mean (SD)	66.9 (7.51)	67.3 (7.53)	67.1 (7.52)
Min; Max	56.0; 89.8	56.0; 97.2	56.0; 97.2
Age group			
Age (56-64 years): M (%)	202 (45%)	200 (44%)	402 (44%)
Mean (SD)	60.4 (2.68)	60.4 (2.48)	60.4 (2.58)
Min; Max	56.0; 64.9	56.0; 65.0	56.0; 65.0
Age (>=65 years): M (%)	249 (55%)	255 (56%)	504 (56%)
Mean (SD)	72.2 (5.77)	72.7 (5.47)	72.4 (5.62)
Min; Max	65.1; 89.8	65.0; 97.2	65.0; 97.2
Racial origin: n (%)			
White	389 (86.3)	404 (88.8)	793 (87.5)
Asian	5 (1.1)	1 (0.2)	6 (0.7)
Black or African American	54 (12.0)	47 (10.3)	101 (11.1)
American Indian or Alaska Native	2 (0.4)	2 (0.4)	4 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)
Missing	1 (0.2)	0 (0.0)	1 (0.1)
Ethnicity: n (%)			
Hispanic or Latino	35 (7.8)	32 (7.0)	67 (7.4)
Not Hispanic or Latino	415 (92.0)	421 (92.5)	836 (92.3)
Missing	1 (0.2)	2 (0.4)	3 (0.3)

Source: Original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 4.3, p. 72-73.

6.4.10.1.3 Subject Disposition

Loss to follow-up was minimal and balanced across arms (Table 21).

Table 21: Disposition by randomized group - All Subjects

Time point	Group 1 MenQuadfi	Group 2 Menomune	All
Total (N)	451	455	907
Enrolled at V01 (D0)	451 (100.0)	455 (100.0)	907* (100.0)
Randomized at V01 (D0)	451 (100.0)	455 (100.0)	906 (99.9)
Provided blood sample at V01 (D0)	448 (99.3)	453 (99.6)	901 (99.3)
Received vaccine at V01 (D0)	448 (99.3)	453 (99.6)	901 (99.3)
Received vaccine at V01 (D0) as randomized	448 (99.3)	453 (99.6)	901 (99.3)
Present at V02 (D30)	444 (98.4)	452 (99.3)	896 (98.8)
Provided blood sample at V02 (D30)	444 (98.4)	451 (99.1)	895 (98.7)
Completed trial	444 (98.4)	452 (99.3)	896 (98.8)
Did not complete trial	7 (1.6)	3 (0.7)	11 (1.2)*
Early termination reason			
SAE	0 (0.0)	1 (0.2)	1 (0.1)
Non-compliance with the protocol	4 (0.9)	2 (0.4)	7 (0.8)*****
Lost to follow-up	2 (0.4)	0 (0.0)	2 (0.2)
Voluntary withdrawal not due to an AE	1 (0.2)	0 (0.0)	1 (0.1)
Performed safety follow-up after last visit	440 (97.6)	447 (98.2)	887 (97.8)

* This number includes 1 subject, Subject (b) (6) , who was enrolled but not randomized or vaccinated, and did not complete the trial. This subject could not be assigned to either group.
Source: Adapted from original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 4.1, p. 66-67.

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

The primary analysis demonstrated MenQuadfi met the non-inferiority success criteria for all four serogroups in comparison to Menomune (Table 22). The results were similar when repeated in the FAS.

Table 22: Non-inferiority of the percentage of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; MenQuadfi) versus Group 2 (G2; Menomune), presented as difference in seroresponders (denoted G1-G2) and 95% CI - Per-Protocol Analysis Set

Serogroup	G1 n/M	G1 Seroresponse rate (%)	G1 (95% CI)	G2 n/M	G2 Seroresponse rate (%)	G2 (95% CI)	G1-G2 Difference (%)	G1-G2 (95% CI)
A	252/433	58.2	(53.4; 62.9)	183/431	42.5	(37.7; 47.3)	15.7	(9.08; 22.2)
C	334/433	77.1	(72.9; 81.0)	214/431	49.7	(44.8; 54.5)	27.5	(21.2; 33.5)
Y	322/433	74.4	(70.0; 78.4)	187/431	43.4	(38.7; 48.2)	31.0	(24.6; 37.0)
W	271/433	62.6	(57.8; 67.2)	193/431	44.8	(40.0; 49.6)	17.8	(11.2; 24.2)

Source: Original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 5.2, p. 75.

6.4.11.2 Analyses of Secondary Endpoints

Geometric mean ratios (GMTs) were reported descriptively (see Table 23). For all four serogroups, the 95% CIs for the GMT ratio were above 1.

Table 23: Comparison of the GMTs of hSBA against meningococcal serogroups A, C, Y, and W at D30 between Group 1 (G1; MenQuadfi) versus Group 2 (G2; Menomune), presented as GMT ratios and 95% CIs - Per-Protocol Analysis Set

	Group 1 MenQuadfi (N=433)			Group 2 Menomune (N=431)			Group 1/Group 2	
Serogroup	**G1 M**	**G1 GMT**	**G1 (95% CI)**	**G2 M**	**G2 GMT**	**G2 (95% CI)**	**G1/G2 Ratio**	**G1/G2 2-sided 95% CI for ratio**
A	433	55.1	(46.8; 65.0)	431	31.4	(26.9; 36.7)	1.75	(1.40; 2.20)
C	433	101	(83.8; 123)	431	24.7	(20.7; 29.5)	4.10	(3.16; 5.33)
Y	433	69.1	(58.7; 81.4)	431	21.0	(17.4; 25.3)	3.30	(2.57; 4.23)
W	433	28.1	(23.7; 33.3)	431	15.5	(13.0; 18.4)	1.81	(1.42; 2.31)

Source: Original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 5.7, p. 82.

6.4.11.3 Subpopulation Analyses

The results for the primary endpoint were stratified by age group, racial origin, and sex.

- By age group: Age was stratified into groups 56-64, 65-74, and 75 or older years of age. For all age groups and across all serogroups, seroresponse was higher in the MenQuadfi arm compared to the Menomune arm. Serogroups W and Y may be less immunogenic in the elderly (≥ 75 years of age), though this study was not powered for formal comparisons and no correlate of protection has been established. See Table 24 for full results.

Table 24: Number and percentage of subjects with hSBA vaccine seroresponse at D30 by age (56 to 64 years of age, 65 to 74 years of age, and ≥ 75 years of age) and vaccine (G1; MenQuadfi and G2; Menomune) group - Per-Protocol Analysis Set

Age/Serogroup	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)
56 to 64 years /A	113/192	58.9	(51.5; 65.9)	84/189	44.4	(37.2; 51.8)
56 to 64 years /C	154/192	80.2	(73.9; 85.6)	100/189	52.9	(45.5; 60.2)
56 to 64 years /Y	151/192	78.6	(72.2; 84.2)	89/189	47.1	(39.8; 54.5)
56 to 64 years /W	129/192	67.2	(60.1; 73.8)	87/189	46.0	(38.8; 53.4)
65 to 74 years /A	99/172	57.6	(49.8; 65.0)	73/175	41.7	(34.3; 49.4)
65 to 74 years /C	127/172	73.8	(66.6; 80.2)	85/175	48.6	(41.0; 56.2)
65 to 74 years /Y	127/172	73.8	(66.6; 80.2)	75/175	42.9	(35.4; 50.5)
65 to 74 years /W	108/172	62.8	(55.1; 70.0)	79/175	45.1	(37.6; 52.8)
≥ 75 years /A	40/69	58.0	(45.5; 69.8)	26/67	38.8	(27.1; 51.5)
≥ 75 years /C	53/69	76.8	(65.1; 86.1)	29/67	43.3	(31.2; 56.0)
≥ 75 years /Y	44/69	63.8	(51.3; 75.0)	23/67	34.3	(23.2; 46.9)
≥ 75 years /W	34/69	49.3	(37.0; 61.6)	27/67	40.3	(28.5; 53.0)

Source: Adapted from original BLA 125701/0; Clinical Study Report MET49, version 2.0, 11 February 2019, Table 5.4, p. 78-79.

- By racial origin: Only the White and Black/African American subgroups had large enough sample sizes for meaningful comparisons. Within the White subgroup, seroresponse was statistically higher in the MenQuadfi arm versus the Menomune arm for all serotypes. In the Black/African American subgroup, MenQuadfi had a statistically significantly higher seroresponse than Menomune for the serogroup C only. Results were not precise enough to compare across racial groups.

- By sex: Similar differences were observed in seroresponse rates in male and female subjects between MenQuadfi (ranging from 57.1% [serogroup A] to 72.0% [serogroup C] in male subjects and from 59.0% [serogroup A] to 80.9% [serogroup C] in female subjects) and in Menomune (ranging from 41.9% [serogroup W] to 45.2% [serogroup Y] in male subjects and from 42.0% [serogroup Y] to 54.3% [serogroup C] in female subjects). The 95% CIs did not overlap across vaccination group for any of the serogroups in female subjects, and did not overlap for the serogroups C, Y, and W in male subjects.

6.4.11.4 Dropouts and/or Discontinuations

In both arms, less than 2% of the sample were lost to follow-up or discontinued. One subject was terminated early from the study between V01 and D30 due to an SAE. This subject experienced worsening coronary artery disease and underwent open heart surgery, leading to discontinuation in the study. Neither the sponsor nor the investigator considered this event related to vaccination.

6.4.11.5 Exploratory and Post Hoc Analyses

N/A

6.4.12 Safety Analyses

6.4.12.1 Methods

All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the subject recorded solicited events through day 7 and unsolicited adverse events through visit 2. Using a memory aid, the subject recorded possible serious adverse events and medically attended adverse events from visit 2 through the end of the study. Results were reported descriptively as percentages and 95% exact binomial/Clopper-Pearson confidence intervals.

6.4.12.3 Deaths

There were 2 deaths in the Menomune vaccine group between Day 30 and the 6 months follow-up call. One subject died due to metastatic lung cancer and was withdrawn from the study. The second subject died due to spinal dislocation due to a road traffic accident and was withdrawn from the study. Neither death was considered related to the vaccine by the investigator.

6.4.12.4 Nonfatal Serious Adverse Events

No nonfatal serious adverse events were reported.

6.4.12.5 Adverse Events of Special Interest (AESI)

N/A

6.4.12.6 Clinical Test Results

N/A

6.4.12.7 Dropouts and/or Discontinuations

No dropouts were attributed to adverse events.

6.5 Trial #5 MET56

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

6.5.1 Objectives (Primary, Secondary, etc)

Primary Objective

To demonstrate the non-inferiority of the vaccine seroresponse of meningococcal serogroups A, C, Y, and W following the administration of a booster dose of MenQuadfi

compared to those observed following the administration of a booster dose of Menactra in subjects who were first vaccinated with 1 dose of a quadrivalent meningococcal vaccine 4 to 10 years before the booster dose.

Secondary Objectives

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

2) To evaluate the antibody responses (GMTs) to serogroups A, C, Y, and W measured using hSBA on Day (D)0 (pre-vaccination) and D30 (+14 days) after vaccination

For safety, there was an observational objective to describe the safety profile of MenQuadfi compared to that of the licensed Menactra after booster vaccination.

6.5.2 Design Overview

The MET56 study was a Phase III, modified double-blind, randomized, parallel-group, active-controlled, multi-center trial to compare the immunogenicity and describe the safety of a booster dose of MenQuadfi to a licensed vaccine in quadrivalent meningococcal conjugate vaccine-primed adolescents (≥ 15 to < 18 years) and adults (≥ 18 years) in the US and Puerto Rico.

A total of 810 healthy adolescents and adults who had received 1 dose of a quadrivalent meningococcal conjugate vaccine 4 to 10 years previously were randomized in a 1:1 ratio to the following groups:

- Group 1: MenACYW conjugate vaccine
- Group 2: Menactra

The first 120 subjects enrolled in the study and randomized 1:1 to each of the 2 study groups (i.e., 60 subjects randomized to Group 1 and 60 subjects randomized to Group 2) comprised a subset from which an additional blood sample was to be obtained on Day (D) 6 (±1 day) post-vaccination. This subset had 3 visits in total. All subjects were to provide blood samples for immunogenicity assessment at baseline (pre-vaccination) and at 30 to 44 days post-vaccination. Solicited adverse event (AE) information was collected for 7 days after vaccination, unsolicited AE information was collected from D0 to D30 (+14 days), and serious adverse event (SAE) information was to be collected from D0 through D180 after vaccination. Medically-attended adverse events (MAAEs) were to be collected from D30 through D180 (+14 days).

6.5.3 Population

Healthy adolescents (≥ 15 to < 18 years of age) and adults (≥ 18 years of age and older) who had received 1 dose of a quadrivalent meningococcal conjugate vaccine sometime in the prior 4 to 10 years.

6.5.4 Study Treatments or Agents Mandated by the Protocol

Trial Product: MenACYW conjugate vaccine [Meningococcal Polysaccharide (Serogroups A, C, Y, and W) Tetanus Toxoid Conjugate Vaccine.] Lot UD18363

Each 0.5 mL dose is a liquid formulated in sodium acetate buffered solution, containing 10 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately (b) (4) µg of tetanus toxoid protein carrier. Tetanus toxoid protein quantity is approximate and dependent on the (b) (4) for the conjugates used in each formulation and was (b) (4) µg for this batch. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

Control Product: Menactra® [Meningococcal (Groups A, C, Y, and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine.] Lot U5260AA.

Each 0.5 mL dose is a solution formulated in sodium phosphate buffered isotonic sodium chloride, containing 4 µg each of serogroups A, C, Y, and W meningococcal capsular polysaccharides and approximately 48 µg of diphtheria toxoid protein carrier. One dose (0.5 mL) was to be administered by an intramuscular (IM) injection into the deltoid muscle of the arm.

6.5.6 Sites and Centers

This study was conducted in 30 centers in the US and Puerto Rico.

6.5.7 Surveillance/Monitoring

N/A

6.5.8 Endpoints and Criteria for Study Success

Primary Endpoints

The primary endpoint for the evaluation of immunogenicity was vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at baseline (D0, before vaccination) and 30 days (+14 days) after vaccination.

Each of the serogroups A, C, Y, and W was tested separately. If the lower limit of the 2-sided 95% CI of the difference between the two percentages was > -10%, the inferiority assumption was rejected.

Secondary Endpoints

1) Vaccine seroresponse against meningococcal serogroups A, C, Y, and W measured by hSBA assessed at 6 days post-vaccination in a subset of 120 subjects
2) GMTs against meningococcal serogroups A, C, Y, and W measured by hSBA before and 30 days after vaccination with MenQuadfi or Menactra

6.5.9 Statistical Considerations & Statistical Analysis Plan

Primary Objective

To demonstrate non-inferiority of vaccine seroresponse 30 days after the administration of MenQuadfi (Group 1) or Menactra (Group 2), the applicant proposed to test the following hypothesis.

- Null hypothesis (H0): $p_{(G1)} - p_{(G2)} \leq -10\%$
- Alternative hypothesis (H1): $p_{(G1)} - p_{(G2)} > -10\%$,

where $p_{(G1)}$ and $p_{(G2)}$ are the percentages of subjects who achieve an hSBA seroresponse in Group 1 and Group 2, respectively. Vaccine seroresponse was defined as post-vaccination titer ≥ 1:16 for subjects with a pre-vaccination titer < 1:8 and post-vaccination titer at least 4-fold greater than the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8.

Each of the serogroups A, C, Y, and W was tested separately. The study was successful if the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 proportions was > -10% for all four serotypes. The difference in proportions was computed using the Wilson Score method without continuity correction.

Secondary Objectives

The seroresponse analysis used for the primary objective was repeated for secondary objective 1, seroresponse at 6 days after vaccination. For secondary objective 2, the difference in log10(GMT) for Groups 1 and 2 was calculated and presented with the 95% CI based on a pooled sample variance. The 95% CI for the hSBA GMTR between Group 1 and Group 2 was formed by taking the antilogarithms of the lower and upper limits of the 95% CI for the difference in log10(GMT) between both vaccine groups.

Analysis Set definitions

- Full Analysis Set (FAS)
  The FAS was defined as the subset of subjects who had received 1 dose of the study vaccine and had a valid post-vaccination serology result. All subjects were analyzed according to the treatment group to which they were randomized.

- Safety Analysis Set (SafAS)
  The SafAS was defined as those subjects who had received at least 1 dose of the study vaccine and had any safety data available. All subjects had their safety analyzed according to the vaccine they received.

- Per-Protocol Analysis Set for D06/D30 (PPAS1 and PPAS2, respectively)
  Each PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:
  - Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
  - Subject did not receive vaccine

- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not receive vaccine in the proper time window (V01, which is D0)
- Subject did not provide post-dose serology sample in the proper time window (D05 to D07 for PPAS1, D30 to D44 for PPAS2) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited Category 2 or Category 3 therapy/medication/vaccine
- Subject's serology sample did not produce a valid test result
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

All immunogenicity analyses were performed on the PPAS1 or PPAS2, and some immunogenicity analyses were performed for exploratory purposes on the FAS. All safety analyses were performed on the SafAS.

Sample size calculations

With 800 subjects to be enrolled and 680 evaluables after an estimated 15% dropout, the applicant calculated >99.9% power to demonstrate non-inferiority with a margin of 10% for each of the four antigens, and an overall power >99%. The assumed seroresponse rate for each of the four antigens, 94%, was based on a previous Menactra-Menactra booster study (NCT01442675).

Subgroup analyses

The applicant proposed additional analyses of the primary and first secondary endpoints stratifying by age at time of boosting (≥ 15 to < 18 years of age, ≥ 18 years of age), time elapsed since the first quadrivalent meningococcal conjugate vaccination (< 7 years or ≥ 7 years), and by the nature of the first vaccine (i.e.,Menactra, Menveo, or unknown) (see Section 3.7.2).

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

Study populations are described in Table 25 and Table 26.

Table 25: FAS and PPAS1 for Day 6 by randomized group – All Randomized Subjects

	Group 1 MenQuadfi	Group 2 Menactra	All
Total (N)	403	407	810
Full Analysis Set count (%)	56 (13.9)	63 (15.5)	119 (14.7)
Per Protocol Analysis Set 1 count (%)	55 (13.6)	62 (15.2)	117 (14.4)
Subjects with at least one deviation count (%)	1 (0.2)	2 (0.5)	3 (0.4)
Did not provide D06 sample or not in time window count (%)	1 (0.2)	2 (0.5)	3 (0.4)

Source: Adapted from original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 4.2, p. 88.

Table 26: FAS and PPAS2 for Day 30 by randomized group – All Randomized Subjects

	Group 1 MenQuadfi	Group 2 Menactra	All
Total (N)	403	407	810
Full Analysis Set count (%)	396 (98.3)	402 (98.8)	798 (98.5)
Per Protocol Analysis Set 2 count (%)	384 (95.3)	389 (95.6)	773 (95.4)
Subjects with at least one deviation count (%)	19 (4.7)	18 (4.4)	37 (4.6)
Did not meet all protocol-specified inclusion/exclusion criteria count (%)	3 (0.7)	3 (0.7)	6 (0.7)
Did not receive vaccine count (%)	1 (0.2)	0 (0.0)	1 (0.1)
Did not provide D30 sample or not in time window count (%)	12 (3.0)	12 (2.9)	24 (3.0)
Received protocol-restricted therapy/medication/vaccine count (%)	3 (0.7)	3 (0.7)	6 (0.7)

Source: Adapted from original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 4.3, p. 88.

6.5.10.1.1 Demographics

Baseline demographics are presented in Table 27 and are well-balanced across study arms. The study population was evenly represented across sex, and a majority were White (~85%) and Black/African American (~10%).

Table 27: Baseline demographics by randomized group – SafAS

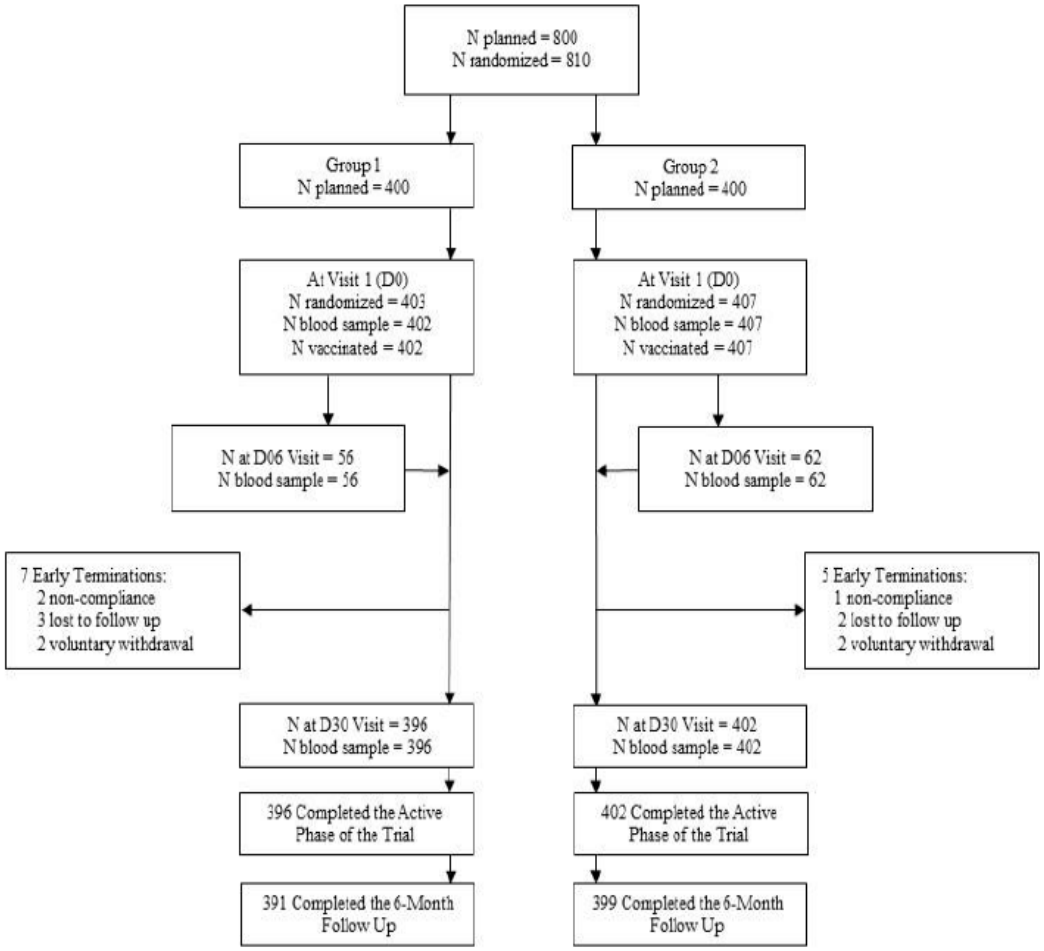
	Group 1 MenQuadfi	Group 2 Menactra	All
Total (N)	**402**	**407**	**809**
Sex: n (%)			
Male	**195 (48.5)**	**207 (50.9)**	**402 (49.7)**
Female	**207 (51.5)**	**200 (49.1)**	**407 (50.3)**
Age: Mean (SD)	**20.0 (5.97)**	**19.9 (5.59)**	**20.0 (5.78)**
Racial origin: n (%)			
White	**342 (85.1)**	**340 (83.5)**	**682 (84.3)**
Asian	**11 (2.7)**	**3 (0.7)**	**14 (1.7)**
Black	**39 (9.7)**	**46 (11.3)**	**85 (10.5)**
American Indian or Alaska	**1 (0.2)**	**0 (0.0)**	**1 (0.1)**
Native Hawaiian or other Pacific Islander	**0 (0.0)**	**1 (0.2)**	**1 (0.1)**
Mixed origin	**8 (2.0)**	**17 (4.2)**	**25 (3.1)**
Missing	**1 (0.2)**	**0 (0.0)**	**1 (0.1)**
Ethnic origin: n (%)			
Hispanic or Latino	**63 (15.7)**	**71 (17.4)**	**134 (16.6)**
Not Hispanic or Latino	**338 (84.1)**	**336 (82.6)**	**674 (83.3)**
Missing	**1 (0.2)**	**0 (0.0)**	**1 (0.1)**

Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 4.4, p. 90.

6.5.10.1.3 Subject Disposition

Subject disposition is presented in Figure 4.

Figure 4: Subject disposition flow chart for MenQuadfi (Group 1) and Menactra (Group 2), MET56



Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Figure 4.1, p. 85.

6.5.11 Efficacy Analyses

6.5.11.1 Analyses of Primary Endpoint(s)

The primary analysis demonstrated MenQuadfi met the non-inferiority success criteria for all four serogroups in comparison to Menactra (Table 28). The results were similar when repeated in the FAS.

Table 28: Primary Objective, comparison of the percentages of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menactra), presented as difference in percent seroresponders and 95% CI – PPAS2

Serogroup	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)	G1-G2 Difference (%)	G1-G2 2-sided 95% CI for Difference
A	354/384	92.2	(89.0; 4.7)	339/389	87.1	(83.4; 0.3)	5.0	(0.74; 9.38)
C	373/384	97.1	(94.9; 8.6)	357/389	91.8	(88.6; 94.3)	5.4	(2.16; 8.76)
Y	374/384	97.4	(95.3; 8.7)	372/389	95.6	(93.1; 97.4)	1.8	(-0.91; 4.55)
W	377/384	98.2	(96.3; 9.3)	353/389	90.7	(87.4; 93.4)	7.4	(4.30; 10.9)

Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 5.1, p. 91.

6.5.11.2 Analyses of Secondary Endpoints

At Day 6, estimates and 95% CIs for the differences in the percentages of subjects with an hSBA vaccine seroresponse were for serogroup A: 6.6% (95% CI: -10.1%, 22.5), for serogroup C: -3.5% (95% CI: -16.9%, 9.5%), for serogroup Y: 7.0% (95% CI: -5.6%, 19.3%), and for serogroup W: 10.7% (95% CI: -1.1%, 22.3%).

At Day 30, the GMTs were higher for MenQuadfi than for Menactra, with estimates and 95% CIs for the GMT as follows: 1.7 (95% CI: 1.4, 2.1), 4.4 (95% CI: 3.5, 5.5), 2.55 (95% CI: 2.1,3.1), 2.4 (95% CI: 1.9, 3.0), for serogroups A, C, Y, and W, respectively.

6.5.11.3 Subpopulation Analyses

In pre-specified analyses, the hSBA immunogenicity data were also analyzed by age at time of the booster dose (≥ 15 to < 18 years of age or ≥ 18 years of age), time elapsed since the first quadrivalent meningococcal conjugate vaccination (< 7 years or ≥ 7 years), and by the nature of the first vaccine (i.e., Menactra, Menveo, or unknown). Distributions of subgroups were balanced across vaccine arms, but subjects were more likely to have been vaccinated within 7 years and been vaccinated with Menactra (see Table 29).

Table 29: Distribution of pre-specified subgroups of interest across study arm – PPAS2

	Group 1 MenQuadfi	Group 2 Menactra
Total N	384	389
Age: ≥ 15 and < 18 years of age	201 (52%)	201 (52%)
Age: ≥ 18 years of age	183 (48%)	188 (48%)
Time since first vaccination: < 7 years	276 (72%)	281 (72%)
Time since first vaccination: ≥ 7 years	108 (28%)	108 (28%)
Primary Vaccine: Menactra	327 (85%)	340 (88%)
Primary Vaccine: Menveo	48 (13%)	39 (10%)
Primary Vaccine: Unknown	9 (2%)	10 (3%)

Source: Adapted from original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Tables 5.18, 5.24, 5.30, pp. 123, 133, 146.

Results of the subgroup analyses of percent difference in seroresponse rates across vaccination arms are reported in

Table **30**-Table 32. While the study was not powered for formal comparisons of subgroup analyses, the lower limit of the 95% CI for each subgroup and serogroup combination was >-10%. This suggests that seroresponse rates are comparable across vaccination arms for each subgroup.

Table 30: Comparison of the percentages of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menactra) by age groups, presented as difference in percent seroresponders (G1 – G2) and 95% CI – PPAS2

Age/Serogroup	G1 n/M	G1 %	G2 n/M	G2 %	G1-G2 Difference (%)	G1 – G2 2-sided 95% CI for Difference
≥ 15 to <18 years/A	183/201	91.0	181/201	90.0	1.0	(-4.86; 6.87)
≥ 15 to <18 years/C	196/201	97.5	190/201	94.5	3.0	(-1.01; 7.29)
≥ 15 to <18 years/Y	198/201	98.5	195/201	97.0	1.5	(-1.74; 5.01)
≥ 15 to <18 years/W	197/201	98.0	188/201	93.5	4.5	(0.465; 8.93)
≥ 18 years/A	171/183	93.4	158/188	84.0	9.4	(2.97; 15.9)
≥ 18 years/C	177/183	96.7	167/188	88.8	7.9	(2.63; 13.5)
≥ 18 years/Y	176/183	96.2	177/188	94.1	2.0	(-2.60; 6.77)
≥ 18 years/W	180/183	98.4	165/188	87.8	10.6	(5.60; 16.2)

Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 5.18, p. 123.

Table 31: Comparison of the percentages of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menactra) by timing elapsed since first vaccination, presented as difference in percent seroresponders (G1 – G2) and 95% CI – PPAS2

Time since initial vaccination/ Serogroup	G1 n/M	G1 %	G2 n/M	G2 %	G1-G2 Difference (%)	G1 – G2 2-sided 95% CI for Difference
<7 years /A	254/276	92.0	250/281	89.0	3.1	(-1.88; 8.03)
<7 years /C	269/276	97.5	262/281	93.2	4.2	(0.689; 8.01)
<7 years /Y	271/276	98.2	274/281	97.5	0.7	(-2.00; 3.44)
<7 years /W	272/276	98.6	256/281	91.1	7.4	(3.88; 11.5)
≥ 7 years /A	100/108	92.6	89/108	82.4	10.2	(1.29; 19.2)
≥ 7 years /C	104/108	96.3	95/108	88.0	8.3	(1.04; 16.1)
≥ 7 years /Y	103/108	95.4	98/108	90.7	4.6	(-2.47; 12.1)
≥ 7 years /W	105/108	97.2	97/108	89.8	7.4	(0.691; 14.8)

Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 5.24, p. 133.

Table 32: Comparison of the percentages of subjects achieving hSBA vaccine seroresponse at D30 between Group 1 (G1; MenQuadfi) and Group 2 (G2; Menactra), by vaccine primed, presented as difference in percent seroresponders (G1 – G2) and 95% CI – PPAS2

Primed Vaccine/ Serogroup	**G1** n/M	**G1** **%**	**G2** n/M	**G2** %	**G1-G2** Difference (%)	**G1 – G2** 2-sided 95% CI for Difference
Menactra/A	303/327	92.7	298/340	87.6	5.0	(0.462; 9.59)
Menactra/C	317/327	96.9	311/340	91.5	5.5	(1.93; 9.19)
Menactra/Y	318/327	97.2	325/340	95.6	1.7	(-1.29; 4.69)
Menactra/W	322/327	98.5	306/340	90.0	8.5	(5.07; 12.2)
Menveo/A	43/48	89.6	31/39	79.5	10.1	(-5.16; 26.2)
Menveo/C	48/48	100.0	36/39	92.3	7.7	(-1.27; 20.3)
Menveo/Y	48/48	100.0	37/39	94.9	5.1	(-3.16; 16.9)
Menveo/W	47/48	97.9	37/39	94.9	3.0	(-6.52; 14.9)
Unknown/A	8/9	88.9	10/10	100.0	-11.1	(-43.5; 18.1)
Unknown/C	8/9	88.9	10/10	100.0	-11.1	(-43.5; 18.1)
Unknown/Y	8/9	88.9	10/10	100.0	-11.1	(-43.5; 18.1)
Unknown/W	8/9	88.9	10/10	100.0	-11.1	(-43.5; 18.1)

Source: Original BLA 125701/0; Clinical Study Report MET56, version 2.0, 7 December 2017, Table 5.30, p. 146.

The hSBA seroresponse rates and GMTs were also stratified by sex and race. Results suggest similar immunogenicity trends in males and females, as well as White/Caucasian and Black/African-American subgroups, as in the overall population. The other racial subgroups were not of sufficient size to suggest trend in immunogenic response.

6.5.11.4 Dropouts and/or Discontinuations

In both arms, less than 3% of the sample were lost to follow-up or discontinued, and none were considered related to vaccine administration. Thus, the complete case immunogenicity analyses presented are acceptable.

6.5.11.5 Exploratory and Post Hoc Analyses

N/A

6.5.12 Safety Analyses

6.5.12.1 Methods

All subjects were observed for 30 minutes after vaccination, with any unsolicited adverse events recorded using an electronic case report form (CRF). Using a diary card, the subject or the subject's parents/guardians recorded solicited events through day 7 and unsolicited adverse events through visit 2. Using a memory aid, the subject recorded possible serious adverse events and medically attended adverse events from visit 2 through the end of the study. Results were reported descriptively as percentages and 95% exact binomial/Clopper-Pearson confidence intervals.

6.5.12.3 Deaths

There were no deaths reported in the study.

6.5.12.4 Nonfatal Serious Adverse Events

During the study, 9 subjects reported nonfatal SAEs, 5 in the MenQuadfi arm (1.2%, 95% CI: 0.4%, 2.9%) and 4 in the Menactra arm (1.0%, 95% CI: 0.3%, 2.5%). None were considered related the vaccination.

6.5.12.5 Adverse Events of Special Interest (AESI)

N/A

6.5.12.6 Clinical Test Results

N/A

6.5.12.7 Dropouts and/or Discontinuations

No dropouts were attributed to adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The applicant is seeking approval of MenQuadfi as a vaccine indicated for active immunization for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y, and W in ages 2 and older.

7.1.1 Methods of Integration

The purpose of the integrated analysis is to provide an overview of the immune response profile of subjects who received one dose of the final formulation of MenQuadfi, where immune response is tested using the hSBA. Because age group is expected to influence immune response to the vaccine, the analysis for the meningococcal vaccine-naïve subjects was performed by the following age groups (with study name and sample size):

- Children 2 through 9 years of age (MET35)
- Adolescents 10 through 17 years of age (pooled MET43 and MET50) with comparator integrated side by side
- Adults 18 through 55 years of age (MET43)
- Older adults and elderly ≥ 56 years of age (pooled MET44 and MET49)
    - Older adults 56 through 64 years of age
    - Elderly adults ≥ 65 years of age
        - Elderly adults 65 through 74 years of age
        - Elderly adults ≥ 75 years of age

An additional analysis was conducted for primed subjects ≥ 15 years old (MET56).

All analyses are conducted using the PPAS definition, defined for the appropriate time point. See Subsection 9 of under each of the study summaries in Section 6 for a more detail definition of PPAS (e.g. Section 6.1.9 Statistical Considerations & Statistical Analysis Plan). Baseline estimates are presented as counts (percents) or means (standard deviations). Immunogenicity seroresponse analyses are presented descriptively as percent responders and 95% Clopper-Pearson CIs.

Reviewer's comment:
For two of the age groups, adolescents (age 10-17 years old) and older adults/elderly (age 56 years and older), the applicant pooled Phase 2 and Phase 3 studies. Due to the similarities in study design and conduct, pooling the studies is reasonable. The included studies are consistent in terms of general study design and operational conduct, vaccine formulation and schedule, and all use the validated hSBA method from the same laboratory to assess antibody titers against the four meningococcal serogroups contained in the MenACYW conjugate vaccine. Though the Phase 2 studies were open-label, the assay technicians were blinded, and thus, the resulting titer is not likely to be biased. The definition of seroresponse was aligned to the Phase 3 definition: post-vaccination titer ≥ 1:16 for subjects with a pre-vaccination titer < 1:8 and post-vaccination titer at least 4-fold greater than the pre-vaccination titer for subjects with a pre-vaccination titer ≥ 1:8. Additionally, some vaccines were administered with concomitant vaccines in MET50 and included in the MenQuadfi arm. This is unlikely to alter the combined results because as suggested in Table 16, there was no interference with MenQuadfi and the concomitant vaccines in terms of meningococcal seroresponse.

Main Objective
Overview of the antibody response against meningococcal serogroups A, C, W, and Y measured by hSBA at baseline and 30 days after vaccination with MenACYW conjugate vaccine or comparator vaccine according to age, and baseline vaccine background, as well as by gender and race group.

7.1.2 Demographics and Baseline Characteristics

Baseline demographics for each of the pooled quadrivalent meningococcal vaccine arms are presented in Table 33 - Table 36. In subjects under 18 and in the primed study, sex was evenly split, and in subjects over 18, there were a slightly higher proportion of females (60%-65%). In all age groups, racial distribution was predominately White (74%-90%), followed by Black/African-American (9%-21%).

Table 33: Baseline demographics for the pooled MenQuadfi arm, by age group – PPAS

MenQuadfi	N	Female n (%)	Male n (%)	Age Mean (SD)	White n (%)	Black n (%)	Asian n (%)	Other n (%)
All Children (2 through 9 years old)	458	225 (49.1)	233 (50.9)	6.0 (2.3)	371 (81.0)	59 (12.9)	2 (0.4)	26 (5.7)
All Adolescents (10 through 17 years old)	1921	955 (49.7)	966 (50.3)	11.8 (1.7)	1565 (81.5)	228 (11.9)	17 (0.9)	111 (5.8)
Adults (18 through 55 years old)	1410	931 (66.0)	479 (34.0)	39.7 (10.1)	1037 (73.5)	294 (20.9)	31 (2.2)	48 (3.4)
Older Adults and Elderly (>= 56 years old)	628	369 (58.8)	259 (41.2)	66.6 (7.4)	560 (89.2)	56 (8.9)	5 (0.8)	7 (1.1)
Primed: 15 through 17 years old	201	87 (43.3)	114 (56.7)	16.6 (0.7)	172 (85.6)	19 (9.5)	4 (2.0)	6 (3.0)
Primed: >= 18 years old	183	115 (62.8)	68 (37.2)	23.7 (6.7)	155 (84.7)	19 (10.4)	5 (2.7)	4 (2.2)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 1.1.2.

Table 34: Baseline demographics for the pooled Menactra arm, by age group – PPAS

Menactra	N	Female n (%)	Male n (%)	Age Mean (SD)	White n (%)	Black n (%)	Asian n (%)	Other n (%)
All Adolescents (10 through 17 years old)	300	129 (43.0)	171 (57.0)	12.2 (2.1)	224 (74.7)	54 (18.0)	8 (2.7)	14 (4.7)
Adults (18 through 55 years old)	290	201 (68.6)	92 (31.4)	39.7 (9.8)	218 (74.4)	61 (20.8)	5 (1.7)	9 (3.1)
Primed: 15 through 17 years old	201	93 (46.3)	108 (53.7)	16.5 (0.8)	171 (85.1)	18 (9.0)	0 (0.0)	12 (6.0)
Primed: >= 18 years old	188	99 (52.7)	89 (47.3)	23.8 (6.2)	152 (80.9)	27 (14.4)	3 (1.6)	6 (3.2)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 1.1.2.

Table 35: Baseline demographics for the pooled Menveo arm, by age group – PPAS

Menveo	N	Female n (%)	Male n (%)	Age Mean (SD)	White n (%)	Black n (%)	Asian n (%)	Other n (%)
All Children (2 through 9 years old)	460	215 (46.7)	245 (53.3)	8.8 (3.30)	385 (83.7)	52 (11.3)	2 (0.4)	21 (4.6)
All Adolescents (10 through 17 years old)	464	212 (45.7)	252 (54.3)	11.4 (1.39)	418 (90.1)	21 (4.5)	2 (0.4)	23 (5.0)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 1.1.2.

Table 36: Baseline demographics for the pooled Menomune arm, by age group – PPAS

Menomune	N	Female n (%)	Male n (%)	Age Mean (SD)	White n (%)	Black n (%)	Asian n (%)	Other n (%)
Older Adults and Elderly (>= 56 years old)	525	296 (56.4)	229 (43.6)	67.0 (7.39)	479 (91.2)	42 (8.0)	1 (0.2)	3 (0.6)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 1.1.2.

7.1.4 Analysis of Primary Endpoint(s)

Vaccine seroresponse across pooled age groups for the four meningococcal quadrivalent vaccines are presented in Table 37. Though seroresponse rates were lower in the older age groups when compared to the 2-9-year-old and 10-17-year old age groups, all serotypes had a higher immune response than the comparator for all age groups.

Table 37: Vaccine seroresponse by age group and serogroup across quadrivalent meningococcal vaccine arms MenQuadfi (G1), Menactra (G2), Menveo (G3), and Menomune (G4), pooled across relevant studies.

Age group	Sero-group	G1 n/M	G1 %	G1 95% CI	G2 n/M	G2 %	G2 95% CI	G3 n/M	G3 %	G3 95% CI	G4 n/M	G4 %	G4 95% CI
2-9 years of age	A	252/455	55	(51, 60)				219/458	48	(43, 53)			
	C	436/458	95	(93, 97)				219/458	48	(43, 53)			
	Y	419/458	92	(89, 94)				364/459	79	(75, 83)			
	W	361/458	79	(75, 83)				294/459	64	(60, 68)			
10-17 years of age	A	1402/1920	73	(71, 75)	166/300	55	(50, 61)	280/464	60	(56, 65)			
	C	1840/1919	96	(95, 97)	160/300	53	(48, 59)	285/463	62	(57, 66)			
	Y	1796/1919	94	(92, 95)	257/300	86	(81, 89)	310/464	67	(62, 71)			
	W	1613/1920	84	(82, 86)	216/300	72	(67, 77)	260/464	56	(51, 61)			
18-55 years of age	A	1034/1406	74	(71, 76)	158/293	54	(48, 60)						
	C	1173/1406	83	(81, 85)	124/293	42	(37, 48)						
	Y	1241/1408	88	(86, 90)	178/293	61	(55, 66)						
	W	1084/1408	77	(75, 79)	147/293	50	(44, 56)						
≥ 56 years of age	A	369/628	59	(55, 63)							223/525	43	(38, 47)
	C	461/628	73	(70, 77)							256/525	49	(44, 53)
	Y	459/628	73	(69, 77)							227/525	43	(39, 48)
	W	395/628	63	(59, 67)							236/525	45	(41, 49)
Primed 10-55 years of age	A	354/384	92	(89, 95)	339/389	87	(83, 90)						
	C	373/384	97	(95, 99)	357/389	92	(89, 94)						
	Y	374/384	97	(95, 99)	372/389	96	(93, 97)						
	W	377/384	98	(96, 99)	353/389	91	(87, 93)						

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Tables 2.1.1, 3.1.1, 4.1.1, 5.1.1, and 6.1.1, pp. 55, 89, 126, 163-167, 327.

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

The primary analysis for the seroresponse endpoint was stratified further across sex and race. When age groups were stratified further by sex and race, MenQuadfi had a higher seroresponse for all serogroups versus the appropriate comparator. In all age groups and serogroups, there were no differences across sex (Table 38-Table 40). After stratifying by race, sample sizes for Asians and Other race were small, resulting in highly variable estimates and/or comparisons across racial subgroups that were not possible. In the remaining subgroups, results suggest a similar pattern across racial group with the higher seroresponse rates in C and Y and slightly lower seroresponse rates in A and W.

Because the 2-9-year old age group was not pooled, please see the study specific subgroup analyses in Section 6.1.11.3. Similarly, please see the study specific subgroup analyses for previously vaccinated subjects in Section 6.5.11.3.

Table 38: In subjects 10-17 years of age. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccines Menactra (G2) and Menveo (G3) by sex - Naive Adolescents - PPAS (Pooled MET43 and MET50)

Sex/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G2 n/M	G2 Rate (%)	G2 95% CI	G3 n/M	G3 Rate (%)	G3 95% CI
Female/A	687/955	71.9	(69.0; 74.8)	68/129	52.7	(43.7; 61.6)	122/212	57.5	(50.6; 64.3)
Female/C	912/953	95.7	(94.2; 96.9)	63/129	48.8	(39.9; 57.8)	138/212	65.1	(58.3; 71.5)
Female/Y	900/954	94.3	(92.7; 95.7)	111/129	86.0	(78.8; 91.5)	148/212	69.8	(63.1; 75.9)
Female/W	820/955	85.9	(83.5; 88.0)	97/129	75.2	(66.8; 82.4)	134/212	63.2	(56.3; 69.7)
Male/A	715/965	74.1	(71.2; 76.8)	98/171	57.3	(49.5; 64.8)	158/252	62.7	(56.4; 68.7)
Male/C	928/966	96.1	(94.6; 97.2)	97/171	56.7	(48.9; 64.3)	147/251	58.6	(52.2; 64.7)
Male/Y	896/965	92.8	(91.0; 94.4)	146/171	85.4	(79.2; 90.3)	162/252	64.3	(58.0; 70.2)
Male/W	793/965	82.2	(79.6; 84.5)	119/171	69.6	(62.1; 76.4)	126/252	50.0	(43.7; 56.3)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 3.2.1, pp. 99-100.

Table 39: In subjects 18-55 years of age. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccine Menactra (G2) by sex - Naive Adults - PPAS (MET43)

Sex/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G2 n/M	G2 Rate (%)	G2 95% CI
Female/A	673/927	72.6	(69.6; 75.4)	107/201	53.2	(46.1; 60.3)
Female/C	788/927	85.0	(82.5; 87.2)	87/201	43.3	(36.3; 50.4)
Female/Y	832/929	89.6	(87.4; 91.5)	122/201	60.7	(53.6; 67.5)
Female/W	736/929	79.2	(76.5; 81.8)	105/201	52.2	(45.1; 59.3)
Male/A	361/479	75.4	(71.3; 79.2)	51/92	55.4	(44.7; 65.8)
Male/C	385/479	80.4	(76.5; 83.8)	37/92	40.2	(30.1; 51.0)
Male/Y	409/479	85.4	(81.9; 88.4)	56/92	60.9	(50.1; 70.9)
Male/W	348/479	72.7	(68.4; 76.6)	42/92	45.7	(35.2; 56.4)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 4.2.1, pp. 136-137.

Table 40: In subjects 56 years of age and older. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccine Menomune (G4) by sex - Naive Older Adults and Elderly - PPAS (Pooled MET44 and MET49)

Sex/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G4 n/M	G4 Rate (%)	G4 95% CI
Female/A	217/369	58.8	(53.6; 63.9)	126/296	42.6	(36.9; 48.4)
Female/C	280/369	75.9	(71.2; 80.2)	154/296	52.0	(46.2; 57.8)
Female/Y	277/369	75.1	(70.3; 79.4)	127/296	42.9	(37.2; 48.8)
Female/W	244/369	66.1	(61.0; 70.9)	137/296	46.3	(40.5; 52.1)
Male/A	152/259	58.7	(52.4; 64.7)	97/229	42.4	(35.9; 49.0)
Male/C	181/259	69.9	(63.9; 75.4)	102/229	44.5	(38.0; 51.2)
Male/Y	182/259	70.3	(64.3; 75.8)	100/229	43.7	(37.1; 50.4)
Male/W	151/259	58.3	(52.0; 64.4)	99/229	43.2	(36.7; 49.9)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 5.2.1, pp. 206-207.

Table 41: In subjects 10-17 years of age. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccines Menactra (G2) and Menveo (G3) by race - Naive Adolescents - PPAS (Pooled MET43 and MET50)

Race/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G2 n/M	G2 Rate (%)	G2 95% CI	G3 n/M	G3 Rate (%)	G3 95% CI
White/A	1142/1564	73.0	(70.7; 75.2)	122/224	54.5	(47.7; 61.1)	244/418	58.4	(53.5; 63.1)
White/C	1499/1564	95.8	(94.7; 96.8)	118/224	52.7	(45.9; 59.4)	249/417	59.7	(54.8; 64.5)
White/Y	1463/1563	93.6	(92.3; 94.8)	192/224	85.7	(80.4; 90.0)	274/418	65.6	(60.8; 70.1)
White/W	1323/1564	84.6	(82.7; 86.3)	163/224	72.8	(66.4; 78.5)	228/418	54.5	(49.6; 59.4)
Black/A	167/228	73.2	(67.0; 78.9)	30/54	55.6	(41.4; 69.1)	16/21	76.2	(52.8; 91.8)
Black/C	217/227	95.6	(92.0; 97.9)	28/54	51.9	(37.8; 65.7)	17/21	81.0	(58.1; 94.6)
Black/Y	216/228	94.7	(91.0; 97.3)	47/54	87.0	(75.1; 94.6)	17/21	81.0	(58.1; 94.6)
Black/W	183/228	80.3	(74.5; 85.2)	35/54	64.8	(50.6; 77.3)	14/21	66.7	(43.0; 85.4)
Asian/A	11/17	64.7	(38.3; 85.8)	5/8	62.5	(24.5; 91.5)	2/2	100.0	(15.8; 100)
Asian/C	17/17	100.0	(80.5; 100)	5/8	62.5	(24.5; 91.5)	2/2	100.0	(15.8; 100)
Asian/Y	16/17	94.1	(71.3; 99.9)	6/8	75.0	(34.9; 96.8)	2/2	100.0	(15.8; 100)
Asian/W	15/17	88.2	(63.6; 98.5)	7/8	87.5	(47.3; 99.7)	1/2	50.0	(1.3; 98.7)
Other/A	82/111	73.9	(64.7; 81.8)	9/14	64.3	(35.1; 87.2)	18/23	78.3	(56.3; 92.5)
Other/C	107/111	96.4	(91.0; 99.0)	9/14	64.3	(35.1; 87.2)	17/23	73.9	(51.6; 89.8)
Other/Y	101/111	91.0	(84.1; 95.6)	12/14	85.7	(57.2; 98.2)	17/23	73.9	(51.6; 89.8)
Other/W	92/111	82.9	(74.6; 89.4)	11/14	78.6	(49.2; 95.3)	17/23	73.9	(51.6; 89.8)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 3.3.1, pp. 118-121.

Table 42: In subjects 18-55 years of age. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccine Menactra (G2), by race - Naive Adults - PPAS (MET43)

Race/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G2 n/M	G2 Rate (%)	G2 95% CI
White/A	775/1035	74.9	(72.1; 77.5)	120/218	55.0	(48.2; 61.8)
White/C	872/1036	84.2	(81.8; 86.3)	86/218	39.4	(32.9; 46.3)
White/Y	922/1037	88.9	(86.8; 90.8)	131/218	60.1	(53.3; 66.6)
White/W	818/1037	78.9	(76.3; 81.3)	102/218	46.8	(40.0; 53.6)
Black/A	198/292	67.8	(62.1; 73.1)	31/61	50.8	(37.7; 63.9)
Black/C	227/291	78.0	(72.8; 82.6)	27/61	44.3	(31.5; 57.6)
Black/Y	249/292	85.3	(80.7; 89.1)	36/61	59.0	(45.7; 71.4)
Black/W	208/292	71.2	(65.7; 76.4)	36/61	59.0	(45.7; 71.4)
Asian/A	27/31	87.1	(70.2; 96.4)	3/5	60.0	(14.7; 94.7)
Asian/C	30/31	96.8	(83.3; 99.9)	4/5	80.0	(28.4; 99.5)
Asian/Y	25/31	80.6	(62.5; 92.5)	4/5	80.0	(28.4; 99.5)
Asian/W	23/31	74.2	(55.4; 88.1)	3/5	60.0	(14.7; 94.7)
Other/A	34/48	70.8	(55.9; 83.0)	4/9	44.4	(13.7; 78.8)
Other/C	44/48	91.7	(80.0; 97.7)	7/9	77.8	(40.0; 97.2)
Other/Y	45/48	93.8	(82.8; 98.7)	7/9	77.8	(40.0; 97.2)
Other/W	35/48	72.9	(58.2; 84.7)	6/9	66.7	(29.9; 92.5)

Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 4.3.1, pp. 155-158.

Table 43: In subjects 56 years of age and older. summary of hSBA vaccine seroresponse rate for MenQuadfi (G1) versus comparator vaccine Menomune (G4) by race - Naive Older Adults and Elderly - PPAS (Pooled MET44 and MET49)

Race/ Serogroup	G1 n/M	G1 Rate (%)	G1 95% CI	G4 n/M	G4 Rate (%)	G4 95% CI
White/A	330/560	58.9	(54.7; 63.0)	203/479	42.4	(37.9; 46.9)
White/C	407/560	72.7	(68.8; 76.3)	234/479	48.9	(44.3; 53.4)
White/Y	411/560	73.4	(69.5; 77.0)	208/479	43.4	(38.9; 48.0)
White/W	352/560	62.9	(58.7; 66.9)	209/479	43.6	(39.1; 48.2)
Black/A	29/56	51.8	(38.0; 65.3)	19/42	45.2	(29.8; 61.3)
Black/C	46/56	82.1	(69.6; 91.1)	19/42	45.2	(29.8; 61.3)
Black/Y	38/56	67.9	(54.0; 79.7)	17/42	40.5	(25.6; 56.7)
Black/W	35/56	62.5	(48.5; 75.1)	24/42	57.1	(41.0; 72.3)
Asian/A	3/5	60.0	(14.7; 94.7)	0/1	0.0	(NC)
Asian/C	4/5	80.0	(28.4; 99.5)	0/1	0.0	(NC)
Asian/Y	3/5	60.0	(14.7; 94.7)	1/1	100.0	(NC)
Asian/W	3/5	60.0	(14.7; 94.7)	0/1	0.0	(NC)
Other/A	7/7	100.0	(59.0; 100)	1/3	33.3	(0.8; 90.6)
Other/C	4/7	57.1	(18.4; 90.1)	3/3	100.0	(29.2; 100)
Other/Y	7/7	100.0	(59.0; 100)	1/3	33.3	(0.8; 90.6)
Other/W	5/7	71.4	(29.0; 96.3)	3/3	100.0	(29.2; 100)

Notes: (NC) indicates the confidence interval is not calculated due to small sample size.
Source: Original BLA 125701/0; Integrated Summary of Immunogenicity Tables and Figures, Table 5.3.1, pp. 287-290.

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

The pooled and integrated analyses demonstrate that MenQuadfi elicits higher immunogenicity across age groups and serogroups versus the respective comparator. The higher seroresponse also held across sex and racial subgroups. Immunogenicity was lower in the older adults/elderly age group.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Please see the description of safety assessment methods for the individual studies in Section 6. For each endpoint, exact 95% CIs for the single proportions and density incidence are calculated using the exact binomial method (Clopper-Pearson method). All statistics are presented descriptively.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Six studies (Table 1) were submitted to support the safety profile in pooled safety analyses. All studies except for MET44 had a safety follow-up period for SAE and MAAE after D30 visit.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Across all studies, 4726 subjects were exposed to MenQuadfi (without concomitant vaccines), with an additional 392 subjects exposed to MenQuadfi, plus Adacel and Gardasil at baseline. In the comparator arms, 1042 subjects were given Menactra, 995 subjects were given Menveo, 553 subjects were given Menomune, and 296 subjects were given Adacel and Gardasil at baseline. Distributions of age, race, and sex across study arms are presented in Table 44.

Table 44: Demographics of the pooled safety data.

	MenQuadfi	Menactra	Menveo	Menomune	MenQuadfi+ Adacel+Gardasil	Adacel+ Gardasil
N	4726	1042	995	553	392	296
Female n(%)	2639 (56%)	555 (54%)	461 (46%)	314 (57%)	191 (49%)	141 (48%)
Males n(%)	2087 (44%)	487 (47%)	534 (54%)	239 (43%)	201 (51%)	155 (52%)
Age: Mean (SD)	28.2 (21.0)	23.5 (12.9)	8.7 (3.3)	67.0 (7.4)	11.3 (1.1)	11.4 (1.4)
White n(%)	3747 (79%)	813 (78%)	862 (87%)	500 (90%)	350 (90%)	258 (87%)
Black/ African American n(%)	717 (15%)	166 (16%)	82 (8%)	48 (9%)	15 (4%)	18 (6%)
Asian n(%)	69 (2%)	17 (2%)	4 (<1%)	1 (<1%)	1 (<1%)	0 (0%)
Other n(%)	193 (4%)	46 (4%)	47 (5%)	4 (1%)	26 (7%)	20 (7%)

Source: Original BLA 125701/0; Integrated Summary of Safety Tables and Figures, Table 2.1.1.

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

The procedures for the collection of the safety data, the time points, safety definitions, and main endpoints were similar enough to facilitate an integrated and/or pooled analysis of the six included studies, and a pooled analysis reflects overall safety across the full age range of the MenQuadfi arm. However, since comparator arms are study-specific, please see safety results for the individual studies in Section 6 for comparisons to currently licensed meningococcal vaccines.

8.4 Safety Results

8.4.1 Deaths

There were two deaths recorded in the combined safety dataset. Both occurred in the comparator arm of MET49, Menomune, and neither was considered by the investigator as related to the vaccine. Please see Section 6.1.12.3 for details.

8.4.2 Nonfatal Serious Adverse Events

Rates of nonfatal serious adverse events were similar across the three conjugated MenACWY vaccines (MenQuadfi, Menactra, and Menveo), and no reported serious adverse event in the combined safety dataset was considered related to vaccine administration.

Table 45: Nonfatal Serious Adverse Events (SAE) by time of onset after vaccination, by vaccination arms Menquadfi (G1), Menactra (G2), and Menveo (G3), presented as count (n), percent of total (N = 4276, 1042, and 995 for MenQuadfi, Menactra, and Menveo, respectively), and 95% CI – SafAS

Time frame after injection	G1 n	G1 %	G1 (95% CI)	G2 n	G2 %	G2 (95% CI)	G3 n	G3 %	G3 (95% CI)
D0 to D7	2	<0.1	(0.0; 0.2)	1	<0.1	(0.0; 0.5)	1	<0.1	(0.0; 0.5)
D8 to D30	10	0.2	(0.1; 0.4)	2	0.2	(0.0; 0.7)	1	0.1	(0.0; 0.6
D30 to end of study	47	1.0	(0.7; 1.3)	6	0.6	(0.2; 1.2)	5	0.5	(0.2; 1.2)
Entire study	59	1.2	(1.0;1.6)	9	0.9	(0.4; 1.6)	7	0.7	(1.5; 4.4)

Source: Integrated Summary of Safety Tables and Figures, Tables 2.2.20-2.2.22, p. 287-316.

Table 46: Nonfatal Serious Adverse Events (SAE) by time of onset after vaccination, by vaccination arms Menomune (G4), MenQuadfi+Adacel+Gardasil (G5), and Adacel+Gardasil (G6), presented as count (n), percent of total (N = 553, 392, and 296 for Menomune, MenQuadfi+Adacel+Gardasil, and Adacel+Gardasil, respectively), and 95% CI - SafAS

Time frame after injection	G4 n	G4 %	G4 (95% CI)	G5 n	G5 %	G5 (95% CI)	G6 n	G6 %	G6 (95% CI)
D0 to D7	2	0.4	(0.0; 1.3)	0	0.0	(0.0; 0.9)	1	0.3	(0.0; 1.9)
D8 to D30	1	0.2	(0.0; 1.0)	0	0.0	(0.0; 0.9)	0	0.0	(0.0; 1.2)
D30 to end of study	13	2.4	(1.3; 4.0)	4	1.0	(0.3; 2.6)	3	1.0	(0.2; 2.9)
Entire study	15	2.7	(1.5; 4.4)	4	1.0	(0.3; 2.6)	4	1.4	(0.4; 3.4)

Source: Integrated Summary of Safety Tables and Figures, Tables 2.2.20-2.2.22, p. 287-316.

8.4.3 Study Dropouts/Discontinuations

Across all studies, there was one discontinuation attributable to an adverse event in the Menomune arm. Neither the investigator nor the sponsor considered this event related to vaccination. Please see Section 6.4.12.7 for more detail.

8.4.4 Common Adverse Events

Please see Sections 8.4.6 and 8.4.7 for common systemic and local adverse events.

8.4.5 Clinical Test Results

N/A

8.4.6 Systemic Adverse Events

Table 47 and Table 48 summarize the reported incidence of solicited systemic reactions during the 7-day post-vaccination period. Across vaccination group and endpoint, most reactions had an onset within 3 days of vaccination and resolved within 3 days. Overall, the injection site safety profile was similar across all three conjugated MenACYW vaccines. The higher systemic AE rates in the MenQuadfi concomitant arm is likely due to the concomitant vaccines, as demonstrated by the similarly high rates in the Adacel+Gardasil arm. Solicited systemic reactions were lower in the youngest (children) and oldest (older adults and elderly) age groups (Table 49).

Table 47: Solicited systemic reactions within 7 days after V01 vaccine injection for the full Safety Analysis Set, for the three conjugated MenACYW arms Menquadfi (G1), Menactra (G2), and Menveo (G3)

Subjects experiencing at least one:	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)	G3 n/M	G3 %	G3 (95% CI)
Fever	56/4572	1.2	(0.9; 1.6)	9/1002	0.9	(0.4; 1.7)	19/967	2.0	(1.2; 3.1)
Fever, Grade 3	7/4572	0.2	(0.1; 0.3)	3/1002	0.3	(0.1; 0.9)	5/967	0.5	(0.2; 1.2)
Headache	1223/4640	26.4	(25.1; 27.7)	305/1017	30.0	(27.2; 32.9)	208/978	21.3	(18.7; 24.0)
Headache, Grade 3	90/4640	1.9	(1.6; 2.4)	28/1017	2.8	(1.8; 4.0)	11/978	1.1	(0.6; 2.0)
Malaise	1009/4640	21.7	(20.6; 23.0)	240/1017	23.6	(21.0; 26.3)	229/978	23.4	(20.8; 26.2)
Malaise, Grade 3	95/4640	2.0	(1.7; 2.5)	28/1017	2.8	(1.8; 4.0)	19/978	1.9	(1.2; 3.0)
Myalgia	1424/4641	30.7	(29.4; 32.0)	348/1017	34.2	(31.3; 37.2)	285/978	29.1	(26.3; 32.1)
Myalgia, Grade 3	102/4641	2.2	(1.8; 2.7)	22/1017	2.2	(1.4; 3.3)	13/978	1.3	(0.7; 2.3)

Notes: n = count of subjects with at least one solicited systemic reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Table 2.2.10, p. 110-111.

Table 48: Solicited systemic reactions within 7 days after V01 vaccine injection for the full Safety Analysis Set, for Menomune (G4), MenQuadfi+Adacel+Gardasil (G5), and Adacel+Gardasil (G6)

Subjects experiencing at least one:	G4 n/M	G4 %	G4 (95% CI)	G5 n/M	G5 %	G5 (95% CI)	G6 n/M	G6 %	G6 (95% CI)
Fever	3/548	0.5	(0.1; 1.6)	6/387	1.6	(0.6; 3.3)	2/285	0.7	(0.1; 2.5)
Fever, Grade 3	0/548	0.0	(0.0; 0.7)	2/387	0.5	(0.1; 1.9)	1/285	0.4	(0.0; 1.9)
Headache	94/551	17.1	(14.0; 0.5)	131/388	33.8	(29.1; 38.7)	84/290	29.0	(23.8; 34.6)
Headache, Grade 3	4/551	0.7	(0.2; 1.8)	11/388	2.8	(1.4; 5.0)	2/290	1.7	(0.6; 4.0)
Malaise	66/551	12.0	(9.4; 15.0)	113/388	29.1	(24.6; 33.9)	81/290	27.9	(22.8; 33.5)
Malaise, Grade 3	10/551	1.8	(0.9; 3.3)	10/388	2.6	(1.2; 4.7)	5/290	1.7	(0.6; 4.0)
Myalgia	95/551	17.2	(14.2; 0.7)	238/388	61.3	(56.3; 66.2)	160/289	55.4	(49.4; 61.2)
Myalgia, Grade 3	8/551	1.5	(0.6; 2.8)	18/388	4.6	(2.8; 7.2)	11/289	3.8	(1.9; 6.7)

Notes: n = count of subjects with at least one solicited systemic reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Table 2.2.10, p. 110-111.

Table 49: Solicited systemic reactions within 7 days after V01 vaccine injection for the full Safety Analysis Set, by age group, for the three conjugated MenACYW arms Menquadfi (G1), Menactra (G2), and Menveo (G3)

	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)	G3 n/M	G3 %	G3 (95% CI)
Children (2-9 years of age)	168/487	34.5	(30.3; 38.9)				180/486	37.0	(32.7; 41.5)
Children, Grade 3	9/487	1.8	(0.8; 3.5)				11/486	2.3	(1.1; 4.0)
Adolescents (10-17 years of age)	857/1867	45.9	(43.6; 48.2)	262/523	50.1	(45.7; 54.5)	251/492	51.0	(46.5; 55.5)
Adolescents, Grade 3	74/1867	4.0	(3.1; 5.0)	19/523	3.6	(2.2; 5.6)	21/492	4.3	(2.7; 6.5)
Adults (18-55 years of age)	783/1646	47.6	(45.1; 50.0)				236/493	47.9	(43.4; 52.4)
Adults, Grade 3	94/1646	5.7	(4.6; 6.9)	28/493	5.7	(3.8; 8.1)			

Notes: n = count of subjects with at least one solicited systemic reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Tables 3.1.1, 4.1.1, 5.1.1.

Table 50: Solicited systemic reactions within 7 days after V01 vaccine injection for the full Safety Analysis Set in older adults and the elderly, for MenQuadfi (G1) and Menomune (G4)

	G1 n/M	G1 %	G1 (95% CI)	G4 n/M	G4 %	G4 (95% CI)
Older Adults and Elderly (≥56 years of age)	231/641	36.0	(32.3; 39.9)	150/551	27.2	(23.5; 31.1)
Older Adults and Elderly, Grade 3	12/641	1.9	(1.0; 3.2)	14/551	2.5	(1.4; 4.2)

Notes: n = count of subjects with at least one solicited systemic reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Table 8.1.1.

8.4.7 Local Reactogenicity

Table 51 and Table 52 summarize the reported incidence of solicited injection site reactions during the 7-day post-vaccination period. Across vaccination groups and endpoints, most events had an onset within 3 days of vaccination and resolved within 7 days. Overall, the injection site safety profile was similar across all three conjugated MenACYW vaccines (MenQuadfi, Menactra, and Menveo), though Menveo had higher rates of redness and swelling. Injection site adverse events were lower in the Menomune arm. Solicited injection site reaction rates within age groups were similar to the overall population (Table 53, Table 54).

Table 51: Solicited injection site reactions within 7 days after V01 vaccine injection for the three conjugated MenACYW arms Menquadfi (G1), Menactra (G2), and Menveo (G3) – Safety Analysis Set

Subjects experiencing at least one:	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)	G3 n/M	G3 %	G3 (95% CI)
Any solicited injection site reaction	1882/4643	40.5	(39.1; 42.0)	440/1016	43.3	(40.2; 46.4)	487/978	49.8	(46.6; 53.0)
Any injection site reaction, Grade 3	94/4643	2.0	(1.6; 2.5)	21/1016	2.1	(1.3; 3.1)	65/978	6.6	(5.2; 8.4)
Pain	1779/4641	38.3	(36.9; 39.7)	431/1016	42.4	(39.4; 45.5)	415/978	42.4	(39.3; 45.6)
Pain, Grade 3	67/4641	1.4	(1.1;1.8)	19/1016	1.9	(1.1; 2.9)	10/978	1.0	(0.5; 1.9)
Redness	328/4642	7.1	(6.3; 7.8)	31/1016	3.1	(2.1; 4.3)	190/976	19.5	(17.0; 22.1)
Redness, Grade 3	27/4642	0.6	(0.4; 0.8)	2/1016	0.2	(0.0; 0.7)	54/976	5.5	(4.2; 7.2)
Swelling	255/4636	5.5	(4.9; 6.2)	28/1014	2.8	(1.8; 4.0)	136/974	14.0	(11.8; 16.3)
Swelling, Grade 3	13/4636	0.3	(0.1; 0.5)	1/1014	<0.1	(0.0; 0.5)	29/974	3.0	(2.0; 4.2)

Notes: n = count of subjects with at least one solicited injection site reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Tables 2.2.1, 2.2.4, 2.2.6, pp. 72, 85, 94-95.

Table 52: Solicited injection site reactions within 7 days after V01 vaccine injection for Menomume (G4) and MenQuadfi given with Adacel and Gardasil (G5) – Safety Analysis Set

Subjects experiencing at least one:	G4 n/M	G4 %	G4 (95% CI)	G5 n/M	G5 %	G5 (95% CI)
Any solicited injection site reaction	78/551	14.2	(11.4; 17.3)	190/388	49.0	(43.9; 54.1)
Any injection site reaction, Grade 3	3/551	0.5	(0.1; 1.6)	11/388	2.8	(1.4; 5.0)
Pain	75/550	13.6	(10.9; 16.8)	183/388	47.2	(42.1; 52.3)
Pain, Grade 3	3/550	0.5	(0.1;1.6)	9/388	2.3	(1.1; 4.4)
Redness	5/551	0.9	(0.3; 2.1)	15/388	3.9	(2.2; 6.3)
Redness, Grade 3	0/551	0.0	(0.0; 0.7)	2/388	0.5	(0.1; 1.8)
Swelling	2/551	0.4	(0.0; 1.3)	17/388	4.4	(2.6; 6.9)
Swelling, Grade 3	0/551	0.0	(0.0; 0.7)	1/388	0.3	(0.0; 1.4)

Notes: n = count of subjects with at least one solicited injection site reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Tables 2.2.1, 2.2.4, 2.2.6, pp. 72, 85, 94-95.

Table 53: Solicited injection site reactions within 7 days after V01 vaccine injection for the three conjugated MenACYW arms Menquadfi (G1), Menactra (G2), and Menveo (G3), stratified by age – Safety Analysis Set

	G1 n/M	G1 %	G1 (95% CI)	G2 n/M	G2 %	G2 (95% CI)	G3 n/M	G3 %	G3 (95% CI)
Overall	1882/4643	40.5	(39.1; 42.0)	440/1016	43.3	(40.2; 46.4)	487/978	49.8	(46.6; 53.0)
Children (2-9 years of age)	228/487	46.8	(42.3; 51.4)				262/486	53.9	(49.4; 58.4)
Children, Grade 3	18/487	3.7	(2.2; 5.8)				54/486	11.1	(8.5; 14.2)
Adolescents	751/1868	40.2	(38.0; 42.5)	225/523	43.0	(38.7; 47.4)	225/492	45.7	(41.3; 50.2)
Adolescents, Grade 3	33/1868	1.8	(1.2; 2.5)	10/523	1.9	(0.9; 3.5)	11/492	2.2	(1.1; 4.0)
Adults (18-55 years of age)	714/1646	43.4	(41.0; 45.8)	215/492	43.7	(39.3; 48.2)			
Adults, Grade 3	35/1646	2.1	(1.5; 2.9)	11/492	2.2	(1.1; 4.0)			

Notes: n = count of subjects with at least one solicited injection site reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Tables 2.2.1, 2.2.4, 2.2.6, pp. 72, 85, 94-95.

Table 54: Solicited injection site reactions within 7 days after V01 vaccine injection for MenQuadfi (G1) and Menomune (G4) in older adults and the elderly – Safety Analysis Set

	G1 n/M	G1 %	G1 (95% CI)	G4 n/M	G4 %	G4 (95% CI)
Older Adults and Elderly (≥56 years of age)	189/642	29.4	(25.9; 33.1)	78/551	14.2	(11.4; 17.3)
Older Adults and Elderly, Grade 3	8/642	1.2	(0.5; 2.4)	3/551	0.5	(0.1; 1.6)

Notes: n = count of subjects with at least one solicited injection site reaction per category; M = total number of subjects per category
Source: Integrated Summary of Safety Tables and Figures, Table 8.1.1.

8.4.8 Adverse Events of Special Interest

N/A

8.5 Additional Safety Evaluations

N/A

8.6 Safety Conclusions

There were no deaths, SAEs, or discontinuations considered related to vaccine administration by the investigator or the sponsor. Solicited systemic reactions were similar to the two licensed conjugated quadrivalent meningococcal vaccines. Local injection site reactions were similar between MenQuadfi and Menactra, which were both lower than the local reaction rate for Menveo. In the elderly, adverse event rates were higher in the MenQuadfi arm, when compared to the polysaccharide vaccine Menveo. Overall, MenQuadfi demonstrated an acceptable safety profile across all age groups.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

In this BLA, the applicant submitted three Phase 3 trials to demonstrate immunogenicity and safety in an MCV4 naïve population across the 2-9-year-old (study MET35), 10-55-year-old (study MET43), and 56-year-old and older (study MET 49) age groups. The applicant also submitted studies to support an indication of revaccination in those 15 years old and older who have been previously vaccinated with an MCV4 (study MET56) and to provide information when MenQuadfi is concomitantly administered with Adacel and Gardasil (study MET50). These studies are summarized as follows.

MET35: The primary immunogenicity objective of non-inferiority of MenQuadfi seroresponse compared to Menveo seroresponse was demonstrated in children aged 2-9

years old, with percent differences ranging from 7.6% for serogroup A (95% CI: 1.1%; 14.0%) to 47.4% for serogroup C (95% CI: 42.2%; 52.2%). Injection site reaction of pain was balanced across arms, while erythema and swelling were lower in MenQuadfi. Solicited systemic reactions (myalgia, malaise, headache, and fever) were balanced across vaccine arms.

MET43: For the first primary objective, the applicant demonstrated equivalence of hSBA GMTs across three lots and all four serogroups. In the second primary immunogenicity objective, MenQuadfi was shown to be non-inferior to Menactra in adolescents and adults aged 10-55 years old, with difference in percents ranging from 18.1% (95% CI: 14.5%; 21.9%) for serogroup Y to 40.9% (95% CI: 36.7%; 45.0%) for serogroup C. Solicited injection site and systemic reactions were balanced across the three lots of MenQuadfi and the Menactra arm.

MET50: In this open-label Phase 2 study, the primary objective was met supporting non-inferiority of MenQuadfi compared to Menveo in subjects 10-17 years of age. The sponsor tested non-inferiority of concomitant vaccines (Adacel and Gardasil) as secondary objectives, though did not power to meet these hypotheses. For the primary objective, non-inferiority criteria were successfully met for all four meningococcal serogroups. Solicited injection site and systemic reactions were balanced across the MCV4 arms, but higher in the concomitant vaccine arms.

MET49: The primary immunogenicity objective of non-inferiority of MenQuadfi seroresponse compared to Menomune seroresponse was demonstrated in older adults and the elderly aged at least 56 years old, with percent differences ranging from 15.7% for serogroup A (95% CI: 9.1%; 22.2%) to 31.0% for serogroup Y (95% CI: 24.6%; 37.0%). Injection site reaction of pain was higher in the MenQuadfi arm, and erythema and swelling were minimally higher in MenQuadfi. Solicited systemic reactions were slightly higher in MenQuadfi. However, this increase in AEs is expected when comparing a conjugated to an unconjugated vaccine.

MET56: The primary immunogenicity objective of demonstrating non-inferiority of MenQuadfi seroresponse compared to Menactra seroresponse was met in quadrivalent meningococcal conjugate vaccine (MCV4)-primed adolescents (≥ 15 to < 18 years) and adults (≥ 18 years), with percent differences ranging from 1.8% for serogroup Y (95% CI: -9.1%; 4.6%) to 7.4% for serogroup W (95% CI: 4.3%; 10.9%). The safety profiles were similar across the two vaccine arms.

10.2 Conclusions and Recommendations

In each of the three age groups, MenQuadfi was shown to be non-inferior to a currently licensed quadrivalent meningococcal vaccine when comparing seroresponse rates, and the primary objectives were fulfilled in the individual and pooled/integrated analyses. The statistical methods used to support these conclusions are acceptable, and there are no concerns on the adequacy of the above conclusions.

As demonstrated in the integrated safety analysis, the safety profile of MenQuadfi appears similar to the safety profile of the other two licensed conjugated meningococcal comparator vaccines, Menactra and Menveo, and improved over the licensed polysaccharide meningococcal comparator vaccine, Menomune. I defer to the clinical reviewer for further review on the acceptability of the full safety profile of MenQuadfi.

Based on my review of the statistical analyses and results presented in this BLA, I recommend approval of MenQuadfi for the proposed indication.