DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION
BLA

DATE:

FDA NUMBER: STN 125300

PRODUCT NAME: Menveo (Novartis ACYW-135 Vaccine)

SPONSOR: Novartis Vaccines & Diagnostics, Inc

SUBJECT: Evaluation of the Immunogenicity, Safety, Reactogenicity, Effectiveness and Lot Consistency of Menveo®

INDICATION: Immunization of individuals 11-55 years of age, for the prevention of disease caused by N. meningitis serogroups A/C/Y/W-135.

FROM: Barbara Krasnicka, PhD

THROUGH: A. D. Horne, Dr. P.H., Chief, Vaccine Evaluation Branch

TO: Willie Vann, PhD, Committee Chair, OVRR/DBPAP
Cara Fiore, PhD, Regulatory Project Manager, OVRR/DVRPA
LCDR Elizabeth Valenti, Regulatory Project Manager
OVRR/DVRPA

CC:

ChronFile/HFM-210
Amelia D. Horne, Dr. P.H/HFM-217
Margaret Bash, MD/HFM-475
Henry Hsu, Ph.D., MPH/HFM-215

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Introduction

Biologics License Application (BLA) STN 125300 was submitted on August 28th, 2008 by Novartis Vaccines and Diagnostics Inc. (Novartis) for licensing of Menveo® (Meningococcal (Groups A, C, W-135 and Y) CRM197 Oligosaccharide Conjugate; in short MenACWY) vaccine. The applicant seeks licensure for active immunization (by a single intramuscular administration) of individuals of age 11 through 55 years for prevention of invasive meningococcal disease caused by Neisseria meningitides, serogroups A, C, W-135 and Y, bacteria.

CBER sent the Complete Response Letter on June 26th, 2009. In the letter, the applicant was asked to supply additional clinical/statistical information, among others, evaluations of the influence of assay runs on the statistical analyses results, and explanations related to some SAEs. The applicant submitted responses to this CR letter on August 21st, 2009.

The statistical review is based on the applicant's submissions listed in Section 2.3.

1.2 Brief Overview of Clinical Studies

License application for use of MenACWY vaccine for subjects aged 11 to 55 years included safety and immunogenicity data obtained during three pivotal clinical studies (in that one safety pivotal study) and two supplemental clinical studies. A summary of the studies is given in Table 1.2.1.

Table 1.2.1: Summary of Clinical Studies

Study Protocol:	Primary Objectives	Study Population Age (years)	Total # of Subjects	Study Design	Test Product	# of subjects Exposed (at Visit 1)
Pivotal Studies						
V59P13 USA	Safety + Lot consistency + Immunogenicity	11-55 11-18 11-55	3432 1575 3432	Randomized Active-Controlled Multi-center Phase III	MenACWY Menactra	2649 875
V59P18 Costa Rica	Safety + Immune Response of MenACWY with or without Tdap and HPV	11-18	1620	Randomized, Open-Label Active-Controllled One-center Phase III	MenACWY +Tdap+HPV MenACWY then Tdap Tdap then MenACWY	540 541 539
V59P17 Colombia Argentina	Safety + (Immunogenicity)	19-55 56-65	2815	Observer-Blind, Randomized Active-Controlled Multi-center Phase III	MenACWY Menactra Menomune	1817 889 109
Supplemental Studies						
V59P6 USA	Safety + Immunogenicity	11-17	524	Single-Blind, Randomized Active-Controlled Phase III, Multi-center	MenACWY IM (b)(4) MenACWY IM Menomune	164 151 209
V59P11 Italy	Safety + Immune Response of MenACWY with or without Boostrix	11-17	524	Observer-Blind, Randomized Active-Controlled Phase III Multi-center	MenACWY IM with (b)(4) Boostrix MenACWY IM (b)(4) Boostrix	359 357 353

1.2 Conclusions, Major Statistical Issues, and Recommendations

The objective of this BLA submission was to provide evidence that MenACWY vaccine can be used for "*active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y.*" With regard to immunogenicity and safety of MenACWY, the applicant's approach was to demonstrate non-inferiority of MenACWY as compared to such licensed by FDA vaccines as Menactra and Menomune.

The statistical evaluation of the submission was based on three pivotal (V59P13, V59P18, and V59P17 (safety pivotal study)) and two supplemental studies.

In the case of Study V59P13, all three primary immunogenicity objectives (lot-to lot-consistency, two non-inferiority hypotheses for two age groups) were met. However, among participants aged 11-18 years, the seroresponse rates for 3 vaccine lots varied meaningfully for each serogroup, particularly for W135 (lot A 74%, lot B 80%, lot C 70%), although they were not consistently high or low for any single lot. Similar remarks are valid for percentages of participants with hSBA titer >1:8.

Additionally, it should be noted that the quality of V59P13 data is questionable. For example:

1. Without the pre-specification in the study protocol of the sample-size re-estimation, the numbers of subjects were increased in the immunogenicity subsets 6 months after finishing the study enrollment.
2. After the special second sample selection, data structure of the first randomization for the immunogenicity testing was not retained for the serogroups W and Y. For these groups, the effective randomization ratio for MenACWY vs. Menactra was 3.5:1.
3. Immunogenicity populations for serogroups W and Y were slightly younger for the MenACWY group (mean: 22, standard deviation: 12) than for the Menactra group (mean: 27, standard deviation: 14). Exploratory analyses showed that Age variable always had influence on the vaccine responses (titers).
4. Each serogroup had its own subset population. Thus, immunogenicity hypotheses were tested on different datasets that contained different number of subjects and sometimes different subjects.
5. The vaccine group assignment in two study sites has been unblinded. However, a statistical testing of a possible influence of these two sites on the primary endpoint results was performed by the applicant and the results revealed that outcomes from these two centers did not have a meaningful influence on the clinical study outcomes.

The second pivotal Study V59P18 was carried out in only one center in Costa Rica. The study population consisted of healthy adolescents 11 to 18 years of age. Subjects in the study received three types of vaccines: MenACWY, Tdap and GARDASIL. Based on a pre-BLA agreement between the applicant and CBER, the HPV safety and immunogenicity data for girls was planned to be reviewed as a separate BLA supplement (the use of GARDASIL was then not approved for boys). Therefore, for study V59P18,

only immune responses to MenACWY when given sequentially before or after Tdap were assessed by the reviewer. The assessment showed that the co-primary immunogenicity objective #3 (non-inferiority immunogenicity hypotheses based on the seroresponse) was not met. This means, the applicant cannot claim the study success because not all three co-primary hypotheses were met. There are also some issues related to the study design and data quality. The ethnic origin of all subjects participating in study V59P18 was Hispanic. As this type of ethnicity does not represent the spectra of the USA and some other countries populations, the study results cannot be fully extended onto other populations. However, a non-U.S. study location for V59P18 was accepted by CBER on the basis that the primary objective was to evaluate a possible interaction of the concomitant vaccinations and not to demonstrate the inferred efficacy. Another flaw of this study was that different serum assay runs were used for different study groups. Sera from Groups II and III were not assigned at random to assay runs. Therefore, additional bias may have been introduced into the results.

Regarding the MenACWY safety profile, based on the pivotal study V59P13, there was a noticeable trend of increased number of severe AEs in the MenACWY group. In the case of solicited severe local reactions, the difference was significant ($p = 0.018$, in the post-hoc analysis). SAEs were reported by 24 (0.93%) subjects (28 adverse events) from the MenACWY group and by 5 (0.59%) subjects (7 adverse events) from the Menactra group. The applicant claimed that none of the SAEs were assessed as related to either of the two study vaccines.

It is also important to note that in the pivotal study V59P13 eight events that occurred in the MenACWY group appear to have been suicide attempts. No such event was reported in the Menactra control group. Due to the observed imbalance in suicide attempts in study groups, the frequency of suicide attempts should be considered as a safety signal for the MenACWY group. Per the reviewer's research, to make any adequate comparison of suicide attempt rates between this study and the US general public is very difficult.

Additionally, it is worth noting that 2 cases of epilepsy and a case of seizure were observed in the MenACWY group. One miscarriage in the MenACWY group was not included by the applicant as a SAE in study V59P18. Also 3 spontaneous abortions occurred in study V59P17. One of these three spontaneous abortions in the MenACWY group was considered by the investigator as possibly related to the study vaccine and was counted as a SAE.

Recommendation: As the statistical evaluations of the three pivotal studies do not provide strong support of some applicant's claims about the MenACWY vaccine, the vaccine use may be considered for approval under conditions that a post-marketing safety study will be conducted and the vaccine will not be used, at this time, concomitantly/sequentially with the Tdap and HPV vaccines.

2. INTRODUCTION

2.1 Overview

MenACWY vaccine is a sterile liquid vaccine, administered by intramuscular injection, that contains N. meningitidis serogroups, A, C, W-135, and Y, oligosaccharides conjugated individually to C. diphtheriae CRM_{197} protein carrier. The vaccine is to prevent disease caused by Neisseria meningitidis, serogroups A, C, W-135, and Y, in adolescents and adults aged 11 to 55 years.

The proposed licensure of MenACWY is based on:

- Demonstration of lot–to-lot consistency
- Demonstration of vaccine efficacy (immunogenicity) as compared to Menactra vaccine
- Demonstration of vaccine safety as compared to Menactra and Menomune vaccines
- Demonstration of vaccine efficacy and safety when the vaccine is administered with sequential (Tdap) vaccination.

2.2 Data Sources

The applicant supplied various important SAS datasets at the time of the BLA submission (08/29/2008). A safety update for study V59P18 was submitted on 12/19/08 while the full data (with a new part of serological data) for this study was submitted on 02/24/09.

2.3 Material Reviewed

The statistical review of BLA submission STN125300 is based on the following main materials:

- STN 125300/0; Module 1; administrative information, labeling.
- STN 125300/0; Module 5; clinical study reports for studies V59P13, V59P17 and V59P18.
- STN 125300/0.2; Updates of the records on serious adverse events that occurred in study V58P18.
- STN 125300/0.3; The applicant's responses to the deficiency letter.
- STN 125300/0.4; The applicant's responses related to pregnancies study in V59P13, and the final immunogenicity data from study V59P17
- SSTN 125300/0.6; A supplementary report for study V59P18.
- STN 125300/0.9; Pediatric Plan.
- STN 125300/0.15; Complete Response to CBER's Complete Response Letter of June 26th, 2009.

3. STATISTICAL EVALUATION OF IMMUNOGENICITY DATA

3.0 List of Studies

Effectiveness of the final MenACWY formulation was evaluated based on the immunogenicity data collected during the following clinical trials:

- Study V59P13 (A comparative trial of the safety and immunogenicity of MenACWY versus Menactra in healthy adults aged 11 to 55 years)
- Study V59P18 (A comparative trial of the safety and immunogenicity of MenACWY alone versus MenACWY administered concomitantly with Tdap (Boostrix) and human Papillomavirus (HPV) (Gardasil™) vaccines, or with sequential Tdap (Boostrix) vaccination in healthy children aged 11 to 18 years).
- Study V59P17 (A comparative trial of the safety and immunogenicity of MenACWY versus Menactra in healthy subjects aged 19 to 55 years and versus Menomune in healthy adults aged 56 to 65 years).
- Study V59P6 (A comparative trial of the safety and immunogenicity of MenACWY (with or without adjuvant) versus Menomune in healthy children aged 11 to 17 years)
- Study V59P11 (A comparative trial of the safety and immunogenicity of MenACWY administered alone versus MenACWY administered concomitantly with Tdap (EU-licensed Boostrix) in healthy adolescents aged 11 to 25 years).

Of these five studies, three were considered pivotal (V59P13, V59P17 (only the safety part), and V59P18) and two supplemental.

Additionally, study V59P13 supplied data on lot-to-lot consistency.

3.1 Study V59P13

Title of the study: "A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age."

3.1.1 Brief Overview of the Study

Study design

The V59P13 clinical trial was a Phase III, randomized, multi-center, observer-blind, and active-controlled study. It was planned that approximately 3432 healthy subjects 11-55 years of age would be enrolled and randomized in a 1:1:1:1 ratio into one of four groups,

namely, MenACWY- Lot 1, MenACWY-Lot 2, MenACWY-Lot 3, and Menactra. The general outline of the study plan is given in Table 3.1.1.1.

Table 3.1.1.1: General outline of study V59P13 plan

Vaccine Group	Vaccine	Total of Subjects Enrolled	Age Stratitification - # of Subjects		
			11-18 years old	19-34 years old	35-55 years old
I	MenACWY- Lot 1		525	100	233
II	MenACWY-Lot 2		525	100	233
III	MenACWY-Lot 3		525	100	233
Subtotals	*MenACWY*	*2574*	*1575*	*300*	*699*
IV	Menactra	858	540	100	233

In reality, 3539 subjects were randomized, as discussed in Section 3.1.2. The enrolled subjects received single doses of either MenACWY or Menactra. These two vaccines differ, among others, by carrier proteins, CRM197 for MenACWY-CRM and diphtheria toxoid for Menactra. Randomization was stratified by center and age (2115 adolescents of age 11-18 years, 400 adults of age 19-34 years, and 932 adults of age 35-55 years).

Subjects participated in the study for up to six months from the moment of vaccination. The scheduled follow-up visit (Visit 2) took place at 29 days after randomization, and telephone contacts took place at 3-5 days and 165-195 days after vaccination. Each enrolled subject or his/her parents/guardians maintained a Diary Card during the first 30 days after vaccination and a worksheet for the remaining 120 days of the follow-up period. Information about the injection site, systemic adverse events, medications, and subject's body temperatures were to be recorded in the Diary Card daily throughout the first 7 days of the follow-up period, and then only adverse events necessitating a physician's visit were to be registered.

At Visit 1 (Day 1), prior to administration of a study vaccine, and at Visit 2 (Day 29), 20 ml blood samples were collected from all enrolled subjects. For all groups, immunogenicity testing was performed only for subsets of randomly selected subjects.

Objectives

Immunogenicity objectives:

1. Primary: To establish clinical lot-to-lot consistency, with respect to hSBA GMTs, pair-wise between three lots of MenACWY in adolescents aged 11 to18 years.
2. Primary: To demonstrate non-inferiority of MenACWY as compared to Menactra, as measured by the percentage of subjects with the observed seroresponse, in adolescents aged 11 to 18 years.
3. Primary: To demonstrate non-inferiority of MenACWY as compared to Menactra, as measured by the percentage of subjects with the observed seroresponse, in adults aged 19 to 55 years.

4. Secondary: To establish clinical lot-to-lot consistency, pair-wise between three lots of MenACWY, as measured by the percentage of subjects with observed seroresponse and hSBA titer ≥1:8, in adolescents aged 11 to 18 years.
5. Secondary: To demonstrate non-inferiority of MenACWY as compared to Menactra, as measured: by the percentages of subjects with the observed seroresponse, hSBA titer ≥ 1:8, and hSBA titer ≥ 1:4, and by GMT ratios, in subjects aged 11 to 55 years.

For the purpose of objectives #2, 3, 4, and 5, by definition, seroresponse took place if:

- At least four-fold increase (relative to baseline) in hSBA titer at Day 29 was observed for a subject who had baseline titer ≥1:4,

or

- At least titer of 1:8 at Day 29 was observed for a subject who had hSBA baseline titer <1:4.

The applicant may declare a trial as positive if statistical significance is demonstrated for all primary endpoints.

Safety objective:

To compare the percentage of subjects with at least one severe systemic reaction to MenACWY during the first 7 days of the follow-up period, to the corresponding percentage of subjects with at least one severe systemic reaction to Menactra™, in subjects of age 11-55 years.

Hypotheses and sample size considerations

Primary immunogenicity hypotheses (lot-to-lot consistency):

The lot-to-lot consistency hypotheses were defined, for the age group 11-18 years and each serogroup A, C, W, and Y, as follows:

For all combinations of i≠j,

H_0: $\varphi_{ij} \leq 0.5$, or $\varphi_{ij} \geq 2$
H_a: $0.5 < \varphi_{ij} < 2$,

where $\varphi_{ij} = \mu_i/\mu_j$, and μ_i and μ_j are the means of GMT values for Day 29 and for the i^{th} and j^{th} lots, respectively.

Non-inferiority primary hypotheses

Non-inferiority primary hypotheses were defined, for two age groups (11-18 and 19 -55 years) and each serogroup A, C, W, and Y, as follows:

H_0: $P_{MenACWY} - P_{Menactra} \leq -0.1$,
H_a: $P_{MenACWY} - P_{Menactra} > -0.1$,

where $P_{MenACWY}$ and $P_{Menactra}$ are proportions of seroresponses for Day 29 for MenACWY and Menactra subjects, respectively.

In the protocol (page 63), the applicant stated that the sample size 3432 was needed to achieve overall power 82%. However, different numbers of serum samples for testing immunogenicity hypotheses were needed for different serogroups and, additionally, the applicant wanted to conserve human complement donor resources. Therefore, the applicant decided to assay a minimal number of evaluable subjects for each serogroup. A discussion on some problems related to immunogenicity serogroup data sets is presented in Paragraph 3.1.2.

History of Study Protocol

The original study protocol was submitted to CBER in October 2006, and was followed by two amendments.

In the first amendment, dated May 2007, the applicant introduced some major and six minor changes and provided clarification regarding the responsible study personnel, and defined the coordinating investigator and sites. Two former immunogenicity secondary objectives were changed to become primary objectives, the immunogenicity endpoint "4-fold rise in hSBA titer" was changed to "seroresponse" (defined in Section 3.1.1), the number of adults in the 35 to 55 year old age stratum was increased by 400 subjects, and medical history, safety assessment, and exclusion criteria were revised.

The second amendment was issued on December 20, 2007. The applicant revised the evaluation of non-inferiority of MenACWY relative to Menactra by increasing the size of the subject subsets to be analyzed for each of the four serogroups and by modifying the power calculations of the non-inferiority comparisons. The amendment also clarified that the immune response for assessing lot-to-lot consistency would be based on the percentages of subjects with a seroresponse, with hSBA titer $\geq$ 1:4, and with titer $\geq$ 1:8.

3.1.2 Evaluation of Study Immunogenicity Results

Disposition of Subjects

In total, 3539 subjects were randomized, but only 3524 (99.6%) subjects were vaccinated and 3442 (97%) subjects completed study procedures through Day 29. The first subject was enrolled on March 1st, 2007, and the last one on July 24th, 2007. During the first visit, 5 subjects withdrew consent. As of the Day 29 contact, 82 subjects were counted as discontinued. The most common reason for discontinuation was loss to follow-up.

The disposition of subjects through Day 29 is summarized in Table 3.1.2.1.

Table 3.1.2.1: Disposition of subjects through Day 29

	Study Treatment				Overall
	MenACWY		Menactra		
	Ages 11-18	Ages 19-55	Ages 11-18	Ages 19-55	
Randomized	1640	1023	540	336	3539
Vaccinated	1631	1018	539	336	3524
Discontinued	46 (3%)	24 (2%)	16 (3%)	11 (3%)	97 (3%)
Lost to Follow-up	31	19	12	9	71
Withdrew consent	10	0	2	1	13
Other Reason	5	5	2	1	13

In order to evaluate all primary and secondary immunogenicity objectives, the applicant utilized per protocol (PP) populations which were selected from subjects who provided evaluable serum samples and for whom titer results were available both before and after vaccination and for whom no major protocol deviations were noticed. Table 3.1.2.2 shows the numbers of subjects, stratified by vaccine, lot, and age group, included in each immunogenicity analysis.

Table 3.1.2.2: Summary of evaluable randomly chosen subjects per sero and age group

Age Group	Study Group	Total # enrolled	PP Population			
			A	C	W	Y
11 - 18 years						
	Lot 1	548	359	499	340	345
	Lot 2	548	357	493	341	345
	Lot 3	544	359	491	343	346
	Menactra	540	359	501	288	294
19 - 55 years						
	MenACWY	1023	963	961	484	503
	Menactra	336	321	318	292	306

The immunogenicity PP populations were selected from the study data for each sero and age group in a special way. As the sample sizes needed for testing consecutive serogroups C, A, Y, and W were different and the sizes decreased as per stated serogroup order, the random selection process started with the largest needed pool of subjects, i.e., the one for serogroup C. Then each next selection was performed only from the pool of previously selected subjects. This means that the immunogenicity tests for all four serogroups were performed only for subjects belonging to the last pool, i.e., to the serogroup W pool.

There were no noticeable differences with respect to demographic baseline characteristics among the MenACWY and Menactra groups of subjects. White subjects constituted 79% and 78% of MenACWY and Menactra groups, respectively, while females represented 58% of subjects in both groups. The mean age was about 23 years in both vaccination groups (range: 11 to 55 years, standard deviation: 13.6 years, median: 17 and 16 years for MenACWY and Menactra groups, respectively). For the age group 11-18, the

distribution of age in both vaccination groups was almost identical (mean: 14 years, median: 14 years, and standard deviation: 2.2 years).

Subjects were enrolled at 44 sites. On average, 80 subjects were enrolled per site (median 63, range: 1 to 347). There were three centers which enrolled less than 10 subjects.

Protocol Deviations

Per the applicant's report, at least one protocol deviation was reported for 951 (27%) subjects, in that at least one major and at least one minor protocol deviation were reported for 146 and 898 subjects, respectively. A summary of protocol deviations by age group is given in Table 3.1.2.3.

Table 3.1.2.3
A. Summary of major protocol deviations

Deviation	Ages 11-18		Ages 19-55	
	MenACWY (N=1640)	Menactra (N=540)	MenACWY (N=1023)	Menactra (N=336)
Any	80 (5%)	26 (5%)	34 (3%)	6 (2%)
Blood Draw Out of Acceptable Window	6 (<1%)	1 (<1%)	7 (<1%)	2 (<1%)
No Pre-vaccination Blood Draw	25 (1.5%)	6 (1%)	7 (<1%)	1 (<1%)
No Post-vaccination Blood Draw	48 (3%)	18 (3%)	18 (2%)	4 (<1%)
Entry Criteria Not Met	24 (1.5%)	10 (2%)	14 (1%)	
No Vaccine Administered	9 (<1%)	1 (<1%)	5 (<1%)	
Wrong Vaccine Administered	3 (<1%)	2 (<1%)	4 (<1%)	

B. Summary of minor protocol deviations

Deviation	Ages 11-18		Ages 19-55	
	MenACWY (N=1640)	Menactra (N=540)	MenACWY (N=1023)	Menactra (N=336)
Any	392 (24%)	135 (25%)	254 (25%)	101 (30%)
Prohibited Medication/Vacination	15 (<1%)	2 (<1%)	3 (<1%)	3 (<1%)
Visit/Contact out of Window	252 (15%)	89 (16%)	140 (14%)	69 (19%)
Entry Criteria Not Met	12 (<1%)	2 (<1%)	11 (1%)	7 (2%)
Procedure not Performed per Protocol	74 (4.5%)	30 (6%)	29 (3%)	10 (3%)
Possible Unblinding	93 (6%)	30 (6%)	109 (11%)	36 (11%)

The most frequent violations were: visit/contact outside the prescribed time window (550 (16%) subjects) and unblinding (268 (8%) subjects).

REVIEWER'S COMMENTS:

At least one protocol deviation was recorded for many subjects (951 (27%)), and 97 subjects withdrew prematurely from the study. The immunogenicity subset, i.e., the immunogenicity data set for which statistical analyses related to immunogenicity hypotheses were performed, was defined after collection of blood samples and after a special selection of samples for testing serum was applied by the applicant. The new random selection introduced an additional selection sampling error, and the data structure

of the first randomization with the ratio 1:1:1:1 was not retained (please see Table 3.1.2.2, serogroup W and Y) after the second selection.

In order to check/confirm the study results, the statistical reviewer ran statistical analyses using the MITT (Modified Intention-to-Treat) population which consisted of enrolled subjects who received a study vaccination and provided for testing at least one evaluable serum sample before or after vaccination.

The applicant reported that the evaluating investigators/study staff of two study sites had been unblinded to vaccine group assignment. To ensure that these incidents did not impact the study integrity, a statistical analysis testing for possible influence of these two sites on the primary endpoint results was performed by the applicant. The results revealed that outcomes from these two centers did not have a meaningful influence on the clinical study outcomes.

Immunogenicity results

I. Primary immunogenicity hypotheses

Primary Objective #1 - Lot-to-lot consistency

Objective #1, primary immunogenicity hypotheses, is related to the clinical lot-to-lot consistency. To support the hypotheses, the applicant should demonstrate that vaccines drawn from three different vaccine lots -- Lot A, Lot B, and Lot C -- elicit equivalent immune responses. For pair-wise comparisons, the 95% CI of the ratio of post-vaccination GMTs for each serogroup A, C, W, and Y should be entirely within the interval (0.5, 2). A summary of the results for the lot-to-lot consistency endpoint is presented in Table 3.1.2.4.

Table 3.1.2.4: Lot-to-lot consistency results for geometric mean titers at Day 29 based on the unadjusted statistical analyses

Serogroup	Lot A			Lot B			Lot C		
	N	GMT	95% CI	N	GMT	95% CI	N	GMT	95% CI
A	367	27.23	(22.56, 32.86)	371	31.39	(25.91, 37.99)	367	30.23	(25.20, 36.26)
C	508	81.94	(67.18, 99.96)	508	60.85	(50.00, 74.05)	501	67.9	(55.17, 83.56)
W	352	87.65	(75.13, 102.25)	357	110.22	(95.30, 127.47)	353	84.26	(72.71, 97.63)
Y	356	48.02	(39.96, 57.71)	358	58.62	(48.54, 70.78)	353	52.85	(44.50, 62.76)

Serogroup	Ratio of GMTs (95% CI)		
	Lot A vs. Lot B	Lot A vs. Lot C	Lot B vs. Lot C
A	0.82 (0.63, 1.07)	0.90 (0.69, 1.17)	1.04 (0.80, 1.35)
C	1.35 (1.02, 1.78)	1.21 (0.91, 1.61)	0.90 (0.67, 1.19)
W	0.76 (0.64, 0.98)	1.04 (0.84, 1.29)	1.31 (1.06, 1.61)
Y	0.82 (0.63, 1.07)	0.91 (0.71, 1.17)	1.11 (0.86, 1.43)

REVIEWER'S COMMENTS:

1. Three investigated lots did meet the pre-defined criteria for lot-to-lot consistency.

2. The estimated average values of GMTs for three lots were comparable for the A and Y serogroups.

3. For the lot-to-lot consistency testing, the reviewer performed exploratory analyses using regression models with adjustment for ASSAY, center, and baseline titers. In almost all cases, ASSAY and baseline titer were significant covariates in the models, which indicates that ASSAY and baseline titer may influence the post-vaccination titer responses. However, conclusions for the primary hypotheses based on these adjusted analyses were similar to those from the non-adjusted analyses.

Primary Objectives #2 and #3 - Non-inferiority Hypotheses

Objectives of the primary non-inferiority immunogenicity hypotheses were to compare immunogenicity of a single injection of MenACWY to that of a single injection of Menactra for different age groups. The comparisons were based on the percentages of subjects with seroresponse directed against N. meningitidis serogroups A, C, W-135, and Y, for each age group. To support the non-inferiority hypotheses, the applicant should demonstrate that the lower limit of the two-sided 95% CI for the difference of the percentages of seroresponses to MenACWY and Menactra for each serogroup was greater than -10%. A summary of the seroresponse rates is given in Table 3.1.2.5.

Table 3.1.2.5: Seroresponse rates at Day 29 Visit

A.: For 11-18 years of age

Serogroup	MenACWY Group		Menactra Group		Estimated difference of seroresponder rates
	n/N	Estimated Endpoint (%)	n/N	Estimated Endpoint (%)	
A	811/1091	74.34	240/363	66.12	8.22 (2.70, 13.74))
C	1129/1500	75.27	368/505	72.87	2.40 (-2.05, 6.85)
W	774/1039	74.49	184/292	63.01	11.48 (5.34, 17.62)
Y	712/1052	67.68	124/298	41.61	26.07 (19.80, 32.34)

B: For 19-55 years of age

Serogroup	MenACWY Group		Menactra Group		Estimated difference of seroresponder rates
	n/N	Estimated Endpoint (%)	n/N	Estimated Endpoint (%)	
A	655/978	66.97	219/323	67.8	-0.83 (-6.72, 5.06)
C	657/976	67.32	187/320	58.44	8.88 (2.73, 15.03)
W	246/490	50.2	119/294	40.48	9.73 (2.58, 16.87)
Y	287/510	56.27	122/308	39.61	16.66 (9.71, 23.62)

REVIEWER'S COMMENTS:

It may be concluded from Table 3.1.2.5, that two primary immunogenicity objectives #2 and #3 were met. The lower limit of the two-sided 95% CI for the difference of the percentages of seroresponses to the MenACWY and Menactra vaccines was greater than -10% (non-inferiority delta) for all four serogroups. Except for the case of age 19-55 years and serogroup A, the percentage of seroresponders was always higher among receivers of the MenACWY vaccine as compared to Menactra vaccine receivers. It is worth noting that when, for the non-inferiority testing, the reviewer performed exploratory analyses with adjustment for Age, in almost all cases (for 11-18 age group serogroups C, W, and Y, and for 19-55 age group serogroups A and Y), Age played a significant role in the models. This suggests that Age should be considered as an important factor in the estimations of the treatment effects.

II. Secondary immunogenicity hypotheses

Two secondary immunogenicity lot-to-lot consistency hypotheses (objectives #4 and #5)

Secondary objective #4.A: Lot-to-lot consistency based on the seroresponse rates

Secondary lot-to-lot consistency hypotheses 4.A are based on differences of the proportions of seroresponders. To support the hypotheses, the applicant should demonstrate that, for each serogroup A, C, W, and Y, and for all three pair-wise comparisons (Lot A vs. Lot B, Lot A vs. Lot C, and Lot B vs. Lot C), the 95% CI for the difference of the proportions of seroresponses to the administered MenACWY vaccine was within the interval (-10, 10). A summary of the results for the secondary lot-to-lot consistency endpoint 4.A is presented in Table 3.1.2.6.

Table 3.1.2.6: Differences of seroresponse rates at Day 29 visit for the age group 11-18 years

Serogroup	Estimated Difference (%) of Seroresponse Rates (95% CI)		
	Lot A vs. Lot B	Lot A vs. Lot C	Lot B vs. Lot C
A	-3.64 (-10.08, 2.80)	-6.13 (-12.48, 0.22)	-2.49 (-8.70, 3.72)
C	4.96 (-0.31, 10.24)	4.38 (-0.90, 9.66)	-0.58 (-6.05, 4.89)
W	-5.82 (-12.10, 0.46)	3.98 (-2.73, 10.69)	9.80 (3.38, 16.23)
Y	-5.95 (-12.78, 0.87)	0.77 (-6.28, 7.82)	6.72 (-0.13, 13.58)

REVIEWER'S COMMENTS:

Three investigated lots did not meet the pre-defined criteria for the secondary lot-to-lot consistency evaluation 4.A. This is especially evident for serogroup W, for which the 95% confidence limits for the estimated differences of the seroresponse ratios are in the range -12.10 to 16.23. Therefore, the applicant failed to achieve the secondary (based on post-vaccination seroresponse rates) immunogenicity objective of the lot-to-lot equivalency among the three lots for each serogroup represented in MenACWY.

Secondary objective #4.B: Lot-to-lot consistency based on the percentage of subjects with hSBA titer≥1:8

A summary of the lot-to-lot consistency results based on the percentage of subjects with hSBA titer≥1:8 is given in Table 3.1.2.7.

Table 3.1.2.7: Estimation of the differences in percentages of subjects with hSBA titer ≥ 1:8 at Day 29

Serogroup	Estimated Difference of Propotions of Subjects with hSBA titers >= 1:8 (95% CI)		
	Lot A vs. Lot B	Lot A vs. Lot C	Lot B vs. Lot C
A	-3.60 (-9.96, 2.76)	-5.92 (-12.19, 0.35)	-2.32 (-8.44, 3.81)
C	1.47 (-2.96, 5.90)	2.83 (-1.69, 7.34)	1.36 (-3.25, 5.96)
W	-2.30 (-5.18, 0.57)	-1.15 (-4.22, 1.92)	1.16 (-1.51, 3.82)
Y	-2.49 (-7.38, 2.41)	-2.67 (-7.56, 2.21)	-0.19 (-4.87, 4.50)

REVIEWER'S COMMENTS:

Three investigated lots did not fully meet the pre-defined secondary criteria for the lot-to-lot consistency based on the percentage of subjects with hSBA titer≥1:8. For serogroup A, the 95% confidence limits for the estimated difference of Lot A vs. Lot C is (-12.19, 0.35), i.e., beyond the interval (-10, 10). Therefore, the applicant failed to achieve the secondary 4.B (based on post-vaccination percentage of subjects with hSBA titer≥1:8) immunogenicity objective.

Secondary Objectives #5: Non-inferiority hypotheses (for age group 11 to 55 years)

Objective #5. A Non-inferiority of MenACWY as compared to Menactra, as measured by the percentages of seroresponders.

A summary of the results is given in Table 3.1.2.8.

Table 3.1.2.8: Differences of seroresponse rates at Day 29 visit in the age group 11-55 years

Serogroup	MenACWY Group		Menactra Group		Estimated difference in seroresponder rate (%)
	Estimated Endpoint (%)	95% CI	Estimated Endpoint (%)	95% CI	
A	70.86	(68.84, 72.81)	66.91	(63.25, 70.42)	3.95 (-0.001, 7.97)
C	72.13	(70.32, 73.89)	67.27	(63.95, 70.47)	4.86 (1.20, 8.52)
W	66.71	(64.29, 69.07)	51.71	(47.58, 55.82)	15.00 (10.32, 19.69)
Y	63.96	(61.52, 66.34)	40.59	(36.66, 44.62)	23.36 (18.79, 27.94)

REVIEWER'S COMMENTS:

Table 3.1.2.8 shows that the percentage of seroresponders for all fours serogroups was higher in the MenACWY group than in the Menactra group. The lower limit of the two-

sided 95% CI for the differences of the percentages of seroresponders between the MenACWY and Menactra groups was greater than -10% (non-inferiority delta) for all four serogroups. The greatest differences were observed for serogroups Y and W. However, please note that the study population was heterogeneous with respect to the reaction to the study vaccinations. Reviewer's analyses showed that the seroresponses to the vaccines were meaningfully different for strata 11-18, 19-34, 35-55, and the estimated differences in seroresponse rates were sensitive to adjustments for age stratum. The reviewer's analyses yielded results different from the ones shown in the last column of Table 3.1.2.8. For example, for serogroup W, for each age stratum: 11-18, 19-35, 36-55, the estimated differences in sero-responders rates were: 11.48%, 12.28%, and 8.56%, respectively, and the adjusted ('weighted') estimated difference in seroresponse rates for the whole range of age was 10.67%. However, the final conclusions on testing the secondary objective 5.A (non-inferiority hypotheses) remain unchanged, i.e., the hypotheses 5.A were met.

Objective #5. B For the age group 11-55 years, the second secondary non-inferiority hypotheses were connected with a comparison of MenACWY to Menactra with respect to the percentage of subjects with the hSBA titer ≥ 1:8 at Day 29. The percentages of subjects with hSBA titer ≥ 1:8 were higher in the MenACWY group than in the Menactra group (serogroup A: 72% vs. 69%, serogroup C: 83% vs. 79%, serogroup W: 95% vs. 89%, serogroup Y: 85% vs. 70%). The lower limit of the two-sided 95% CI for the difference of the percentages of subjects with hSBA titer ≥ 1:8 was greater than -10%. The applicant met the non-inferiority criterion 5.B for each serogroup. However, it is worth noting that when regression logistic models with adjustment for AGE and CENTER were utilized by the reviewer, in almost all cases, AGE and CENTER covariates were significant in the models.

Objective #5. C Similar results as discussed in 5.B sub-section were obtained for the percentage of subjects with hSBA titer ≥ 1:4.

Objective #5. D The last secondary non-inferiority hypotheses were related to the ratio of hSBA GMTs for the MenACWY and Menactra groups. To support the hypotheses, the applicant should demonstrate that the lower limits of the two-sided 95% CIs for the ratio of average hSBA GMTs for the MenACWY and Menactra groups were greater than 0.5 (non-inferiority delta) for all four serogroups. A summary of the results for the non-inferiority hypotheses related to the ratio of hSBA GMTs endpoint is presented in Table 3.1.2.9.

Table 3.1.2.9: Results of statistical analyses of non-inferiority based on hSBA GMTs at Day 29 post-vaccination by treatment groups for each serogroup

Serogroup A

Endpoint	Type of Statistical Analysis	MenACWY Group			Menactra Group			Estimated GMTs Ratio and 95% CI
		n	Estimated Endpoint	95% CI	n	Estimated Endpoint	95% CI	
GMT	non adjusting	2069	29.59	(27.21, 32.18)	686	22.07	(19.21, 25.37)	1.34 (1.14, 1.58)
GMT	adjusting **	2069	28.7	(26.46, 31.13)	686	22.83	(19.84, 26.27)	1.26 (1.07, 1.48)

Serogroup C

Endpoint	Type of Statistical Analysis	MenACWY Group			Menactra Group			Estimated GMTs Ratio and 95% CI
		n	Estimated Endpoint	95% CI	n	Estimated Endpoint	95% CI	
GMT	non adjusting	2476	63.25	(57.89, 69.11)	825	45.37	(39.05, 52.71)	1.39 (1.17, 1.66)
GMT	adjusting **	2476	56.01	(51.88, 60.47)	825	43.87	(38.39, 50.14)	1.28 (1.09, 1.49)

Serogroup W

Endpoint	Type of Statistical Analysis	MenACWY Group			Menactra Group			Estimated GMTs Ratio and 95% CI
		n	Estimated Endpoint	95% CI	n	Estimated Endpoint	95% CI	
GMT	non adjusting	1529	97.49	(90.09, 105.49)	586	55.51	(48.35, 63.72)	1.76 (1.51, 2.05)
GMT	adjusting **	1529	97.33	(90.00, 105.25)	586	56.9	(50.47, 64.15)	1.71 (1.49, 1.96)

Serogroup Y

Endpoint	Type of Statistical Analysis	MenACWY Group			Menactra Group			Estimated GMTs Ratio and 95% CI
		n	Estimated Endpoint	95% CI	n	Estimated Endpoint	95% CI	
GMT	non adjusting	1562	49.73	(45.40, 54.46)	606	19.76	(17.23, 22.65)	2.52 (2.13, 2.98)
GMT	adjusting **	1562	46.62	(42.57, 51.04)	606	21.37	(18.55, 24.62)	2.18 (1.85, 2.57)

** Day 29 post-vaccination estimations of GMTs, GMTs ratio ($GMT_{MenACWY}/GMT_{Menactra}$), and 95% CI were based on a regression model with adjustment for Pre-vaccination Titer and ASSAY variables.

REVIEWER'S COMMENTS:

As can be concluded from Table 3.1.2.9, the lower limits of the 95% CIs for the GMT ratios, as estimated alone or using a regression model with additional adjustments for pre-vaccination TITER and ASSAY factors, are greater than 0.5. This means that the antibody responses to MenACWY vaccine for the A, C, W, and Y serogroups are non-inferior to the responses to Menactra. The covariates pre-vaccination TITER and ASSAY were significant in the reviewer-generated exploratory regression models.

III. Exploratory analyses

A. *Analyses for X-fold Increases of hSBA MenA, MenC, MenW and MenY Antibodies*

In order to compare better two treatment groups (MenACWY and Menactra), four figures of reverse cumulative distribution of the x-fold increases of hSBA MenA, MenC, MenW and MenY antibodies are presented in Figs. 3.1 through 3.4.

Fig 3.1.1: Reverse cumulative distribution of the x-fold increases in hSBA MenA antibody (log scale)

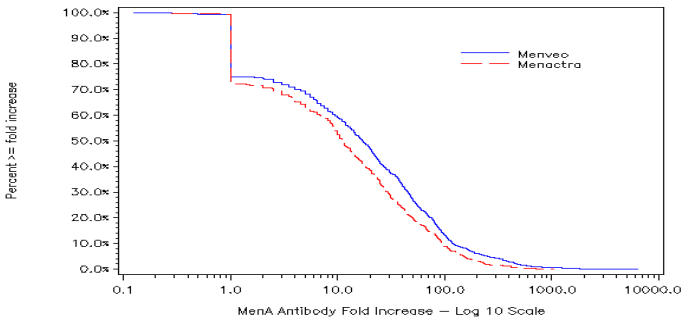


Fig 3.1.2: Reverse cumulative distribution of the x-fold increases in hSBA MenC antibody (log scale)

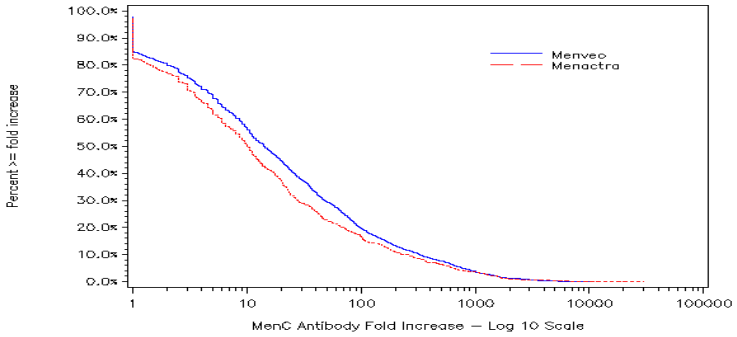


Fig 3.1.3: Reverse cumulative distribution of the x-fold increases in hSBA MenW antibody (log scale)

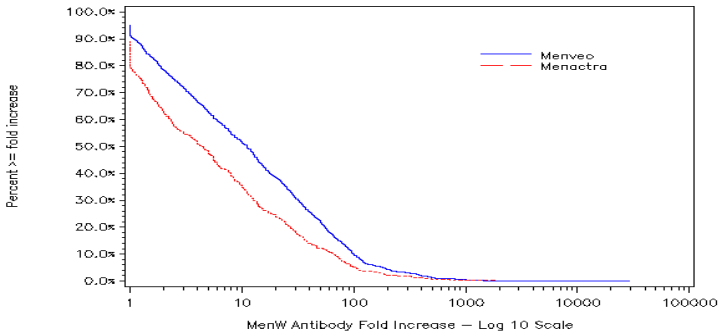
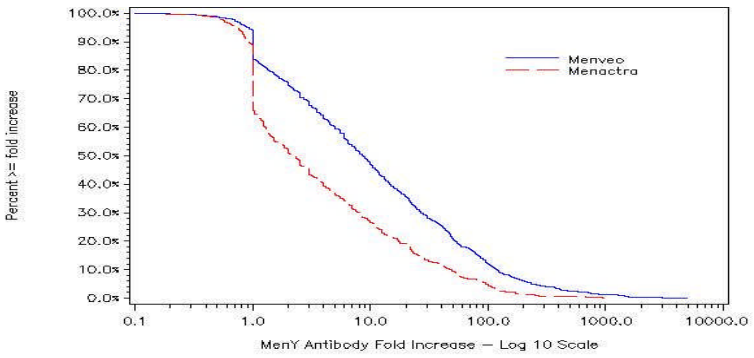


Fig 3.1.4: Reverse cumulative distribution of the x-fold increases in hSBA MenY antibody (log scale)



REVIEWER'S COMMENTS:

Please note that at least 10% of subjects did not have greater than 1-fold increases in hSBA for each serogroup antibody at Day 29 after vaccination. For serogroup A, not greater than 1-fold increases in hSBA MenA occurred for more than 25% subjects in both MenACWY and Menactra groups.

B. Analyses of GMTs per gender

A summary of the univariate analyses of the GMTs per gender and treatment (type of vaccination) is given in Table 3.1.2.10.

Table 3.1.2.10: Summary of statistical analyses of GMTs per gender and treatment

	GMT at Day 29					
	MenACWY			Menactra		
	Number of obs.	Estimated Endpoint	95% CI	Number of obs.	Estimated Endpoint	95% CI
Female						
Serogroup						
A	1270	28.96	(26, 32)	412	23.1	(19, 28)
C	1456	59.7	(53, 67)	476	45.3	(39, 55)
W	880	96.31	(87, 107)	360	54.92	(46, 66)
Y	892	50.78	(45, 58)	369	19.2	(16, 23)
Male						
Serogroup						
A	816	29.99	(26, 34)	279	20.8	(17, 26)
C	1040	67.05	(58, 77)	354	45.29	(36, 57)
W	680	99.6	(88, 112)	239	56.59	(46, 70)
Y	686	48.68	(43, 56)	242	20.61	(17, 26)

On average, at Day 29 after MenACWY or Menactra vaccination, females and males had similar titers for each serogroup. An ANCOVA model with adjustment for covariates Age, Gender, and Treatment was developed by the reviewer. Almost always, the covariates Treatment and Age were significant in the reviewer-generated exploratory

regression models. Utilizing the model, estimations of Day 29 GMTs were generated for both genders. The estimations with their 95% CIs are presented in Table 3.1.2.11.

Table 3.1.2.11: Summary of statistical analyses of GMTs per gender

	GMT at Day 29					
	Female			Male		
	Number of obs.	Estimated Endpoint	95% CI	Number of obs.	Estimated Endpoint	95% CI
Serogroup						
A	1682	25.33	(22, 28)	1095	25.61	(23, 28)
C	1932	52.7	(46, 60)	1394	53.64	(48, 60)
W	1240	76.07	(68, 85)	919	71.56	(65, 85)
Y	1261	30.16	(27, 34)	928	32.86	(30, 37)

C. Analyses of GMTs per site

It appears that results for GMTs, at Day 29 after MenACWY or Menactra vaccination, for different sites (or a combination of some sites with small number of subjects) were not similar/consistent, especially for serogroups C, W, and Y. Exploratory ANOVA models with two factors Treatment and Site were developed by the reviewer to check the influence of sites on the GMTs. In all models, the covariate Site was significant. Based on the univariate analyses, the ranges of GMTs for different sites after MenACWY vaccination are presented in Table 3.1.2.12.

Table 3.1.2.12: Ranges of site GMT after MenACWY vaccination

	GMT at Day 29	
Serogroup	Minimum	Maximum
A	18.8	44.4
C	28.2	84.4
W	56.8	169.6
Y	27.1	91.3

REVIEWER'S COMMENTS:

Reasons for site differences in GMTs are not clear. This variability of GMTs may be caused not only by site characteristics (population, etc) but could also be due to assay-to-assay variability. Additionally, please note that these analyses are only exploratory.

D. Analyses of GMTs per race

Day 29 GMTs after MenACWY vaccination by serogroup and race are shown in Table 3.1.2.13.

Table 3.1.2.13: Day 29 GMTs by serogroup and race

Serogroup	GMT (95% CI)			
	African-American	Asian	Latino/Hispanic	White/Caucasian
A	27.15 (20, 37)	62.22 (39, 99)	48.22 (34, 68)	27.31 (25, 30)
C	69.77 (51, 95)	140.74 (89, 223)	85.12 (62, 117)	57.84 (52, 64)
W	81.58 (58, 114)	74.18 (44, 126)	118.80 (92, 154)	97.52 (90, 106)
Y	62.87 (45, 88)	60.66 (37, 99)	77.70 (55, 110)	46.56 (42, 52)

REVIEWER'S COMMENTS:

Numbers of subjects per race group utilized for the analyses were different for different serogroups. For example, for serogroup A, there were 163, 66, 138 and 1668 subjects in African-American, Asian, Latino/Hispanic and White/Caucasian race groups, respectively. It appears that the immune response to MenACWY vaccine measured by titers, on average, may depend on the race. However, please remember that these analyses were only exploratory and numbers of subjects in some race groups were rather small.

E. Analyses of GMTs per age group

Day 29 GMTs after MenACWY or Menactra vaccination arranged by serogroup and age group are shown in Table 3.1.2.14.

Table 3.1.2.14: Summary of statistical analyses of GMTs per age group

	GMT at Day 29					
	MenACWY			Menactra		
	Number of obs.	Estimated Endpoint	95% CI	Number of obs.	Estimated Endpoint	95% CI
Age Group 11-18						
Serogroup						
A	1105	29.56	(27, 33)	366	18.37	(15, 22)
C	1517	69.71	(62,78)	508	55.97	(46,68)
W	1062	93.43	(86, 102)	297	46.32	(39, 55)
Y	1067	52.99	(48,59)	301	18.53	(15, 22)
Age Group 19-34						
Serogroup						
A	298	35.1	(28, 44)	99	30.93	(31, 22)
C	298	59.39	(47, 75)	97	30.27	(20, 46)
W	142	112.75	(88, 145)	93	64.21	(47, 88)
Y	145	89.27	(66, 121)	94	25.44	(18, 36)
Age Group 35-55						
Serogroup						
A	683	26.88	(23, 32)	226	25.77	(20, 34)
C	681	50.41	(43, 59)	225	33.67	(25, 45)
W	356	104.89	(86, 128)	209	68.26	(52, 89)
Y	366	33.1	(27, 41)	216	19.34	(15, 25)

It appears that results for GMTs at Day 29 after MenACWY or Menactra vaccination for different age groups exhibit significant scattering. The biggest differences between MenACWY and Menactra vaccine responses in titers can be noticed in the 19-34 age group. Except for serogroups C and W, on average, vaccine responses in this age group were stronger than in other age groups.

3.1.3 Summary of the Statistical Results

In total, 3524 subjects were vaccinated and 3442 (97%) subjects completed study procedures through Day 29. MenACWY vaccine was administered to 2649 subjects while Menactra to 875 subjects. Baseline and other demographic characteristics were similar for both vaccine groups. All three primary immunogenicity objectives, lot-to-lot-consistency and two non-inferiority hypotheses for two age groups, were met.

Two secondary immunogenicity lot-to-lot consistency objectives (based on the differences of proportions of the seroresponders and the percentages of subjects with hSBA titer≥1:8) were not met. However, all three secondary immunogenicity non-inferiority hypotheses defined for the whole study population (subjects of age 11-55 years) were met.

It is important to note some issues connected with the data quality. They could influence the study results.

1. The numbers of subjects in the immunogenicity subsets were increased 6 months after finishing the study enrollment.
2. Each serogroup had its own subset, thus, immunogenicity hypotheses were tested on different datasets that contained different number of subjects and sometimes different subjects.
3. A special selection of samples for testing sera was applied by the applicant. As the sample sizes needed for testing consecutive serogroups C, A, Y, and W were different and the sizes decreased in the same order as stated, the random selection process started with the largest needed pool of subjects for serogroup C. Then each next selection was performed only from the pool of previously selected subjects. This means that the immunogenicity tests for all four serogroups were performed only for subjects belonging to the last pool, i.e., the serogroup W pool. However, after the second selection, the data structure of the first randomization was not retained for the serogroups W and Y for which the randomization ratio of MenACWY vs. Menactra became 3.5:1.
4. Immunogenicity populations for serogroups W and Y were slightly younger for the MenACWY group (mean: 22, standard deviation: 12) than for the Menactra group (mean: 27, standard deviation: 14). Exploratory analyses showed that Age variable always had influence on the vaccine response (titers).

The statistical reviewer performed statistical analyses on the study data which contained subjects who provided evaluable serum samples and for whom titer results were available before and/or after vaccination. The results of these analyses were similar to the applicant's results obtained for the pre-specified hypotheses for the PP study population.

In applicant's submission terms like 'superiority criterion met' and 'statistically superior' are mentioned. As such terms are not generally recognized/used in vaccine studies and may be misleading for patients/physicians, such terminology should be removed from the submission. Additionally, it is not certain that statistically significant differences in immunogenicity of two examined vaccines can be translated to clinically significant differences in efficacy. It should also be remembered that immunogenicity endpoints, measured by assay runs, are one dimensional outcome of immune response and these measurements bear some errors.

3.2. Study V59P18

Title of the study: "A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (Gardasil®) in Healthy Adolescents."

3.2.1 Brief Overview of the Study

History of the Study Protocol

The original study protocol, issued on 05/21/ 2007, was followed by two major amendments:

1. Amendment 1, submitted on 11/13/2007; it introduced nine changes to the original study protocol, e.g., updated total number of subjects.
2. Amendment 2, submitted on 04/03/2008; it introduced 26 changes to the protocol and included a SAP.

In the last amendment, among other modifications, a new primary objective was added, namely, the previous secondary objective 'To demonstrate that the immune response to MenACWY administered alone one month after Tdap is not inferior to the immune response to MenACWY administered alone one month prior to Tdap' was elevated to become the third co-primary objective.

Study design

Study V59P18 was a Phase III open-label, controlled, randomized study to evaluate the safety and immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papilloma virus (HPV), Types 6, 11, 16, 18, recombinant vaccine (GARDASIL®) to healthy adolescents 11 to 18 years of age. The study was carried out in Costa Rica.

In total, 1620 healthy subjects of age 11-18 years were randomized in a 1:1:1 ratio into 3 arms (I, II, and III) of the study. At Day 1 (Visit 1), the following vaccines were administered: in Group I - MenACWY concomitantly with Tdap and HPV, in Group II - only MenACWY, and in Group III - only Tdap. The randomization was stratified by center and age (11-14 and 15-18 years of age). However, additional vaccines were administered at later days as shown in Table 3.2.1.1.

Table 3.2.1.1: The general structure of study V59P18

Study Arm (N)	Month 0 Visit 1	Month 1 Visit 2	Month 2 Visit 3	Month 4 Visit 4	Month 6 Visit 5	Month 7 Visit 6	Month 8 Visit 7	Month 9 Visit 8
I (540)	Serology **MenACWY + Tdap + HPV**	Serology	**HPV**		**HPV**	Serology		
II (541)	*Serology*	*Serology*	Serology					Serology
	Follow-up							
	MenACWY	*Tdap*	**HPV**	**HPV**			**HPV**	
III (539)	*Serology*	*Serology*	Serology					Serology
	Follow-up							
	Tdap	*MenACWY*	**HPV**	**HPV**			**HPV**	

Study Objectives

The applicant formulated the following objectives pertaining to the whole study:

Immunogenicity objectives:

1. Primary: To demonstrate that the immune responses to MenACWY vaccine, when co-administered with Tdap and HPV vaccines, were non-inferior to the corresponding antibody responses when MenACWY vaccine was given alone (comparison of Group I vs. Group II, Visit 2).
2. Primary: To demonstrate that the immune responses to Tdap vaccine, when co-administered with MenACWY and HPV vaccines, were non-inferior to the corresponding antibody responses when Tdap vaccine was given alone (comparison of Group I vs. Group III, Visit 2).
3. Primary: To demonstrate that the immune responses to MenACWY administered alone one month after Tdap were non-inferior to the immune response to MenACWY administered alone one month prior to Tdap, as measured by seroresponses directed against N. meningitidis serogroups A, C, W, and Y.
4. Secondary: To demonstrate that the immune responses to HPV vaccine, when the 1st dose was co-administered with MenACWY and Tdap, were non-inferior to the corresponding antibody responses to HPV vaccine given alone.
5. Secondary: To demonstrate that the immune responses to Tdap administered alone one month after MenACWY were non-inferior to the immune responses to Tdap administered alone one month prior to MenACWY.

6. Secondary: To assess the immunogenicity of MenACWY as measured by hSBA GMTs and by the percentages of subjects with hSBA ≥1:4 and hSBA ≥1:8, for all N. meningitidis serogroups A, C, W and Y, when given: (a) concomitantly with Tdap and HPV; (b) alone; and (c) when given one month after Tdap.
7. Secondary: To assess the immunogenicity of Tdap administered alone or concomitantly with MenACWY and HPV, as measured by antidiphtheria and antitetanus GMCs and the percentages of subjects with a 4-fold rise over baseline of antibodies: anti-PT, anti- FHA, and anti-PRN titer.

For the purpose of objectives #2, 5, and 7, immunogenicity response of Tdap was characterized by:

- Percentage of subjects with anti-diphtheria toxin ≥0.1 IU/mL,
- Percentage of subjects with anti-tetanus toxin ≥0.1 IU/mL
- Seroresponse (4-fold increase as measured by ELISA) for pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN).

Safety objectives:

1. To describe and compare the safety profiles following a single injection of MenACWY given alone one month after Tdap and one month before Tdap.
2. To describe the safety profiles following a single injection of MenACWY given alone or concomitantly with Tdap and HPV vaccines.
3. To describe and compare the safety profiles following an HPV vaccine given alone or concomitantly with Tdap and MenACWY.

REVIEWER'S COMMENTS:

The study V59P18 population consisted of healthy adolescents 11 to 18 years of age. GARDASIL (HPV) vaccine was administered to all study subjects according to different schedules. However, in the US, at the time of the pre-BLA meeting and this BLA submission, GARDASIL was still not approved for boys and, additionally, the goal of this study was not to show that GARDASIL is immunogenic and safe for the male population. Due to this situation, during the pre-BLA meeting, CBER agreed to accept in the BLA 125300 submission only results related to evaluation of immune response to MenACWY when given sequentially before or after Tdap. Therefore, in this memo only immunogenicity data for Group II, Visit 1, 2, and 3, and Group III, Visit 1, 2, and 3, i.e., follow-up periods marked in green color in Table 3.2.1.1, were considered. This also means that only immunogenicity primary/secondary objectives #3, 5, and 6 are evaluated in this memo. However, it is important to stress that the whole study design was taken into consideration when evaluations of the immunogenicity (objective #3) and safety (safety endpoint #1) profiles following a single injection of MenACWY given alone one month after Tdap and one month before Tdap were performed.

Hypotheses and sample size considerations

Non-inferiority co- primary hypotheses (#3)

Non-inferiority co-primary hypotheses were defined, for each serogroup A, C, W, and Y, as follows:

H_0: $P_{III} - P_{II} \leq -0.1$,
H_a: $P_{III} - P_{II} > -0.1$,

where P_{II} and P_{III} are proportions of sero-responders, for Day 31, to MenACWY vaccine in Group II (Visit 2) and Group III (Visit 3), respectively.

In the final version of the protocol (Amendment 2, 03/11/08, page 20), the applicant stated that, "for all three co-primary hypotheses and for combining across the two sets of four MenACWY serogroups and five Tdap antigens," the overall power of the study was 80.1% with 500 evaluable subjects per group. Under the assumption that approximately 8% of subjects would be un-evaluable for the immunogenicity analyses, as per the applicant's estimation, 540 (should be 544 subjects, not 540) subjects per group were needed.

3.2.2 Evaluation of Study Immunogenicity Results

The study results presented by the applicant in the submission (Amendment 6, 02/24/09) were based on statistical analyses of data pertaining to immunogenicity and safety objectives of the whole study. However, the reviewer's further thorough evaluations of the applicant's results were based on data that excluded GARDASIL® vaccine use.

Disposition of Subjects

In total, 1620 subjects were randomized, but only 1410 (87%) subjects completed study procedures. As of Visit 3, 137 (9%) subjects were counted as discontinued. The most common reason for discontinuation was withdrawal of consent (79).

A disposition of subjects for whom analyses were performed is given in Table 3.2.2.1.

Table 3.2.2.1: Numbers of per protocol population subjects who were included in analyzes

Study Group	PP Population		
	Total # enrolled	MenACWY	Tdap
Group II - MenACWY then Tdap	541	490 (91%)	461 (86%)
Group III Tdap then MenACWY	539	458 (85%)	487 (90%)

The most frequent reasons for subjects not being included in the immunogenicity data analyses were: missing blood draw (at Visit 2 - 67 cases and at Visit 3 - 52 cases for MenACWY and 47 cases for Tdap), and not receiving the second vaccination (37 cases in Group III and 31 cases in Group II).

No noticeable differences with respect to demographic baseline characteristics among the groups of subjects were observed. The mean age was about 14 years in the three vaccination groups, and almost 100% of the study population was of Hispanic origin.

Protocol Deviations

Per the applicant's report, at least one protocol deviation was reported for 1054 (64%) subjects participating in the whole study. A summary of protocol deviations by age group is given in Table 3.2.2.2.

Table 3.2.2.2: Summary of protocol deviations

Deviation	Study Arm		
	I (N=540)	II (N=541)	III (N=539)
Any	344 (64%)	349 (65%)	361 (67%)
Blood Draw Out of Acceptable Window	184 (34%)	283 (52%)	289 (54%)
No Blood Draw	96 (18%)	147 (27%)	170 (32%)
No HPV vaccine Administered	96 (18%)	121 (22%)	148 (28%)
No MenACWY vaccine Administered			37 (6.9%)
No Tdap Vaccine Administered		31 (5.7%)	
Vaccine Administered Outside Window	228 (42%)	270 (50%)	255 (47%)
Withdrawals from the study	65 (12%)	69 (13%)	82 (15%)

The most frequent violations were: blood drawn outside the prescribed time window (756 cases) and vaccine administered outside the pre-defined window. Protocol deviations were approximately balanced over the three study groups.

REVIEWER'S COMMENTS:

Study P18 was carried out in Costa Rica in one center and almost all study subjects were of Hispanic origin. Ethnicity spectra of US and Costa Rica populations are different. Therefore, extension of the study results to the US population is questionable. Additionally, the quality of datasets may not be good. There were many missing information. Due to the missing data, almost every group of hypotheses was tested on a different subset of the study data. This means almost each hypothesis had "its own" PP (Per Protocol) population. The PP populations related to MenACWY, Tdap, and HPV hypotheses included 86% to 92%, 85% to 91% and 67% to 70%, respectively, of the enrolled population. Additionally, at least one protocol deviation was recorded for many subjects (1054 (64%)).
Due to many missing data, the statistical reviewer performed statistical analyses based on the population that included all subjects who actually received vaccination and provided evaluable serum samples before and/or after vaccinations.

Immunogenicity results

I. Primary immunogenicity hypotheses

Co-primary Objective #3 – Non-inferiority hypotheses based on seroresponse rates

The purpose of the co-primary #3 non-inferiority immunogenicity hypotheses was to examine a possible influence of administration of Tdap vaccine on responses to MenACWY. The applicant's goal was to prove, based on seroresponse rates, that the immunogenicity responses to MenACWY given after Tdap were non-inferior to the immunogenicity responses to MenACWY administered alone. For this purpose, the applicant should show that, for each serogroup, the lower limit of the two-sided 95% CI of the difference $P_{III} - P_{II}$, i.e., the difference between the percentages of subjects with seroresponse, one month after MenACWY vaccination, in Group III and II, was greater than -10%. A summary of the seroresponse rates and their confidence intervals is given in Table 3.2.2.3.

Table 3.2.2.3: Seroresponse rates at Day 29 visit after MenACWY vaccination (Group II and Group III)

Serogroup	Tdap then MenACWY (Group III)		MenACWY then Tdap (Group II)		Estimated difference in seroresponse rates
	n/N	Estimated Endpoint (%)	n/N	Estimated Endpoint (%)	
A	414/479	86.43	409/504	81.15	5.28 (0.69, 9.87)
C	400/478	83.68	423/505	83.76	-0.0008 (-4.7, 4.54)
W	312/479	65.14	393/492	79.88	-14.74 (-20.29, -9.20)
Y	376/480	78.33	416/505	82.38	-4.04 (-9.01, 0.92)

REVIEWER'S COMMENTS:

It may be concluded from Table 3.2.2.3, that the co-primary immunogenicity objective #3 was not met. The lower limit of the two-sided 95% CI for the difference of the percentages of seroresponse rates to MenACWY administered after Tdap and MenACWY alone was lower than -10% (non-inferiority delta) for the W serogroup (the lower limit of CI was -20.29). For other serogroups, the estimated differences of seroresponse rates were small and the lower limits of the two-sided 95% CIs were greater than -10%. The smallest difference was observed for serogroup C.

II. Secondary immunogenicity hypotheses

Secondary Objective #5 - Non-inferiority hypotheses for immune responses to Tdap (sequential administration)

The applicant's goal regarding the secondary objective #5 was to show that the immune responses to Tdap administered alone one month after MenACWY (Group II) vaccination were non-inferior to the immune responses to Tdap administered alone one

month prior to MenACWY vaccination (Group III). To support the hypotheses, the applicant should demonstrate that

1. for the diphtheria and tetanus antigens, lower limits of the two sided 95% CIs for the difference of the percentages (P_G) of subjects with -b(4)- anti-D toxin and anti-T toxin ≥ 1.0 IU/mL were greater than -10%, i.e., $P_{Group\ II} - P_{GroupIII} > -10$ for both types of antigens,
2. for the pertussis PT, FHA and PRN antigens, lower limits of the two-sided 95% CIs for the vaccine group ratios of the GMCs, i.e., for $GMC_{Group\ II}/GMC_{Group\ III}$, were greater than 0.67.

Results of statistical analyses pertaining to objective #5 are presented in Table 3.2.2.4.

Table 3.2.2.4: Statistical results showing effects of sequential vaccination with Tdap

		MenACWY then Tdap (Group II)			Tdap then MenACWY (Group IIII)			Estimated
		N	Estimated Endpoint	95% CI	N	Estimated Endpoint	95% CI	Difference of P_G Group II - Group III
Diphteria	P^*_G	488	100	(99.25, 100.00)	500	97.60	(95.85, 100.00)	2.40 (1.06, 3.74)
Tetanus	P^*_G	488	99.8	(98.86, 99.99)	500	99.80	(98.89, 99.99)	-0.0 (-0.57,0.57)
Pertussis antigen								Ratio Group II/Group III
PT	GMC	484	81.10	(74.03, 88.84)	495	62.96	(57.35, 69.11)	1.29 (1.13, 1.47)
FHA	GMC	485	1146.66	(1022.82, 1285.50)	498	499.87	(451.69, 553.18)	2.29 (1.97, 2.63)
PRN	GMC	485	1560.49	(1399.35, 1740.18)	498	1192.36	(1049.72, 1354.38)	1.31 (1.11, 1.55)

*Percentage of subjects with -b(4)- >=1.0 IU/mL.

One month after Tdap vaccination, almost all subjects in both groups had antibody concentrations against diphtheria and tetanus equal to or greater than 1.0 IU/mL. Exceptions were: in the case of tetanus, 1 subject in each group and in the case of diphtheria, 12 subjects in Group III.

For the pertussis antigens, non-inferiority for PT, FHA, and PRN (lower limits of the two-sided 95% CIs for the vaccine group ratios of the GMCs, i.e., for $GMC_{Group\ II}/GMC_{Group\ III}$) were not only greater than 0.67 but also greater than 1, for all three pertussis antigens. The non-inferiority hypotheses were met.

Secondary Objective #6 - Non-inferiority hypotheses for immune responses to MenACWY administered sequentially with Tdap

Remark: Please note that these hypotheses were not pre-specified in the protocol.

The applicant's goal for the secondary objective #6 was to assess that the immunogenicity responses, for all four serogroups, to MenACWY administered after Tdap were non-inferior to the responses when MenACWY was given alone. This time, the evidence would be based on three other criteria.

Part I - Non-inferiority hypotheses utilizing hSBA GMTs ratio

For this endpoint, the criterion for non-inferiority was: the lower limit of the two-sided 95% CI for the ratio of the GMTs ($GMT_{groupIII}$ at visit 3/$GMT_{Group\ II}$ at visit 2), one month after vaccination should be > 0.50.

Results of the reviewer's statistical analyses that utilized hSBA GMTs ratios are presented in Table 3.2.2.5.

Table 3.2.2.5: Results of statistical analyses for the non-inferiority of MenACWY when vaccine was administered sequentially with Tdap based on hSBA GMT ratios

Serogroup	Tdap then MenACWY (Group III)			MenACWY then Tdap (Group II)			Estimation	
	N	GMT	95% CI	N	GMT	95% CI	$GMT_{GroupIII}/GMT_{GroupII}$	95% CI
A	479	92.13	(78.44, 108.21)	504	63.42	(53.39, 75.33)	1.45	(1.15, 1.84)
C	478	67.82	(58.73, 78.32)	505	69.26	(59.18, 81.06)	0.98	(0.79, 1.21)
W	479	104.41	(91.55, 119.07)	492	160.48	(142.35, 180.92)	0.65	(0.55, 0.78)
Y	480	56.74	(49.50, 65.04)	505	80.72	(69.44, 93.83)	0.7	(0.57, 0.86)

REVIEWER'S COMMENTS:

The post-hoc non-inferiority hypotheses utilizing hSBA GMT ratio criterion were met for all four serogroups. However, for serogroups W and Y, when MenACWY was administered after Tdap , the hSBA GMTs were lower than when MenACWY was administered before Tdap. When adjusting for AGE and 'hSBA GMT' (at the time of MenACWY vaccination) covariates, the results for the ratios of hSBA GMTs and their 95% CIs are only slightly different. However, in the regression models for four serogroups, the factor 'hSBA GMT' (at the time of MenACWY vaccination) was always very significant, while AGE was significant only at the level 0.07 and only for the C serogroup. Results of exploratory analyses performed by the reviewer with adjustment for AGE and 'hSBA GMT' covariates are summarized in Table 3.2.2.6.

Table 3.2.2.6: Results of adjusted* statistical analyses,based on hSBA GMTs ratios, for the non-inferiority of MenACWY when vaccine was administered sequentially with Tdap.

Serogroup	Tdap then MenACWY (Group III)			MenACWY then Tdap (Group II)			Estimation	
	N	GMT	95% CI	N	GMT	95% CI	$GMT_{GroupIII}/GMT_{GroupII}$	95% CI
A	479	90.27	(77.15, 105.61)	504	64.66	(54.67, 76.48)	1.4	(1.11, 1.76)
C	478	67.34	(58.44, 77.59)	505	69.74	(59.95, 81.12)	0.97	(0.78, 1.19)
W	479	102.17	(90.02, 115.95)	492	163.91	(145.82, 184.25)	0.62	(0.52, 0.74)
Y	480	56.1	(49.09, 64.13	505	81.59	(70.37, 94.60)	0.69	(0.56, 0.84)

*Day 29 post-vaccination estimations of GMT, GMT ratios ($GMT_{Group\ III}/GMT_{Group\ II}$), and 95% CIs are based on regression models with adjustment for AGE and 'hSBA GMT' (at the time of MenACWY vaccination).

Part II – Post-hoc non-inferiority hypotheses for MenACWY based on hSBA titer ≥1:8 and titer ≥1:4

Based on the percentage of subjects with hSBA titer ≥ 1:4 and hSBA titer ≥ 1:8, the applicant showed that the lower limits of the two-sided 95% CIs of the difference $P_{III} - P_{II}$, i.e., the difference between the percentages of subjects in groups III and II with hSBA titer ≥ 1:4 and hSBA titer ≥ 1:8, respectively, one month after MenACWY vaccination, for each serogroup, were greater than -10%.

In summary, it may be concluded that the secondary immunogenicity post-hoc hypotheses (#6) were met.

III. Exploratory analyses

A. X-fold Increases of hSBA MenA, MenC, MenW and MenY Antibodies

In order to give better insight into the comparison of two treatment groups (MenACWY alone and MenACWY after Tdap) some figures of the reverse cumulative distributions of the x-fold increases of hSBA MenA, MenC, MenW, and MenY antibodies, at one month after vaccination, are presented in Figs. 3.2.1 through 3.2.4.

Fig 3.2.1: Reverse cumulative distribution of the x-fold increases in hSBA MenA antibody (log scale)

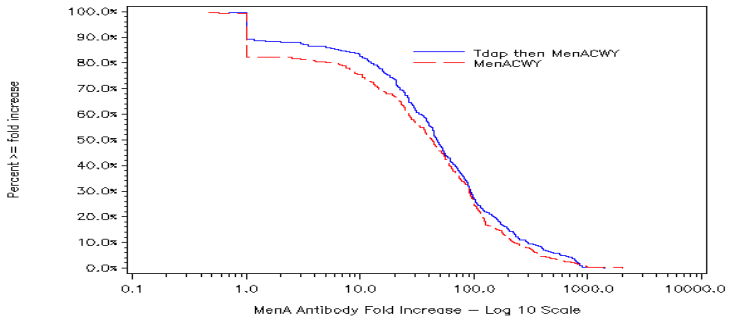


Fig 3.2.2: Reverse cumulative distribution of the x-fold increases in hSBA MenC antibody (log scale)

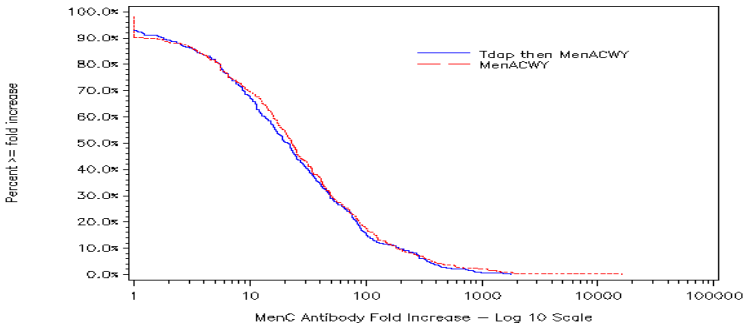


Fig 3.2.3: Reverse cumulative distribution of the x-fold increases in hSBA MenW antibody (log scale)

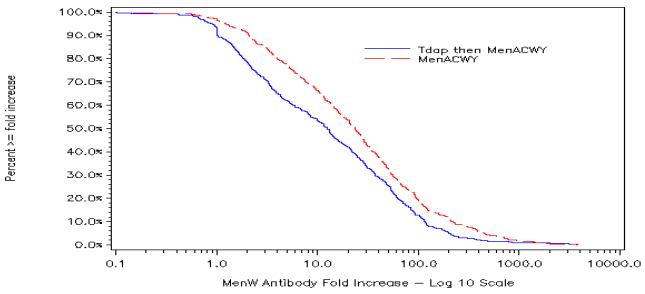
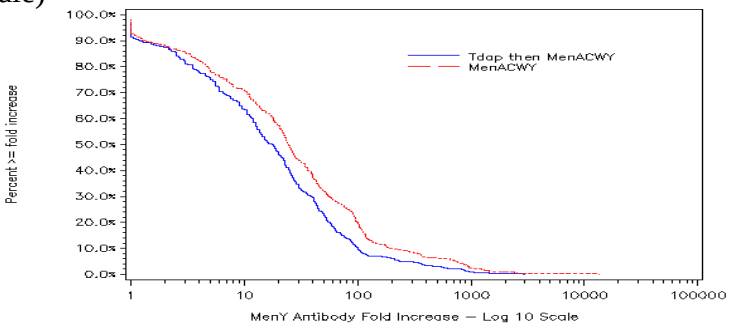


Fig 3.2.4: Reverse cumulative distribution of the x-fold increases in hSBA MenY antibody (log scale)



REVIEWER'S COMMENTS:

Please note that one month after vaccination at least 10% of the subjects had 1-fold or smaller increases in hSBA for each serogroup antibody. For serogroup A, 1-fold or smaller increases in hSBA MenA occurred for more than 20% subjects in Group II.

B. Analyses of GMTs per gender

A summary of the univariate analyses per gender of the GMTs is given in Table 3.2.2.7.

Table 3.2.2.7: Summary of statistical analyses per gender and treatment group for GMTs

	GMT one Month after MenACWY vaccination					
	Tdap then MenACWY (Group III)			MenACWY then Tdap (Group II)		
	Number of obs.	Estimated Endpoint	95% CI	Number of obs.	Estimated Endpoint	95% CI
Female						
Serogroup						
A	283	97.23	(78, 121)	287	65.38	(53, 82)
C	284	81.52	(68, 98)	289	83.62	(68, 102)
W	284	94.81	(80, 112)	284	177.67	(152, 208)
Y	284	54.05	(46, 64)	288	84.34	(69, 103)
Male						
Serogroup						
A	197	83.62	(26, 34)	219	61.81	(47, 81)
C	195	51.61	(58, 77)	217	54.71	(43, 70)
W	197	119.12	(88, 112)	216	141.51	(119, 169)
Y	197	61.22	(43, 56)	219	74.88	(60, 94)

REVIEWER'S COMMENTS:

The exploratory analyses of gender factor influence on GMTs one month after MenACWY vaccination revealed that for serogroups A and C, on average, females had higher titers than males, while for serogroups W and Y, males had higher titers than females. Moreover, when MenACWY was administered after Tdap, the hSBA GMTs were lower than when MenACWY was administered before Tdap.

C. Analyses per gender for Pertussis antigen

A summary of the univariate analyses per gender of the GMC pertussis antigen is given in Table 3.2.2.8.

Table 3.2.2.8: Summary of statistical analyses of GMCs per gender

	GMC one Month after Tdap vaccination					
	MenACWY then Tdap (Group II)			Tdap then MenACWY (Group III)		
	Number of obs.	Estimated Endpoint	95% CI	Number of obs.	Estimated Endpoint	95% CI
Female						
Pertussis Antigen						
PT	281	85.91	(76, 97)	288	54.86	(49, 62)
FHA	281	1061.63	(907, 1243)	291	423.84	(378, 476)
PRN	281	1183.46	(1183, 1597)	291	926.31	(791, 1082)
Male						
Pertusis Antigen						
PT	206	73.98	(64, 85)	209	76.92	(66, 90)
FHA	207	1255.1	(1069, 1474)	209	637.99	(535, 762)
PRN	207	1585.52	(1586, 2147)	209	1718.32	(1408, 2098)

The exploratory analyses of gender factor effect on pertussis antigen revealed that, on average, almost always males had higher antigen than females, except for PT in Group II.

Please note that, one month after Tdap vaccination, almost all subjects in both Groups II and III had concentrations of antibodies against diphtheria and tetanus equal to or greater than 1.0 IU/mL. Therefore, there was no reason to perform an exploratory statistical analysis evaluating influence of Gender on this output.

Remarks: Age and ethnicity subgroup analyses were not performed for this study because the whole study population was of Hispanic origin and the range of ages was from 11 to 18.

3.2.3 Summary of the Statistical Results

Study V59P18 was carried out in one center in Costa Rica. The population consisted of healthy adolescents 11 to 18 years of age. In total, 1620 subjects were enrolled into the study and 1410 (87%) subjects completed all study procedures. Baseline and other demographic characteristics were similar for the three vaccine groups. Subjects in the

study received three types of vaccines: MenACWY, Tdap, and GARDASIL. The vaccines were administered at different study time points depending on the study group. A non-U.S. study location for V59P18 was accepted by CBER on the basis that the primary objective was to evaluate a possible interaction of the concomitant vaccinations and not to demonstrate the inferred efficacy. Based on a pre-BLA agreement between the applicant and CBER, V59P18 HPV safety and immunogenicity data for girls were planned to be reviewed as a separate BLA supplement (GARDASIL was then not approved for boys in the US). Therefore, only immune responses to MenACWY given sequentially before or after Tdap were assessed by the reviewer.

The co-primary immunogenicity objective #3 (non-inferiority immunogenicity hypotheses based on seroresponse) was not met. Therefore, the applicant cannot claim study success (not all co-primary hypotheses were met) according to the pre-specified statistical criteria.

The secondary immunogenicity objective #5 (non-inferiority hypotheses for immune responses to Tdap) was met. However, please note that, from the statistical stand point, the secondary hypotheses should not even be considered when the primary hypotheses were not met. Other secondary immunogenicity non-inferiority hypotheses, with respect to immune responses to MenACWY administered sequentially with Tdap, were not pre-specified in the protocol. Therefore, they should be treated as exploratory analyses.

Additionally, some issues connected with the study design and data quality should be pointed out. The study was carried out in one Costa Rica center (ethnic origin – 100% Hispanic). Ethnicity spectra of US and Costa Rica populations are different. Therefore, extension of the study results to the US population is questionable. Moreover, quality of the datasets was not good. There were many missing information. Due to the missing data, almost every group of hypotheses was tested on a different subset of the study dataset. This means almost each hypothesis had “its own” PP (Per Protocol) population. The PP populations related to MenACWY, Tdap, and HPV hypotheses included 86% to 92%, 85% to 91% and 67% to 70%, respectively, of the enrolled population. At least one protocol deviation was recorded for 1054 (64%) subjects.

Different assay runs (hSBA) were used for different study groups. Sera from Groups II and III were not assigned at random to assay runs. Therefore, additional bias may have been introduced into the results.

4. Statistical Evaluations of Safety Data

4.1 Overview of safety data assessment

In the Integrated Summary of Clinical Safety (ISS), the applicant presents reports on three pivotal and two supplemental clinical studies in the indicated age range of 11-55 years. The safety profile of MenACWY was evaluated in 3,579 adolescents of age 11-18 years and in 2,606 adults of age 19-55, and results were presented in the application. Per

the applicant, no safety issue had been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS) at this time.

For safety assessment, the applicant presented only descriptive analyses and showed that there were no differences between MenACWY and Menactra vaccines regarding safety. However, the analysis was based on data that were pooled from 5 different studies. Studies were dissimilar with respect to populations and protocols (design, data collections, etc.). Therefore, it is unknown whether the safety profiles for these studies were comparable or not. For the sake of the safety assessment, the details of safety issues encountered in pivotal study V59P13 are discussed later.

Table 4.1.1 that was prepared based on the applicant's analyses presents an overview of the common solicited and unsolicited adverse events that occurred during the 7-day and 180-day post-vaccination periods, respectively, in all 5 studies under review.

Table 4.1.1 a: Overview of common solicited adverse events by vaccine groups based on the pooled data

	MenACWY		Menactra	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Days 1 to 7	N=6185		N=1757	
Solicited AE				
Any reaction	3966	0.6412	1146	0.6522
Severe	507	0.082	110	0.0626
Local reaction				
Any	2934	0.4744	906	0.51565
Severe	225	0.03637	54	0.0307
Systemic reaction				
Any	2740	0.443	725	0.4126
Severe	355	0.0574	70	0.0398
Other reaction	1180	0.1908	345	0.1964

Table 4.1.1 b: Overview of unsolicited adverse events that occurred during 180 days after vaccination; based on the pooled data

	MenACWY		Menactra	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Unsolicited AEs				
Days 1 to 29	N=6185		N=1757	
Any AE	1076	0.174	174	0.099
Any severe AE	59	0.0095	16	0.0091
Possibly related AEs	378	0.0611	133	0.0757
Any SAE	7	0.0011	4	0.00227
Possibly related SAEs	0		0	
Days 30 to 180	N= 5068		N = 1746	
Any AE	460	0.091	134	0.077
Any severe AE	42	0.0083	14	0.008
Possibly related AEs	3	0.0006	1	
Any SAE	31	0.0061	10	0.0057
Possibly related SAEs	1		0	

REVIEWER'S COMMENTS:

Based on the pooled data, rates of common solicited and unsolicited adverse events in both MenACWY and Menactra groups were similar. Few subjects had severe reactions that continued beyond Day 7.

4.2 Evaluation of V59P13 safety data

The reviewer's Table 4.2.1, which was prepared based on the applicant's analyses, presents a summary of the common solicited and unsolicited adverse events that occurred during the 7-day and 180-day post-vaccination periods, respectively. These events were reported either spontaneously or in response to general queries about changes in health status.

Table 4.2.1 a: Summary of solicited adverse events, Day 1 through Day 7

	MenACWY		Menactra	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Days 1 to 7	N=2649		N=875	
Solicited AE				
Any reaction	1649	0.62	585	0.67
Local reaction				
Any	1275	0.48	467	0.53
Severe	95	0.0359	17	0.0194
Systemic reaction				
Any	1086	0.41	350	0.4
Severe	94	0.0355	24	0.027
Other reaction	555	0.21	183	0.21

Table 4.2.1 b: Summary of unsolicited adverse events that occurred during 30 days after vaccination

	MenACWY		Menactra	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Unsolicited AEs				
Days 1 to 29	N=2621		N=866	
Any AE	509	0.194	174	0.2
Possibly related AEs	156	0.06	51	0.059
SAEs	4	0.0015	2	0.0023
Days 30 to 180	N= 2593		N = 849	
Any AE	253	0.098	60	0.071
Possibly related AEs	0		0	
SAEs	19	0.0073	3	0.0035

REVIEWER'S COMMENTS:

Tables 4.2.1 show frequencies of solicited and unsolicited adverse events. It can be concluded that frequencies of AEs for both treatment groups (MenACWY and Menactra) were similar. However, there was a noticeable trend of increased number of severe AEs in the MenACWY group. In the case of solicited severe local reactions, the difference was significant ($p = 0.018$).

SAEs were reported by 24 (0.93%) subjects (28 adverse events) in the MenACWY group and by 5 (0.59%) subjects (7 adverse events) in the Menactra group. The applicant claimed that none of the SAEs was assessed as related to either of the two study vaccines. Among 24 subjects from the MenACWY group, 5 of them reported 8 events that appeared to have been suicide attempts (0.62% per year) during the 6 months follow-up period. None occurred in the Menactra control group. The observed imbalance in suicide attempts may constitute, in the reviewer's opinion, a safety signal. In 'Clinical Responses' (page 50), the applicant stated that 'it is reasonable to accept that the rate of suicide attempts among adolescents ranges between 7-9% per year.' This conclusion was based on two references: Mulye et al, J Adolescent Health, 2009, and MMWR, surveillance summaries, 2002. According to Mulye's paper, in a school survey in 2007, 6.9% of high school students reported a suicide attempt. However, based on the other survey, the National Co-morbidity Survey (household survey, Kessler, JAMA 2005), the rate of suicide attempts among people aged 18 to 54 years was 0.6%. The findings of the three mentioned papers/reports are subject to some limitations and the studies were dissimilar with respect to study population, definition of suicide attempt event, etc. Additionally, please note that in study V59P13, events of attempted suicide required inpatient hospitalization and this definition was different than the definitions of suicide attempt in the above mentioned three references. Therefore, the percentage of attempted suicides in study V59P13 should not be compared to the results in the papers cited by the applicant. Due to the observed imbalance in suicide attempts in study groups, frequency of the suicide attempts in the MenACWY group should be considered as a safety signal. Additionally, it is worth noting that 2 cases of epilepsy and a case of seizure, other important SAEs, were observed in the MenACWY group. One miscarriage that occurred in the MenACWY group was not included by the applicant as a SAE.

4.3 Evaluation of V59P17 safety data

4.3.1 General Information

Study V59P17 was a Phase 3, randomized, controlled, multi-center trial to compare the safety and immunogenicity of MenACWY vaccine to the safety and immunogenicity of Menactra™ when one dose of a vaccine was administered to healthy subjects 19-55 years of age and to the safety and immunogenicity of Menomune® when one dose of a vaccine was administered to healthy subjects 56-65 years of age. The study was carried out in Argentina and Colombia. Ethnicity spectra of the US and study populations are different. Therefore, extension of the study results to the US population is questionable.

During a pre-BLA meeting, CBER agreed to accept in the BLA 125300 submission only results related to evaluation of safety of MenACWY vaccine when it was administered to healthy subjects 19-55 years of age. Therefore, in this memo, only safety data for population 19-55 years of age were considered.

A total of 2505 subjects aged 19 to 55 years were enrolled and randomized, in that 1606 and 899 subjects belonged to the MenACWY and Menactra groups, respectively. Overall, 44 subjects withdrew from the study, while 2461 subjects completed the protocol. Of the 44 subjects who withdrew, six withdrew the consent, 27 were lost to follow-up, and 11 were enrolled inappropriately. At least one major protocol deviation was reported for 51 subjects (32 (2%) MenACWY subjects and 19 (2%) Menactra subjects).

The primary objective of the study was to compare the percentage of subjects who experienced at least one severe systemic reaction to MenACWY with the percentage of subjects who experienced at least one severe systemic reaction to Menactra during the first 7 days (Days 1 to 7) following a single dose of a vaccine administered to healthy subjects 19 to 55 years of age. The null hypothesis associated with the primary safety objective was that the upper limit of the 2-sided 95% CI for the difference between the MenACWY and Menactra groups ($P_{MenACWY}$ - $P_{Menactra}$) in the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination was $\geq$ 6%.

4.3.2 Evaluation of V59P17 safety data

To support the primary safety non-inferiority hypothesis, the applicant should demonstrate that, the upper limit of the 2-sided 95% CI of the difference, $P_{MenACWY}$ - $P_{Menactra}$, of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (Days 1 to 7) after vaccination was < 6%. A summary of results of the primary safety analysis is given in Table 4.3.2.1.

Table 4.3.2.1: Primary Safety Analysis: rate of subjects with at least one severe systemic reaction, Days 1 to 7

	MenACWY Group (N=1588)		Menactra (N=882)		Estimated percent
Systemic Reaction	n	Estimated Endpoint (%)	n	Estimated Endpoint (%)	difference (95% CI)
Severe	95	5.98	46	5.22	0.77 (-1.11, 2.64)

The upper limit of the 2-sided 95% CI, 2.64%, was below the criterion set by the non-inferiority assumption (i.e., < 6%). Thus the primary objective was met. It can be concluded that MenACWY was non-inferior to Menactra in the percentage of subjects who experienced at least one severe systemic reaction.

Overall, 19 SAEs were reported during the study, 11 in the MenACWY group and 8 in the Menactra group. One of the three spontaneous abortions (in the MenACWY group) was considered by the investigator as possibly related to the study vaccine and was counted as SAE.

5. SUMMARY AND CONCLUSIONS

5.1 Summary of Statistical Results

The objective of this BLA submission was to provide evidence that MenACWY vaccine can be used for "*active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y.*" With regard to immunogenicity and safety of MenACWY, the applicant's approach was to demonstrate non-inferiority of MenACWY as compared to such FDA licensed vaccines as Menactra and Menomune.

The statistical evaluation of the submission was based on three pivotal studies (V59P13, V59P18, and V59P17 (safety pivotal study)) and two supplemental studies.

In the case of Study V59P13, all three primary immunogenicity objectives (lot-to-lot-consistency, two non-inferiority hypotheses for two age groups) were met. However, among participants aged 11-18 years, the seroresponse rates for 3 vaccine lots varied meaningfully for each serogroup, particularly for W135 (lot A 74%, lot B 80%, lot C 70%), although they were not consistently high or low for any single lot. Similar remarks are valid for percentages of participants with hSBA titer >1:8.

Additionally, it should be noted that the quality of V59P13 data is questionable. For example:

1. Without the pre-specification in the study protocol of the sample-size re-estimation, the numbers of subjects were increased in the immunogenicity subsets 6 months after finishing the study enrollment.
2. After the special second sample selection, data structure of the first randomization for the immunogenicity testing was not retained for the serogroups W and Y. For these groups, the effective randomization ratio for MenACWY vs. Menactra was 3.5:1.
3. Immunogenicity populations for serogroups W and Y were slightly younger for the MenACWY group (mean: 22, standard deviation: 12) than for the Menactra group (mean: 27, standard deviation: 14). Exploratory analyses showed that Age variable always had influence on the vaccine responses (titers).
4. Each serogroup had its own subset population. Thus, immunogenicity hypotheses were tested on different datasets that contained different number of subjects and sometimes different subjects.
5. The vaccine group assignment in two study sites has been unblinded. However, a statistical testing of a possible influence of these two sites on the primary endpoint results was performed by the applicant and the results revealed that

outcomes from these two centers did not have a meaningful influence on the clinical study outcomes.

The second pivotal Study V59P18 was carried out in only one center in Costa Rica. The study population consisted of healthy adolescents 11 to 18 years of age. Subjects in the study received three types of vaccines: MenACWY, Tdap and GARDASIL. Based on a pre-BLA agreement between the applicant and CBER, the HPV safety and immunogenicity data for girls were planned to be reviewed as a separate BLA supplement (the use of GARDASIL was then not approved for boys). Therefore, for study V59P18, only immune responses to MenACWY when given sequentially before or after Tdap were assessed by the reviewer. The assessment showed that the co-primary immunogenicity objective #3 (non-inferiority immunogenicity hypotheses based on the seroresponse) was not met. This means, the applicant cannot claim the study success because not all three co-primary hypotheses were met. There are also some issues related to the study design and data quality. The ethnic origin of all subjects participating in study V59P18 was Hispanic. As this type of ethnicity does not represent the spectra of the USA and some other countries populations, the study results cannot be fully extended onto other populations. However, a non-U.S. study location for V59P18 was accepted by CBER on the basis that the primary objective was to evaluate a possible interaction of the concomitant vaccinations and not to demonstrate the inferred efficacy. Another flaw of this study was that different serum assay runs were used for different study groups. Sera from Groups II and III were not assigned at random to assay runs. Therefore, additional bias may have been introduced into the results.

Regarding the MenACWY safety profile, based on the pivotal study V59P13, there was a noticeable trend of increased number of severe AEs in the MenACWY group. In the case of solicited severe local reactions, the difference is significant ($p = 0.018$, in the post-hoc analysis). SAEs were reported by 24 (0.93%) subjects (28 adverse events) from the MenACWY group and by 5 (0.59%) subjects (7 adverse events) from the Menactra group. The applicant claimed that none of the SAEs were assessed as related to either of the two study vaccines.

It is also important to note that in the pivotal study V59P13, eight events that occurred in the MenACWY group appear to have been suicide attempts. No such event was reported in the Menactra control group. Due to the observed imbalance in suicide attempts in study groups, the frequency of suicide attempts should be considered as a safety signal for the MenACWY group. Per the reviewer's research, any adequate comparison of suicide attempt rates between this study and the US general public is very difficult.

Additionally, it is worth noting that 2 cases of epilepsy and a case of seizure were observed in the MenACWY group. One miscarriage in the MenACWY group was not included by the applicant as a SAE in study V59P18. Also 3 spontaneous abortions occurred in study V59P17. One of these three spontaneous abortions in the MenACWY group was considered by the investigator as possibly related to the study vaccine and was counted as a SAE.

5.2. Recommendations

As the statistical evaluations of the three pivotal studies do not provide strong support of some applicant's claims about the MenACWY vaccine, the vaccine use may be considered for approval under conditions that a post-marketing safety study will be conducted and the vaccine will not be used, at this time, concomitantly/sequentially with the Tdap and HPV vaccines.