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

FDA NUMBER: STN 125300/226

PRODUCT NAME: MENVEO® (Novartis ACYW-135 Vaccine)

SPONSOR: Novartis Vaccines & Diagnostics, Inc

SUBJECT: Statistical evaluation of the sBLA MENVEO® infant/toddler vaccine

INDICATION: Active immunization of infants from 2 months to 2 years of age for the prevention of invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y

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1. Executive Summary

Note
This BLA review was written in support of a CR letter to the applicant and should not be treated as the final statistical review. Future applicant's response to the CR letter may influence the final review conclusions. Therefore, the statistical reviewer reserves the right to revise conclusions and update this review upon receipt of additional material and applicant's responses.

1.1 Introduction

MENVEO® (referred to as MenACWY), produced by Novartis Vaccines and Diagnostics Inc., is a meningococcal CRM197 oligosaccharide conjugate vaccine for prevention of invasive disease caused by Neisseria meningitides, serogroups A, C, W-135, and Y, bacteria. Administration of a single dose of vaccine in adolescents and adults 11 to 55 years of age was approved in February 2010. An expansion of this indication for the vaccine use in children 2 to 10 years of age was approved in January 2011.

The goal of the efficacy sBLA 125300/226 (revision of the sBLA 125300/201), submitted on April 13th, 2011, is to expand the indication of the MenACWY® to infants starting at 2 months of age.

The same vaccine formulation as for individuals aged 2 years and greater is being proposed for children 2 to 23 months of age. While the formulation remains the same, the proposed dosing regimen for infants and toddlers differs from that approved for the older populations. Based on the applicant's research, a single dose of MenACWY led to adequate immune responses for subjects 2 to 55 years of age. However, for infants and toddlers, multiple doses of MenACWY vaccine appear to be necessary for protection. The data from some studies carried out in infant and toddler populations indicated that the dosing regimen for MenACWY for younger infants, i.e., between 2 to < 6 months of

age, could be 3 doses separated by at least 6 weeks, with the fourth dose in the complete series to be administered in the second year of life. For older infants/toddlers (i.e., ≥6 months of age), 2 doses separated by at least 2 months may be adequate for the complete series, with the second dose to be administered in the second year of life. The evidence supporting the proposed schedules was generated in some studies by using different dosing regimens and formulations. These studies are discussed in detail in this statistical review.

1.2 Brief Overview of Clinical Studies

The applicant submitted safety and/or immunogenicity data from seven clinical trials in infants/toddlers aged 2-23 months to support the proposed expansion of licensure of MENVEO® (MenACWY). These seven clinical trials include three pivotal clinical studies (V59P14, V53P23 (only safety), and V59P21) conducted in the US, Argentina, Colombia, and Saudi Arabia and four supportive studies conducted in various countries. A summary of the studies is shown in Table 1.2.1.

Table 1.2.1: Summary of Clinical Studies Characteristics

Study Protocol:	Primary Objectives	Study Population Age	Study Design	Test Product	# of subjects
Pivotal Studies					
V59P14 **USA** **Argetyna** **Colombia**	Safety of and Immune response to MenACWY given with routine infant vaccine vs routine infant vaccine alone	Infants 2 months	Open -Label Randomized Multicenter Phase III	MenACWY + Routine Vaccines Routine Vaccines	3022 1511
V59P23 **USA** **S.&C.** **America** **Saudi Arabia**	Safety of MenACWY given with or without routine Infant vaccines	Infants 2 months	Open -Label Randomized Multicenter Phase III	MenACWY + Routine Vaccines Routine Vaccines	1973 1973
V59P21 **USA**	Safety of and Immune response to MenACWY given with or after ProQuad or ProQuad alone	Infants 7 - 12 months	Open -Label Randomized Multicenter Phase III	MenACWY+ProQuad MenACWY followed by ProQuad ProQuad	500 503 600
Supplemental Studies					
V59P9 **Canada**	Safety of and immune response after one or two doses of MenACWY	Infants 6 - 12 months	Open -Label Partialy-Randomized Multicenter Phase II	MenACWY Menjugate followed by MenACWY	125 50
V59P8 **USA**	Safety of and Immune response to MenACWY vs Menomune	Children 2-7 years Toddlers	Single-Blind Partialy-Randomized Multicenter	MenACWY MenACWY +PCV7 MenACWY + DTaP	453 71 73

		12-23 months	Phase II	Menomune	310
V59P7 **Finland** **Poland**	Safety of and Immune response to MenACWY -------(b)(4)---------- vs Mancevax	Toddlers/Children 12-35 months Children 36-59 months	Observer-Blind Randomized Phase II Multi-center	MenACWY (b)(4) MenACWY Mancevax followed by MenACWY	205 331 81
V59P5 **UK** **Canada**	Safety of and Immune response to MenACWY given with routine infant vaccine Persistence of antibodies Booster and memory response	Infants 2 months	Open -Label Randomized Multicenter Phase II	MenACWY (b)(4) Boost MenACWY (b)(4) MenACWY(b)(4) then 1/5th of Menomune MenACWY with MenACWY Boost MenACWY(b)(4) then 1/5th of Menomune Menjugate with MenACWY (b)(4) Boost	229 49 98 135 45 45

Source: Reviewer's Analysis

1.3 Conclusions, Major Statistical Issues, and Recommendations

The statistical evaluation of the safety and immunogenicity of the four-dose regimen of MENVEO administered to infants/toddlers at 2, 4, 6, and 12-16 months of age, is based mainly on the data collected during the Phase III safety and immunogenicity clinical trial V59P14 (conducted in the US and Latin America) and during safety clinical trial V59P23 (conducted in the US and other countries). Furthermore, the pivotal clinical trial V59P21, submitted in this sBLA, included data allowing characterization of the immune response, in older infants and toddlers, to a 2-dose catch-up series (two injections administered at least 2 months apart, with the second dose of vaccine administered in the second year of life) of MENVEO. However, data collected in these three pivotal clinical trials and submitted by the applicant have inconsistencies, are not currently verifiable, and may not be sufficient to draw firm conclusions. Thus, the data as submitted by the applicant are limited in demonstrating the safety and immunogenicity of MENVEO in infant and toddler populations.

After each section that summarizes a given pivotal study, the statistical reviewer presents a summary of evaluation results and discusses major statistical issues related to the clinical trial under consideration. A separate document (CR letter) gives a comprehensive list combining both clinical and statistical recommendations and questions to the applicant.

2. Introduction

2.1 Overview

MenACWY vaccine is a sterile liquid, administered by intramuscular injection, that contains *Neisseria meningitidis* serogroups A, C, W-135, and Y, oligosaccharides

conjugated individually to C. diphtheriae CRM_{197} protein carrier. The vaccine is intended to prevent invasive meningococcal disease caused by Neisseria meningitides, serogroups A, C, W-135, and Y, bacteria. The applicant submitted a supplement to the Biologics License Application (sBLA STN 125300/226) and seeks extension of the use of MENVEO® (MenACWY) to infants (starting at 2 months of age) and toddlers.

The main objectives of this sBLA are to demonstrate:

1. The safety and immunogenicity of MenACWY when administered as:
    a. a 4-dose series in young infants - beginning at 2 months of age with the fourth dose administered in the second year of life
    b. a 2-dose 'catch-up' series in older infants and toddlers - starting from 6 months of age with the 2 doses administered at least 2 months apart, and the second dose given in the second year of life
2. A possibility of integration of MenACWY (MENVEO) vaccination with the existing schedule of routine infant and toddler vaccinations with an overall acceptable safety profile and without interfering with the immune responses to routine vaccines.

2.2 Data Sources

The clinical study reports (CSRs) and SAS datasets, as well as other related materials, were provided by the applicant at the time of the sBLA STN 125300/226 submission and were located in Module 5 of the eCTD submission package. This statistical review is based on the clinical study reports (CSRs) for the pivotal studies V59P14, V59P23, and V59P21, and for four supportive studies V59P5, V59P7, V59P8, and V59P9. The applicant supplied various SAS datasets (with proper documentations) that were used for verification of the results by the statistical reviewer who also performed independent statistical analyses.

2.3 Material Reviewed

The statistical review of the STN125300/226 sBLA submission is based on the following main materials:

- STN 125300/226; Module 1; administrative information, labeling.
- STN 125300/226; Module 5; clinical study reports/datasets for pivotal studies V59P14, V59P23 and V59P21, and supporting studies.
- STN 125300/226; Module 5; report on analyses of data from more than one study (ISE and ISS– integrated summary of efficacy and safety).

3. Statistical Evaluation of Immunogenicity

To support the proposed indication for the use of MenACWY in infants/toddlers 2 to 23 months of age (US IND 11, 278), MenACWY immunogenicity was evaluated in two

Phase III (V59P14 and V59P21) and four Phase II (V59P5, V59P7, V59P8, and V59P9) studies. The proposed extension of MenACWY vaccine for use in infants/toddlers is based on the studies that tried to answer key questions:

- Can MenACWY be adequately immunogenic in infants?
- Can MenACWY be co-administered with existing routine vaccines?
- Can MenACWY be adequately immunogenic as a 2-dose catch-up schedule in older infants and toddlers?

In particular, the studies provided in this submission tried to address the following issues:

1) Study V59P5 evaluated the immune responses to 3 or 4 doses of MenACWY of final and non-final formulations in infants from 2 months of age.
2) Study V59P8 evaluated the safety and immunogenicity of one dose of MenACWY in toddlers 12-23 months of age.
3) Study V59P9 evaluated the immune response to 1 or 2 doses of MenACWY in subjects 6 or 12 months of age.
4) Study V59P7 evaluated the immune response to 1 or 2 doses of MenACWY in subjects 12-23 months of age.
5) Study V59P14 (pivotal study) evaluated the immunogenicity of a 4-dose series of MenACWY.
6) Study V59P21 (pivotal study) evaluated the immunogenicity of a 2-dose series of MenACWY in subjects 7-9 months of age.

MenACWY (MENVEO®) efficacy was inferred based on immune responses measured, in all above listed trials, by human complement serum bactericidal assay (hSBA) titers (against the four meningococcal serogroups A, C, W, and Y) one month after relevant/required doses of vaccines. The primary endpoint was the percentage of subjects with hSBA titer ≥1:8.

The selection of the serum bactericidal assay as the primary immunologic endpoint followed the Vaccines and Related Biological Products Advisory Committee (1999 and 2011) opinions/advice. The committee concluded that the presence of bactericidal antibodies could be used as a surrogate marker of protection against meningococcal disease.

3.1 Clinical Trial V59P14

Title of the clinical trial: "A Phase 3, Open-Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine When Administered with Routine Infant Vaccinations to Healthy Infants."

Study Initiation Date: 29 Mar 07 (first subject enrolled)
Study Completion Date: 13 Nov 09 (last subject completed)

History of Study Protocol

The original study protocol was submitted to CBER on October 16th, 2006, and was followed by seven amendments. New amendments were needed (CSR, page 103) because: "*Study V59P14 was an evolutionary process in which various changes were incorporated in response to new information and feedback from regulatory authorities.*" The last amendment of this study protocol was submitted in October, 2009. The seven protocol amendments implemented many modifications to the study design. The changes were related to such issues as: inclusion criteria, primary and secondary hypotheses, sample sizes, the vaccination or blood draw schedule of one or more groups, and division of subjects into new subgroups.

The study statistical analysis plan (SAP) was finally updated on April 2nd, 2010, and incorporated some changes already implemented in Amendments 6 and 7 of the protocol and the changes requested by the Agency (the addition of a toddler 4-fold rise analysis, revision of the polio non-inferiority margin, a revised pertussis response definition, and additional adverse event analyses to address rates over time). The applicant stated that these changes were implemented prior to the database lock. The first version of the clinical report for V59P14 (sBLA 125300/201), called by the applicant "the final version," was finalized on August 19th, 2010.

3.1.1 Brief Overview of the Study

Study design

The V59P14 clinical trial was a Phase III, open-label, multi-center, parallel-group, randomized, observer-blind, and active-controlled study in healthy infants in the United States and Latin America. Subjects were enrolled into the study if in good health, as judged by physical assessment and medical history, and if they met all inclusion criteria and none of the exclusion criteria. It was planned that approximately 4500 healthy infants about 2 months of age (55 – 89 days inclusive) would be enrolled and randomized in a 2:1 ratio to receive, during the first year of life, either MenACWY together with routine vaccines or routine vaccines alone. The randomization was stratified by center and geographic region (Latin America, US). Approximately 3000 subjects (1000 US (vaccination at 2, 4, and 6 months of age), 1700 Latin America (vaccination at 2, 4, and 6 months of age), and 300 Latin America (vaccination at 2 and 4 months of age)) received MenACWY together with the routine vaccines. A subset of study centers enrolled subjects into the immunogenicity portion of the study. Once the enrollment for the immunogenicity subset had been completed, these sites continued enrollment only into the "safety study groups" (safety portion of the study). There were a total of 13 groups in this study, including 9 to provide immunogenicity data and 4 to support safety claims only. The general outline of the vaccinations during the course of the study is given in Table 3.1.1.1.

Table 3.1.1.1: General outline of vaccinations during the course of clinical trial V59P14

A. Summary of vaccination schedule for immunogenicity and safety groups

	Months of Age								
Group	2	4	6	12	13	15	16	17	18
US1A	ACWY Routine	ACWY Routine	ACWY Routine	ACWY Routine					
US1B	ACWY Routine	ACWY Routine	ACWY Routine	Routine	ACWY				
US2	Routine	Routine	Routine	ACWY		ACWY			
LA1A	ACWY Routine		ACWY Routine	ACWY Routine					
LA1B	ACWY Routine	Routine	ACWY Routine	Routine	ACWY				
LA2	Routine	Routine	Routine	ACWY Routine		ACWY			
LA3A	ACWY Routine	ACWY Routine	ACWY Routine				ACWY Routine		
LA3B	ACWY Routine	ACWY Routine	ACWY Routine	Routine			Routine	ACWY	
LA4	Routine	Routine	Routine	ACWY Routine		ACWY Routine			

Source: Reviewer's Table
***ACWY = MenACWY (MENVEO®)** vaccine*
***Routine** = **Primary Vaccination Series (2, 4 and 6 months of age):** ActHIB® (Hib), Pediarix® (HBV, DTaP, IPV), Prevnar® (pneumococcal conjugate), RotaTeq® rotavirus vaccine **and 12-Month Concomitant Vaccinations:** ProQuad® (MMR-V), Prevnar® (pneumococcal conjugate), Havrix® (Hepatitis A)*

B. Summary of vaccination schedule for safety (only) groups

Group	2	4	6	12	13	15	16	17	18
US3	ACWY Routine	ACWY Routine	ACWY Routine	ACWY Routine					
US4A	Routine	Routine	Routine	ACWY Routine					
US4B				Routine	ACWY	ACWY			
US4c				Routine					ACWY
LA5	ACWY Routine	ACWY Routine	ACWY Routine	ACWY Routine					
LA6A	Routine	Routine	Routine	ACWY Routine		ACWY			
LA6B				Routine	ACWY	ACWY			
LA6C				Routine					ACWY

Source: Reviewer's Table
***ACWY = MenACWY (MENVEO®)** vaccineRoutine = **Primary Vaccination Series (2, 4 and 6 months of age):** ActHIB® (Hib), Pediarix® (HBV, DTaP, IPV), Prevnar® (pneumococcal conjugate), RotaTeq® rotavirus vaccine **and 12-Month Concomitant Vaccinations:** ProQuad® (MMR-V), Prevnar® (pneumococcal conjugate), Havrix® (Hepatitis A)*

Rules of vaccination in the second year were defined by the applicant as follows: *"Subjects in the immunogenicity subset randomized to receive MenACWY with the routine infant vaccines will be randomized at time of enrollment (1:1 ratio) to receive vaccines in the second year of life either alone or with MenACWY. Subjects in the safety only subset randomized to receive MenACWY with the routine infant vaccines will receive a fourth dose of MenACWY at 12 months of age. All subjects randomized to receive only routine* infant *vaccines (no MenACWY) will receive MenACWY at 12 and 15 months of age"* (V59P14 protocol, page 6). All subjects randomized to receive only routine infant vaccines (no MenACWY) in the safety only subset (US4 and LA6) received one dose of MenACWY at 18 months of age. A summary of the study design is given in Table 3.1.1.2.

Table 3.1.1.2: Summary of the study design

Geographic Region	Total Subjects	Vaccine Group	Total Subjects **Safety Only**	Total Subjects **Immunogenicity**
US	1500	MenACWY + Routine Vaccinations	700	300
		Routine vaccinations Only	350	150
LA	3000	MenACWY + Routine Vaccinations	1400	600
		Routine vaccinations Only	700	300

Source: Clinical Study Protocol (Am 6), page 48

Reviewer's Remarks

During the course of the V59P14 study, the protocol of the study was changed many times to incorporate new information (e.g., from Phase II studies), feedback from regulatory authorities, and to improve the study design.

Some protocol amendments had major impacts on the course of the study. Groups US4 and LA6 were affected by Amendments 4 and 5 to the protocol as subjects in these groups were at varying stages in the study when these amendments were implemented. This resulted in three subsets of subjects within US4 and LA6 receiving MenACWY at different times from 12 months of age forward: some subjects at 12 and 15 months (denoted as US4A and LA6A), some subjects at 13 and 15 months (denoted as US4B and LA6B), and the majority of subjects at 18 months of age only (denoted as US4C and LA6C). New study groups denoted by US4C and LA6C were initiated to serve as a "control" for the 4-dose MenACWY groups up to 6 months after the final MenACWY dose.

It is worth noting that this clinical trial was not designed with adaptive features (e.g., possibility to change primary hypotheses, to add a new study arm) nor was it a well-controlled study. Therefore, bias could be introduced and the potential for false positive study results might be increased.

Additionally, the pivotal study V59P14 contained many sub-studies. The total study population was divided into 17 groups that differed with respect to the type and time of vaccination and tested hypotheses. The primary immunogenicity endpoint was linked only to one schedule of vaccination, namely 2, 4, 6, and 12 months of age.

Immunogenicity Objectives

Primary objectives were:

1. To assess the immunogenicity of four doses of MenACWY given to infants at 2, 4, 6, and 12 months of age as measured by the percentage of subjects with hSBA titer ≥1:8 directed against N. meningitidis serogroups A, C, W, and Y (US subjects, US1A group).

To compare the immunogenicity of the fourth dose of MenACWY given at 12 months of age in subjects who previously received three doses of MenACWY given at 2, 4, and 6 months of age to the immunogenicity of a single dose of MenACWY given to naïve subjects at 12 months of age by testing the ratio of GMTs directed against N. meningitidis serogroups A, C, W, and Y (US subjects, US1A, and US2 groups).

Secondary objectives were:

1. To assess the immunogenicity of three doses of MenACWY given to infants at 2, 4, and 6 months of age as measured by hSBA geometric mean titers (GMTs) and by the percentage of subjects with hSBA ≥1:8 and ≥1:4 directed against N. meningitides serogroups A, C, W, and Y (US subjects, US1).
2. To compare the immunogenicity of two doses of MenACWY given to infants at 2 and 6 months of age to the immunogenicity of three doses of MenACWY given to infants at 2, 4, and 6 months of age, with immunogenicity assessed by hSBA GMTs and by the percentage of subjects with hSBA ≥ 1:4 and hSBA ≥ 1:8 directed against N. meningitidis serogroups A, C, W, and Y (Latin American [LA] subjects)
3. To demonstrate that the immunogenicity of routine infant vaccines (i.e., DTaP, IPV, HBV, pneumococcal conjugate, Hib), when given concomitantly with MenACWY at 2 and 6 or 2, 4, and 6 months of age, is non-inferior to the immunogenicity of routine infant vaccines given without MenACWY (US and LA subjects being assessed separately)
4. To assess the persistence of bactericidal antibodies at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY at 2 and 6 or 2, 4, and 6 months of age, as measured by hSBA GMT, hSBA ≥ 1:4, and hSBA ≥ 1:8 directed against N. meningitidis serogroups A, C, W, and Y (US and LA subjects being assessed separately)
5. To assess the immunogenicity of the third or fourth dose of MenACWY given at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY given at 2 and 6 or 2, 4 and 6 months of age, as measured by hSBA GMT, hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA ≥ 1:16 directed against N.

meningitides serogroups A, C, W, and Y (US and LA subjects being assessed separately);

6. To demonstrate that the immunogenicity of routine booster vaccinations administered in the second year of life (i.e., pneumococcal conjugate booster, Hib) when given concomitantly with MenACWY in subjects who previously received two or three doses of MenACWY given at 2 and 6 or 2, 4, and 6 months of age is non-inferior to the immunogenicity of routine booster vaccines given alone (US and LA subjects, assessed separately);
7. To assess the immunogenicity of one or two doses of MenACWY given at 12 months or 12 and 15 months of age, respectively, as measured by hSBA GMTs, hSBA ≥ 1:4, and hSBA ≥ 1:8 directed against N. meningitidis serogroups A, C, W, and Y (US and LA subjects being assessed separately).

Hypotheses and sample size considerations

Co-primary immunogenicity hypotheses:

1) The first co-primary immunogenicity hypothesis

The co-primary hypothesis was defined as follows:
for each serogroup A, C, W, and Y

H_0: $P_i \leq \Delta_i$
H_a: $P_i > \Delta_i$,

where P_i (i=1,2,3, and 4) are proportions of subjects (in US1A group) with hSBA ≥1:8 one month after the fourth dose of MenACWY, and Δ_i (i=1,2,3, and 4) are equal to 0.8, 0.85, 0.85, and 0.85 for MenA, MenC, MenW, and MenY, respectively.

2) The secondary co-primary hypothesis

The secondary co-primary hypothesis is related to the comparison of the immunogenicity of the fourth dose of MenACWY given at 12 months of age to the immunogenicity of a single dose of MenACWY given to naïve subjects at 12 months of age, where the immunogenicity was assessed by the ratio of GMTs directed against N. meningitidis serogroups A, C, W, and Y (US subjects, US1A and US2 groups). The hypothesis was defined as follows:
for serogroup A, C, W, and Y:

H_0: $\varphi_{12} \leq 2$
H_a: $\varphi_{12} > 2$,

where $\varphi_{12} = \mu_1/\mu_2$, and μ_1 and μ_2 are the GMT values for the US1A and US2 groups, respectively.

In the protocol (page 171), the applicant stated that the sample size of 120 subjects was needed to achieve overall (across four serogroups and both primary endpoints) power 86%.

Reviewer's Remarks

Please note that clinical trial V59P14:

1. Encompassed many "sub-studies" which should be performed as Phase II studies (e.g., evaluations of the immune responses to different dose schedules of vaccination with MenACWY), not as parts of the Phase III study
2. Had 15 objectives (9 for US and 6 for LA groups), among others, the following objectives:
    - to support indication for a 4-dose vaccination series at the schedule 2, 4, 6, and 12 months of age (primary objective)
    - to evaluate concomitant use of MENVEO and routine infant vaccines (secondary objectives)
    - to assess alternative vaccination schedules: at 2, 6, and 13 months and at 2, 4, 6, and 16 months (LA) (secondary objective)
3. Encompassed 17 study groups (9 to provide immunogenicity and safety data and 8 to support safety claims only).

Additionally, please note that the applicant did not address multiplicity issues related to multiple clinical endpoints. The criterion for study success was only based on the primary hypothesis involving administration of MENVEO. The multiplicity adjustments for the family of secondary endpoints were not pre-defined in the protocol. Additionally, reliability of results related to the secondary (non-inferiority) hypotheses is uncertain due to extreme missingness (results were sometimes based only on about 50% of evaluable immunogenicity subjects). Therefore, results for the secondary endpoints are applicable purely for descriptive purposes.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

General comment

In clinical study V59P14, four main study populations were created, namely:

1. US immunogenicity population
2. LA immunogenicity population
3. US safety population
4. LA safety population.

The US and LA immunogenicity populations are discussed in the current section of the review. Safety populations are characterized in the safety section of the review.

Disposition of Subjects

US Immunogenicity Subjects (US1 and US2 groups)

A total of 479 subjects were enrolled into the US immunogenicity groups US1 and US2, but only 351 (73%) subjects completed the study.

The disposition of subjects in the US immunogenicity groups is summarized in Table 3.1.2.1.

Table 3.1.2.1: Disposition of subjects in the US immunogenicity groups

	Immunogenicity Subjects				Overall
	US1			US2	
	US1A	US1B	Total		
Enrolled	154	166	320	159	479
Completed Study	121 (79%)	120 (72%)	241 (75%)	110 (69%)	351 (73%)
Discontinued	33 (21%)	46 (28%)	79 (25%)	49 (31%)	128 (27%)
AE	2 (1%)	0	2	2 (1%)	4 (1%)
Lost to Follow-up	8 (5%)	6 (4%)	14 (4%)	13 (8%)	27 (6%)
Withdrew consent	9 (6%)	24 (14%)	33 (10%)	13 (8%)	46 (10%)
Administrative reason	11 (7%)	9 (5%)	20 (6%)	9 (6%)	29 (6%)
Other Reason	3 (1%)	6 (4%)	9 (3%)	4 (3%)	13 (3%)

Source: Reviewer's Analysis

The percentages of subjects with premature withdrawals ranged from 21% to 31% across the US immunogenicity groups, with the highest withdrawal rate for the US2 group. Most (46 out of 479 (10%)) premature withdrawals were connected with withdrawals of consent. Other reasons for premature withdrawals included adverse events, lost to follow-up, and administrative reasons.

The applicant carried out evaluations of all primary and secondary immunogenicity objectives on the per protocol (PP) populations (7 different PPs). They were selected from US1 and/or US2 groups and were comprised of subjects who provided evaluable serum samples and for whom no major protocol deviations were noted.

Protocol Deviations

Protocol deviations were reported for 88% of US immunogenicity subjects. Most of them (59%) were classified as major protocol deviations, with the US2 subjects exhibiting the highest percentage. A summary of protocol deviations by study group is given in Table 3.1.2.2.

Table 3.1.2.2: Summary of some major protocol deviations

Deviation	Immunogenicity Subjects				Overall
	US1			US2	
	US1A (154)	US1B (166)	Total (320)	159	479
Any protocol deviations	131 (85%)	139 (84%)	270 (84%)	150 (94%)	420 (88%)
Any major deviations	90 (58%)	87 (52%)	177 (55%)	104 (65%)	281 (59%)
Blood draw out of acceptable window	22 (17%)	16 (12%)	39 (14%)	18 (11%)	57 (12%)
No blood draw at any visit	7 (5%)	7 (4%)	14 (4%)	6 (4%)	20 (4%)
No blood draw at one of visits	63 (41%)	52 (31%)	115 (42%)	75 (50%)	190 (40%)
Incomplete infant series	16 (10%)	21 (13%)	37 (12%)	16 (10%)	53 (11%)
Incomplete Toddlers series	9 (6%)	5 (3%)	14 (4%)	0 (0%)	

Source: Reviewer's Analysis

The most frequent violation was "not providing the baseline blood sample."

Demographic Characteristics

At baseline, demographic and other baseline characteristics of the enrolled infants were balanced across different US immunogenicity groups (US1A, US1B, and US2). The majority of the population consisted of Caucasians (52% to 61%), while Asians, Blacks, Hispanics, and others constituted the rest. Gender ratios were similar across the study groups; however, there were more (about 12%) males than females. On average, age, height, and weight were similar across the immunogenicity groups.

LA Immunogenicity Subjects (LA1, LA2, LA3, and LA4 groups)

A total of 900 subjects were enrolled in the LA immunogenicity groups LA1, LA2, LA3, and LA4. Subjects were only enrolled into the LA immunogenicity groups from Argentina. Colombia did not contribute subjects to these cohorts. Of the enrolled subjects, 825 completed the study. Based on the CSR, the percentages of subjects with premature withdrawals ranged from 4% - 18% across the vaccination groups, with the highest withdrawals in LA2.

The disposition of subjects in the LA immunogenicity groups is summarized in Table 3.1.2.3.

Table 3.1.2.3: Disposition of subjects in the LA immunogenicity groups

	Immunogenicity Subjects				
	LA1A	**LA1B**	**LA2**	**LA3**	**LA4**
Enrolled	151	150	148	301	150
Completed Study	145 (96%)	144 (96%)	121(82%)	280 (93%)	135 (90%)
Discontinued[a]	6 (4%)	6 (4%)	27 (18%)	21 (7%)	15 (10%)
Withdrew consent	4 (3%)	4 (3%)	13 (9%)	9 (3%)	4 (3%)
Lost to Follow-up	1 (<1%)	0	6 (4%)	6 (2%)	6 (4%)
Administrative reason	0	2 (1%)	1 (<1%)	2 (<1%)	1 (<1%)
Protocol Deviation	0	0	4 (3%)	4 (1%)	4 (3%)
Other Reason	1 (<1%)	0	3 (2%)	0	0

a: primary reason

Source: CSR, page 110, Table 10.1-1B

From the above table, it can be seen that the major reason for premature withdrawal was withdrawal of consent (3% - 9% of subjects). Other reasons included adverse events, lost to follow-up (0%-4% of subjects), inappropriate enrollment, administrative reasons and protocol deviations/violations (0%-3% of subjects).

Protocol Deviations

Protocol deviations were reported for 75% of LA (LA1A, LA1B, LA2, LA3A, LA3B, and LA4) immunogenicity subjects. Most of them (49%) were classified as major protocol deviations, with the LA2 subjects exhibiting the highest percentage. A summary of protocol deviations by study group is given in Table 3.1.2.4.

Table 3.1.2.4: Summary of some major protocol deviations

	Immunogenicity Subjects					
	LA1A	LA1B	LA2	LA3A	LA3b	LA4
Deviation	151	150	148	151	150	150
Any protocol deviations	99 (66%)	113 (75%)	124 (84%)	103 (68%)	119 (79%)	118 (79%)
Any major deviations	60 (40%)	56% (37%)	72 (49%)	40 (26%)	54 (36%)	47 (31%)
Protocol Procedure not Performed Per Protocol	26 (17%)	36 (24%)	35 (24%)	25 (17%)	48 (22%)	35 (23%)
Blood draw out of window	39 (25%)	40 (27%)	39 (27%)	14 (9%)	15 (10%)	26 (17%)
No blood draw at one of visits	8 (5%)	5 (3%)	3 (2%)	4 (3%)	4 (3%)	2 (1%)
Incomplete infant series	2	2	17 (12%)	5 (3%0	6 (4%)	3 (2%)
Incomplete Toddlers series	0	0	3 (2%)	1	3 (2%)	5 (3%)

Source: CSR, Table 10.2-1C, page 117

Many subjects (up to 27%) had their blood draw out of the time window which was considered to be a major protocol deviation.

Demographic Characteristics

The demographic and other baseline characteristics were balanced across different vaccination groups. The majority of the immunogenicity subjects were Caucasians (65% to 66%) followed by Hispanics (33% to 35%), while the majority of the safety subjects were Hispanics (66% to 85%).The proportions of various ethnic group, gender ratios, and age, height, and weight characteristics were similar across the vaccination groups.

Reviewer's Comments - Data Quality:

Statistical analyses related to eight (two co-primary and 6 secondary) US immunogenicity hypotheses were tested on the immunogenicity dataset. Almost each immunogenicity hypothesis was tested on its own PP population (e.g., Infant PP ACWY population, PP Concomitant vaccine population). These populations exhibited many missing immunogenicity data, mainly due to major protocol deviations (up to 65% of subjects with "major" deviations in US2) and withdrawal of subjects (10%) from the study.

When the hSBA assays were performed originally on the sera from the US subjects in study V59P14, the infant series, samples for the control group were not included for testing against the MenACWY vaccine antigens. Additionally, due to subject numbering and labeling conventions, it was possible for the laboratory personnel to anticipate which samples should have had higher titers, CBER raised concern about potential bias that could have been introduced in the original test results. Therefore, at CBER's request, a blinded retest of all remaining sera from US subjects was performed. The primary objective of the re-testing was to show that there was no bias in the original serological testing of the study sera samples. The re-test data were reviewed by Dr. Martha Lee. She concluded in her review that the agreement analyses showed acceptable results. However, compared to the original assays, lower values were systematically observed in the re-test (for serotypes C, Y, and W). The applicant has noted that any observed systematic difference between the old-test and the re-tests may have been due to systematic effects from either new reagents or conscious or unconscious bias in the original testing. Therefore, from the statistical point of view, it is difficult to reach a conclusion regarding the reliability of the serology generated under open label conditions. In addition, in response to CBER's information request on November 15, 2011 regarding the issue of corrections of "VISIT" on 100 observations in the re-test analysis, the applicant disclosed that there were cases where the site placed the label for the wrong visit on the tube and it was determined that the visit number from the CRF entry, rather than the label, was used in the re-test analysis. These issues raise concerns about the quality of the applicant's clinical trial process.

The data issues noted in this study create concerns related to the data integrity.

3.1.4 Evaluation of Study Immunogenicity Results

I. Primary immunogenicity hypotheses

Primary Objective #1

Objective #1 was to assess the immunogenicity of four doses of MenACWY given to infants at 2, 4, 6, and 12 months of age by measuring the percentage of subjects with hSBA≥ 1:8 directed against N. meningitidis serogroups A, C, W, and Y. The criteria for testing the hypothesis related to objective #1 were: the lower limits of the two-sided 95% CIs for the estimated proportions of subjects with hSBA≥ 1:8 were greater than or equal to 80%, 85%, 85%, and 85% for MenA, MenC, MenW, and MenY, respectively. A summary of the results for these endpoints is presented in Table 3.1.4.1.

Table 3.1.4.1: Percentages of subjects with hSBA ≥ 1:8 at 1 month after the fourth dose of MenACWY - US Subjects (PP Population)

Serogroup	US1A		
	PP Population		
	n	Estimated Endpoint (%)	95% CI
A (N=87)	82	94	(87, 98)
C (N=87)	85	98	(92, 100)
W-135 (N=86)	86	100	(96, 100)
Y (N=87)	87	100	(96, 100)

Source: Reviewer's analysis

Reviewer's comments:

1. The pre-specified primary immunogenicity criteria related to immune response to the four-dose MenACWY vaccination series at 2, 4, 6, and 12 months of age were met.

2. The statistical analyses performed by the applicant were carried out on the PP MenACWY Toddler population, which comprised subjects (US1A) for whom no major protocol deviations were noticed and who provided evaluable serum MenACWY. The total PP MenACWY Toddler population (91 toddlers) constituted only 59% of 154 subjects enrolled into the US1A group.

3. The reliability of the results related to the primary hypothesis, which were based on only 55% of the evaluable subjects, may be of concern as the results might be influenced by excessive missingness.

4. An assessment of the primary objective on the MITT (Modified Intention to Treat) population, i.e., on all subjects in the enrolled population who received a

study vaccination and provided at least one evaluable serum sample after baseline, yields results that are presented in Table 3.1.4.2.

Table 3.1.4.2: Estimations of primary endpoints performed on the MITT population

Serogroup	US1A		
	MITT Population		
	n	Estimated Endpoint (%)	95% CI
A (N=103)	96	93	(87, 97)
C (N=102)	98	96	(90, 99)
W-135 (N=102)	102	100	(97, 100)
Y (N=102)	101	99	(95, 100)

Source: Reviewer's analysis

It can be concluded from Table 3.1.4.2 that testing of the primary hypothesis on the MITT population (67% of enrolled infants) yielded results similar to those from the analyses performed on PP population. [Actually, this statement is not true, technically, because the only way the table can lead to that conclusion is if the table shows both the PP and MITT results. Also, it might be good to add a footnote to the table, defining the endpoint.]Thus, the criteria related to the primary hypothesis were met.

5. Table 3.1.4.3 illustrates how many study vaccines (MenACWY and routine vaccines) were administered during different clinical visits.

Table 3.1.4.3: Distribution of study vaccines administration per infant visit

Visit	Total number administered			
	3	4	5	6
1			153 (153)	
2		2 (2)	139 (139)	
3		2 (2)	134 (134)	2 (2)
4	7 (7)	106 (106)	11 (9)	

Numbers in ( ) show numbers of subjects who received MenACWY
Source: Reviewer's Analysis

Please note that, after the first dose of the routine and MenACWY vaccines, 12 (8%) infants did not receive any additional doses. These 12 infants dropped out from the study. This drop-out was caused by 2 AEs, 4 withdrawals of consent, 1 loss to follow-up, and 5 administrative reasons. Furthermore, in the US1A group, a total of 31 (20%) infants missed at least one dose of the MenACWY vaccine. Additionally, please note that 31 "other" vaccines were administered to infants during Visits 3 and 4.

Co-Primary Objective #2

Objective #2 was to compare the immune responses after the fourth dose of MenACWY vaccine given at 12 months of age in subjects who previously received three doses of MenACWY given at 2, 4, and 6 months of age and the immune responses to a single dose of MenACWY given to naïve subjects at 12 months of age. The criteria for testing the hypothesis related to objective #2 were: the lower limits of 95% CIs for the ratio of GMTs (GMT_{US1A} / GMT_{US2}) at 13 months of age for MenA, MenC, MenW, and MenY should be greater than or equal to 2.0. A summary of the results for the co-primary objective #2 is presented in Table 3.1.4.4.

Table 3.1.4.4: Comparison of immune response to MenACWY vaccine when administered at 2, 4, 6, and 12 months (US1A) vs. immune response to a single dose of MenACWY vaccine when administered at 12 months of age (US2) (US subjects- MITT population)

Serogroup	US1A			US 2			Estimation	
	N	GMT	95% CI	N	GMT	95% CI	GMT_{US1a}/GMT_{US2}	95% CI
A	103	77	(59, 101)	91	17	(13,23)	4.5	(3.0, 6.9)
C	102	220	(163, 297)	90	38	(29, 50)	5.8	(3.9, 8.7)
W	102	385	(297, 498)	89	13	(9, 17)	31	(21, 47)
Y	102	381	(294,493)	87	11	(8, 16)	33	(22, 51)

Source: Reviewer's analysis

Table 3.1.4.4, illustrates that criteria for the co-primary immunogenicity hypothesis #2 were met. The lower limit of the two-sided 95% CI for the GMT ratio was greater than 2 for all four serogroups.

II. Summary of the statistical results related to the secondary objectives

Objective # 1: Estimations of the infants' immune responses to the primary series of MenACWY vaccinations are presented in Table 3.1.4.5.

Table 3.1.4.5: Estimations of immune responses to MenACWY administered at 2, 4, and 6 months of age (US1 subjects –MITT population)

Serogroup	N	GMT	95% CI	% of subjects with hSBA >=1:8	95% CI
A	236	12	(10, 15)	65	(59, 71)
C	225	99	(84, 118)	96	(93, 99)
W	217	95	(81, 111)	97	(93, 99)
Y	201	71	(60, 84)	97	(94, 99)

Source: Reviewer's analysis

The range of the hSBA GMTs in the US1 group one month post-infant series vaccination is 12 to 99.

Reviewer's comments:

The results presented by the applicant (CSR, page 131) are slightly different from the results shown in Table 3.1.4.5 (created by the statistical reviewer) because the applicant's analyses were based on the PP population. The applicant's GMTs are slightly higher than those calculated by the Agency statistician. The PP population for this objective (US1 Group, 320 enrolled infants) consisted of about 62% of enrolled subjects and was a subset of the MITT (about 75% of US1 group) population.

Objective # 2: The second secondary objective was to compare the immunogenicity of two doses of MenACWY given to infants at 2 and 6 months of age (LA1B) to the immunogenicity after three doses of MenACWY given to infants at 2, 4, and 6 months of age (LA3), by measuring hSBA GMTs and the percentages of subjects with hSBA ≥1:8 directed against N. meningitidis serogroups A, C, W, and Y. A summary of the statistical analyses results are presented in Tables 3.1.4.6 A and B.

Table 3.1.4.6

A.: GMTs (and corresponding 95% CIs) at 1 month after the last infant MenACWY series vaccination for different schedules of infant MenACWY series – LA subjects, MITT population

Serogroup	LA 1B			LA 3			Estimation	
	N	GMT	95% CI	N	GMT	95% CI	GMT Ratio	95% CI
A	141	29	(21, 40)	273	43	(37, 51)	0.67	(0.49, 0.92)
C	140	143	(109, 187)	278	149	(129, 172)	0.96	(0.72, 1.27)
W	140	267	(215, 331)	270	180	(159, 204)	1.48	(1.18, 1.88)
Y	142	158	(125, 201)	269	124	(108, 142)	1.28	(0.99, 1.65)

Source: Reviewer's analysis
LA1B - MenACWY given to infants at 2 and 6 months of age
LA3 - MenACWY given to infants at 2, 4 and 6 months of age

B.: Percentages of infants with hSBA titer ≥ 1:8 at 1 month after the last infant MenACWY series vaccination for different schedules of infant MenACWY series – LA subjects, MITT population

Serogroup	LA 1B			LA 3			Estimated difference in rate (%)
	N	% hSBA ≥ 1:8	95% CI	N	% hSBA ≥ 1:8	95% CI	
A	141	72	(64, 80)	273	89	(85, 93)	-17 (-25, -8.4)
C	140	94	(88, 97)	278	97	(94, 99)	-3 (-8, 1.4)
W	140	98	(96, 99)	270	98	(96, 99)	-0.3 (-3, 2.6)
Y	142	97	(92, 99)	269	98	(95, 99)	-1.3 (-5, 2.2)

Source: Reviewer's analysis
LA1B - MenACWY given to infants at 2 and 6 months of age
LA3 - MenACWY given to infants at 2, 4 and 6 months of age

Reviewer's comments:

- One month after completion of the infant series vaccination, the ratio GMT_{LA1}/GMT_{LA3} ranged from 0.67 to 1.48, with the lower limits of the two-sided 95% CIs for this ratio being considerably greater than 0.5 for serogroups C, W, and Y, but narrowly less than 0.5 (0.49) for serogroup A. The differences in the percentages of infants with hSBA titer ≥ 1:8 at one month after the infant MenACWY series ranged from -17% to -0.31%, with the lower limit of the two-sided 95% CI for the difference $P_{LA1B} - P_{LA3}$ in percentage of subjects with hSBA titer ≥ 1:8 being greater than -10% for serogroups C, W, and Y (LA1B non-inferior to LA3) but less than -10% (-25%) for serogroup A. This means that some of the pre-specified criteria for Objective #4 (related to immune responses to two or three MenACWY vaccinations) **were met, but not all weremet**.

- The statistical analyses performed by the applicant were carried out on the PP immunogenicity LA MenACWY dataset (LA1 (1A+1B), and LA 3 group). The statistical reviewer performed statistical analyses on the MITT population of the LA1B and LA 3 groups. The LA1A group did not have the same series of routine vaccines, i.e., routine vaccines at 4 months of age. Therefore, the comparison of immunogenicity of two vs. three dose series of infants MenACWY vaccinations was performed on the LA1B vs. LA3 population groups which had the same routine vaccine schedule.

Objective #3: The third secondary objective was to demonstrate that the immunogenicity of the routine infant vaccines (i.e., DTaP, IPV, HBV, pneumococcal conjugate, Hib), when given concomitantly with MenACWY at 2 and 6 (LA1 group) or 2, 4, and 6 months of age (US1, LA3 groups), is non-inferior to the immunogenicity of routine infant vaccines given without MenACWY (US2, LA2, LA4 groups; US and LA subjects being assessed separately).

Based on Table 11.4.1-5a one month post-infant series vaccination (i.e., at Month 7), the GMCs for pertussis and pneumococcal antigens in the subjects who received MenACWY concomitantly with routine infant vaccines (US1 group) were non-inferior (Table 3.1.4.7) to those in subjects who received only routine infant vaccines (US2 group).

Table 3.1.4.7: GMCs or GMTs (95% CI) of concomitant antigens 1 month after infant series in US subjects (PP population)

	US1	US2	US1:US2 ratio (95% CI)
	N = 214	**N = 102**	
Diphtheria	2.52 (2.28, 2.78)	2.88 (2.5, 3.32)	0.87 (0.74, 1.04)
Tetanus	2.5 (2.28 , 2.74)	2.31 (2.01, 2.64)	1.08 (0.92, 1.28)
Pertussis Ags	**N = 174**	**N = 83**	
PT	54 (48, 62)	54 (44, 66)	1 (0.79, 1.26)
FHA	118 (106 – 132)	114 (97, 134)	1.03 (0.85, 1.25)
Pertactin	114 (100 – 130)	110 (90, 134)	1.04 (0.83, 1.32)
Polio Ags	**N = 176**	**N = 98**	
Polio type1	422 (363, 491)	441 (361, 540)	0.96 (0.75, 1.23)
Polio type 2	348 (297, 408)	290 (235, 358)	1.2 (0.93, 1.55)
Polio type 3	733 (607, 885)	635 (493, 818)	1.15 (0.85, 1.56)
	N = 148	**N = 98**	
Hepatitis B	1863 (1538, 2257)	2112 (1668, 2674)	0.88 (0.65, 1.2)
	N = 213	**N = 101**	
Hib	4.64 (3.9, 5.53)	3.56 (2.77, 4.58)	1.31 (0.97, 1.77)
Pneumococcal Ags	**N = 181**	**N = 102**	
PnC 4	1.67 (1.5, 1.86)	2 (1.73, 2.3)	0.84 (0.7, 1)
PnC 6B	1.94 (1.6, 2.34)	2.55 (1.99, 3.27)	0.76 (0.56, 1.03)
PnC 9V	1.83 (1.6, 2.06)	2.15 (1.83, 2.53)	0.85 (0.7, 1.04)
PnC 14	6.97 (6.18, 7.86)	6.79 (5.78, 7.96)	1.03 (0.84, 1.26)
PnC 18C	1.96 (1.75, 2.19)	2.54 (2.18, 2.95)	0.77 (0.64, 0.93)
PnC 19F	2.24 (2.02, 2.48)	2.73 (2.39, 3.13)	0.82 (0.69, 0.97)
PnC 23F	1.71 (1.47, 1.98)	2.15 (1.76, 2.62)	0.79 (0.62, 1.02)

Source: CSR, page 129

Moreover, one month post the infant series vaccination (Month 7) and for the US1 group, the seroresponse rates against polio, PT, FHA, diphtheria, tetanus, hepatitis B, Hib, and against 6 of 7 pneumococcal antigens were non-inferior to corresponding rates in subjects who received only routine infant vaccines (US2 group). [Please note that a table related to seroresponse rates (95% CI) for concomitant vaccines antigens at 1 Month after the Infant Series (PP US Population) is not included in this review.] However, the non-inferiority criteria related to seroresponse for serotype 6B antigen and the PRN pertussis antigen were not met**.**

Objective #4: The fourth secondary objective was to assess the persistence of bactericidal antibodies at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY at 2 and 6 or 2, 4, and 6 months of age. For US subjects, at 12 months of age, 12% to 69% of the subjects, who had previously received three doses of MenACWY (US1), had hSBA titers (against the four meningococcal serogroups) ≥1:8, whereas only 1% to 7% subjects, who did not have any previous MenACWY vaccination (US2), had hSBA titers ≥1:8.

The Latin America data are not discussed here, because it is known that the meningococcal immune responses to meningococcal vaccines in Latin American subjects are not predictive of responses in US subjects.

Objective #5: The fifth secondary objective was to assess the immunogenicity of a third or fourth dose of MenACWY given at 12 or 16 months of age in subjects who previously received two or three doses of MenACWY given at 2 and 6 or 2, 4, and 6 months of age, as measured by hSBA GMT, hSBA ≥1:4, hSBA ≥1:8, and hSBA ≥1:16 directed against N. meningitidis serogroups A, C, W, and Y.
Before the fourth dose (US1), the majority of subjects demonstrated bactericidal antibody persistence for serogroups C, W, and Y (percentage of subjects with hSBA ≥1:8, for serogroup C,was 52%; for serogroup W was 69%; for serogroup Ywas 60% (CSR, Table 11.4.1-7A). For serogroup A, the persistence of bacterial antibodies was lower, with 12% of the subjects maintaining an hSBA ≥ 1:8. However, as previously presented for the primary endpoint, at 13 months, 100% subjects achieved hSBA ≥1:8 against serogroups W and Y while 94% and 98% subjects achieved hSBA ≥1:8 against serogroups A and C, respectively. Similarly, 100% subjects achieved hSBA ≥1:16 against serogroups W and Y while 90% and 95% subjects achieved hSBA ≥1:16 against serogroups A and C, respectively. One month post toddler vaccination, the GMTs ranged from 77 to 416 against the four meningococcal serogroups.

Objective #6: The sixth secondary objective was related to immunogenicity one month post-toddler vaccination (Month 13). The GMCs for pneumococcal antibodies in the subjects who received pneumococcal conjugate booster vaccine concomitantly with the fourth dose of MenACWY at age 12 months (US1A) were non-inferior to GMCs for subjects who received only pneumococcal conjugate booster vaccine alone at age 12 months (US1B). Criteria related to this objective were met.

3.1.5 Summary of the Immunogenicity Statistical Results

Based on the data for the four-dose MenACWY vaccination series at 2, 4, 6, and 12 months of age (i.e., for the PP MenACWY population), the pre-specified primary immunogenicity criteria related to the immunogenicity hypothesis were met. The statistical analyses performed by the applicant were carried out on the PP MenACWY toddler population (US1A). The PP MenACWY toddler population constituted only 59% of 154 subjects enrolled into the US1A group. Therefore, the reliability of results, based

on about 55% of enrolled subjects, related to the primary hypothesis may be uncertain due to excessive missingness. After the first dose of routine and MenACWY vaccines, more than 8% of enrolled infants (12 infants in US1A, and 14 infants in US1B) did not receive any additional study (investigational?) vaccine doses. Further, in the control arm, 5% of enrolled subjects withdrew from the study. In the US1A immunogenicity group, altogether 31 (20%) infants missed at least one dose of MenACWY vaccine. Additionally, please note that during Visits 3 and 4, a total of 31 "other" vaccines, i.e., not included in the study protocol specification, were administered to infants.

Conclusions related to the primary hypothesis drawn on the MITT population (67% of enrolled infants) data are similar to those from the analyses performed on the PP population.

Some important secondary hypotheses were formulated to evaluate concomitant use of MENVEO® and routine infant vaccines. These secondary hypotheses were to answer the question whether immune responses to concomitant vaccines in subjects who received MENVEO® with routine vaccines were similar to the responses in subjects who received routine vaccines alone. From the statistical standpoint, to answer this question, the multiplicity issue should be addressed properly and pre-specified in the study protocol. However, the handling of these issues was not pre-planned and addressed in the protocol. Therefore, such results for the secondary endpoints are typically viewed as descriptive only, i.e., not usually the basis for drawing conclusions.

The descriptive results are, according to the pre-specified key secondary criteria for each antigen response: non-inferiority was achieved for diphtheria, tetanus, pertussis (FHA, PRN, and PT antigens), poliovirus types 1-3, hepatitis B and Hib, but not for pertactin and PnC 6B (one of 7 pneumococcal antigens).

As MenACWY and Prevnar are both CRM-197 conjugate vaccines, there were concerns that co-administration of two vaccines bearing the same carrier protein could result in an immunologic interference. Non-inferiority comparisons were conducted for both the infant series and the toddler dose. They compared subjects who received MenACWY along with routine vaccines, including Prevnar, versus subjects who only received the routine vaccines. For the infant series, non-inferiority was based on a comparison of the proportion of subjects achieving an (b)(4) concentration of $\geq 0.35\mu g/mL$ for each serotype, whereas for the toddler dose, non-inferiority was based instead on the ratio of GMCs. Following the three infant injections, non-inferiority was achieved for all serotypes, except for serotype 6B in the US subjects. Following the toddler dose, for the US subjects, non-inferiority was demonstrated for all serotypes, including serotype 6B.

However, the reliability of results related to the secondary (non-inferiority) hypotheses is unclear due to excessive missingness. Results were sometimes based on approximately 50% of the enrolled subjects.

In summary, excessive missing data is one of the difficilties encountered in evaluation of data derived from the V59P14 clinical trial. More than 45% of enrolled subjects were not

included in the PP immunogenicity populations used in analyses. The primary endpoint was assessed on data comprising only about 55% of enrolled subjects. Therefore, the interpretation of study results is challenging from the statistical perspective, and an adequate, rigorous statistical assessment of the vaccine immunogenicity data, based on currently submitted data/datasets for study V59P14, is not feasible.

It is worth noting that the study immunogenicity results could also be influenced by uncertain data quality. The immunogenicity data were not adequately controlled and blinded with respect to sera sample assignment to assay runs. Thus, introduction of bias into the immunogenicity data could be possible. Therefore, the applicant was asked to retest the immunogenicity data. Based on Dr. Martha Lee's evaluations of the retest results (Martha Lee, Statistical (Retest) Review and Evaluation, December 10th 2011), it is still difficult to reach a clear conclusion regarding the reliability of the serology data generated under open label conditions. During the review process, Dr. Lee raised a question regarding the process of tube labeling. She stated "The applicant disclosed that there were cases where the site placed the label for the wrong visit on the tube and it was determined that the visit number from the CRF entry, rather than the label, was used in the retest analysis. These mishaps raise concerns about the quality of the applicant's clinical trial process."

3.2. Study V59P21

Title of the study: "A Phase 3, Open-Label, Randomized, Multi-Center Study to Evaluate the Safety and Immunogenicity of ProQuad™ Vaccine when Administered Concomitantly with Novartis Meningococcal ACWY Conjugate Vaccine to Healthy Toddlers."

Study Initiation Date: 27 February 2008
Study Completion Date: 26 October 2010

History of the Study Protocol

The original study protocol was submitted on 09/19/ 2007 and was updated by five amendments.

The first amendment included two important changes to the study design:

(1) Group III was modified in such a way that subjects in this group would not at all receive MenACWY and were to be enrolled into a separate open-label group at 12 months of age
(2) A new primary immunogenicity objective was added to assess the immunogenicity of two doses of MenACWY given to healthy young children at 7 to 9 and 12 months of age.

Study enrollment was initiated under protocol Amendment 1.

Due to a shortage of ProQuad™ on the US market, the study protocol was again amended two times in 2009 to allow subjects to receive M-M-R™ II and Varivax™ (MMR+V) in place of ProQuad™ and to allow pooling of the data. The applicant stated that statistical power calculations indicated that the power of the study would be unaffected by the changes, since immune responses to ProQuad™ and MMR+V were reported to be very similar. The applicant performed statistical analyses showing that the immune responses to ProQuad™ and M-M-R-II +Varivax were equivalent and that the groups could be combined without introducing bias into the statistical analysis.

3.2.1 Brief Overview of the Study

The main objectives of this Phase III study were assessments of the safety and immune responses to the concomitant administration of ProQuad™ with MenACWY to healthy infants/toddlers. ProQuad™ (Merck & Co., Inc.) is a measles, mumps, rubella, and varicella vaccine licensed in the U.S. in 2005 for children 12 months to 12 years of age.

Study design

Study V59P21 was a Phase 3, open-label, randomized, multi-center study to evaluate the safety and immunogenicity of ProQuad™ and MenACWY vaccines when administered concomitantly with each other to healthy toddlers.

Two age groups of subjects, those 7 to 9 months old and those 12 months old, were enrolled concurrently. In the group of subjects 7 to 9 months of age at enrollment, approximately 1014 subjects were randomized in a 1:1 ratio to one of two vaccination groups, Group I or II. At the same time, 616 subjects who were 12 months old at the time of enrollment entered the open label Group III. The general study design is shown in Table 3.2.1.1.

Table 3.2.1.1: The general structure of study V59P21

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Age	**7 to 9 Months**	**8 to 10 Months**	**12 Months**	**13.5 Months**
Group 1 N=504	Enrollment MenACWY	N/A	Blood Draw MenACWY MMRV	Blood Draw
Group II N=510	Enrollment MenACWY	Blood Draw	MenACWY	Blood Draw MMRV
Group III N=616	N/A	N/A	Enrolment Blood Draw MMRV	Blood Draw

Source: Clinical Study Protocol (Am 3), Table 6.1.1-1; page 38

Duration of Study

The duration of the individual subject participation in the trial was up to 11 months for subjects in Groups I and II, while participation was only up to 6 months for subjects in Group III.

Process of Data Collection

Immunogenicity:

Blood samples (5 mL) for immunogenicity assays were collected at Visit 2 for subjects in Group II, at Visit 3 for subjects in Groups I and III, and at Visit 4 for all groups. Due to a shortage of ProQuad in 2009, a subset of subjects received MMR™-II and Varivax™ in place of ProQuad™. The term MMRV, used in what follows, denotes vaccination with either ProQuad™ or MMR™-II + Varivax™.

Safety:

During the 15 minutes following each vaccination, signs or symptoms of anaphylaxis, local injection site, and systemic reactions were evaluated and information collected. Following each vaccination, both local (i.e., tenderness, erythema, and induration) and systemic reactions (i.e., change in eating habits, sleepiness, persistent crying, irritability, vomiting, diarrhea, and rash) were recorded. Any SAEs (especially hospitalization) were to be immediately reported. Data on local and systemic reactions, daily auxiliary temperatures and all AEs and medications used were also collected for 7 days following each study vaccination. Protocol-specified reactions of interest (measles-like rash, rubella-like rash, varicella-like rash, injection site rash, mumps-like symptoms) including daily auxiliary temperatures were collected for 28 days after vaccinations given at Visit 3. The use of analgesic or antipyretic medication was also collected in this time interval.

Special attention was paid to measles-like rash, rubella-like rash, varicella-like rash, injection site rash, mumps-like symptoms and, if these reactions occurred, the subject was asked to return to the clinic for examination within 48 hours of the onset of the symptoms.

From Day 8 through 28, after each vaccination, only AEs that required a medical office visit/consultation and/or resulted in premature withdrawal from the study were collected. All AEs were to be monitored until resolution.

Immunogenicity Objectives

<u>Primary immunogenicity objectives:</u>

1. To assess the immune responses to ProQuad™ vaccine administered concomitantly with MenACWY vaccine or given alone to healthy young children

aged 12 months, as measured by seroconversion rates to measles, mumps, and rubella, as well as seroprotection rates for varicella [Comparison of Group I vs. Group III, Visit 4].

2. To compare the immune responses to two doses of MenACWY given to healthy young children at 7 to 9 and 12 months of age, when the second dose of MenACWY was given at 12 months of age either concomitantly with ProQuad™ vaccine or alone, as measured by percentage of subjects with hSBA titer ≥ 1:8 directed against N. meningitidis serogroups A, C, W-135, and Y [Comparison of Group I vs. Group II, Visit 4].
3. To assess the immunogenicity of two doses of MenACWY given to young children at 7 to 9 and 12 months of age, as measured by percentage of subjects with hSBA titer ≥ 1:8 directed against N. meningitidis serogroups A, C, W-135, and Y [Assessment of Group II].

Secondary immunogenicity objectives:

1. To compare the immune responses to two doses of MenACWY given to healthy young children at 7 to 9 and 12 months of age, when MenACWY is administered either concomitantly with ProQuad™ vaccine at 12 months of age or alone, as measured by percentage of subjects with hSBA titer ≥1:4 and hSBA geometric mean titers (GMTs) directed against N. meningitides serogroups A, C, W-135, and Y.
2. To assess the immune responses to ProQuad™ vaccine when it is administered concomitantly with MenACWY vaccine or given alone to healthy young children aged 12 months, as measured by GMTs for measles, mumps, rubella and varicella.
3. To assess the anti-varicella antibody response to ProQuad™ vaccine administered concomitantly with MenACWY vaccine or given alone to healthy young children aged 12 months, as measured by the percentage of subjects who show seroconversion.
4. To assess the immunogenicity of a single dose of MenACWY given at 7 to 9 months of age.

Safety objectives:

To describe the safety profile of subjects in each vaccine group in terms of:

1. Immediate (within 15 minutes) hypersensitivity reactions following vaccination
2. Local and systemic reactions during day 1 to day 7 after each vaccination
3. Adverse events (AEs) that required medical visits and took place between day 8 to day 28 after each vaccination
4. Medically significant AEs and SAEs throughout the study.

Endpoints for assessing vaccine immunogenicity and safety

Immunogenicity endpoints

The immunogenicity endpoints related to immune responses to MMRV vaccine were:

(1) the percentage of initially seronegative subjects who showed seroconversion for measles (as determined by Enzyme-Linked Immunosorbent Assay [ELISA]) at 6 weeks after vaccination and the percentage of initially seronegative subjects who showed seroconversion for mumps (as determined by ELISA) at 6 weeks after vaccination
(2) the percentage of initially seronegative subjects who showed seroconversion for rubella (as determined by ELISA) at 6 weeks after vaccination
(3) the percentage of initially seronegative subjects who showed seroprotection for varicella (as determined by glycoprotein-based ELISA [gpELISA]) at 6 weeks after vaccination
(4) the percentage of initially seronegative subjects who showed seroconversion for varicella (as determined by gpELISA) at 6 weeks after vaccination
(5) the geometric mean titers (GMTs) for antibodies to measles, mumps, rubella and varicella.

Seroconversion was defined as a change from a negative (pre-vaccination) to a positive (post vaccination) result. Detailed definitions of cut-off points in the definition of seroconversion are shown in Table 3.2.1.2.

Table 3.2.1.2: MMRV cut-offs for baseline and post-vaccination responses used in the definition of seroconversion

Antigen	**Cut-off for baseline**	**Cut-off for post-vaccination response**
Measles	<255 mIU/mL	≥ 255 mIU/mL
Mumps	<10 ELISA Ab units	≥ 10 ELISA Ab units
Rubella	<10 IU/mL	≥10 IU/mL
Varicella Seroconversion	<1.25 gp ELISA units/mL	≥ 1.25 gp ELISA units/mL
Varicella Seroprotection	<1.25 gp ELISA units/mL	≥ 5 gp ELISA units/mL

Ab units= Antibody units
IU= International Units
ELISA= Enzyme-linked Immunosorbent Assay
gpELISA= Glycoprotein-based ELISA
Source: Clinical Study Protocol (Am 3), Table 6.5.3-1; page 55

The immunogenicity endpoints for immune responses to MenACWY vaccine for all serogroups were:

(1) percentage of subjects with hSBA ≥1:8
(2) percentage of subjects with hSBA ≥1:4
(3) hSBA Geometric Mean Titers (GMTs).

Hypotheses and sample size considerations

There were three co-primary objectives in this study:

1. To show that concomitant administration of MenACWY vaccine does not interfere with the immunogenicity of MMRV (ProQuad™ or MMR™-II/ Varivax™ (MMR+V))
2. To show that concomitant administration of MMRV vaccine does not interfere with the immunogenicity of MenACWY
3. To show that two doses of MenACWY given at 7 to 9 and 12 months of age induce adequate antibody responses.

Primary immunogenicity hypotheses:

For Objective #1:

H_o: ($P_{MMRV+MenACWY} - P_{MMRV}$) $\geq -\Delta$ for at least one antigen of MMRV (measles or mumps or rubella or varicella)

H_a: ($P_{MMRV+MenACWY} - P_{MMRV}$) $< -\Delta$ for all antigens of MMRV,

where $P_{MMRV+MenACWY}$ and P_{MMRV} are percentages of subjects with seroconversion for either measles or mumps or rubella or with seroprotection rate for varicella in Group I (receiving MMRV+MenACWY) and Group III (receiving MMRV alone), respectively. Delta (Δ) is equal to 5% for measles, mumps and rubella antigens and 10% for varicella antigen.

For Objective #2:

H_o: ($P_{MMRV+MenACWY} - P_{MenACWY}$) $\geq -10\%$ for at least one serogroup A, or C, or W, or Y

H_a: ($P_{MMRV+MenACWY} - P_{MenACWY}$) $< -10\%$ for all serogroups A, C, W, and Y,

where $P_{MenACWY}$ and $P_{MMRV+MenACWY}$ are percentages of subjects with hSBA $\geq$1:8 at 6 weeks after vaccination in Group II (receiving only MenACWY) and Group I (receiving MMRV+MenACWY), respectively.

For Objective #3:

For each serogroup A, C, W, and Y

H_0: $P_i \leq \Delta_i$
H_a: $P_i > \Delta_i$,

where P_i (i=1,2,3, and 4) are proportions of subjects in Group II with hSBA ≥1:8 for the i^{th} serogroup at 6 weeks after the second dose of MenACWY, and Δ_i (i=1,2,3, and 4) are equal to 0.65, 0.85, 0.85, and 0.85 for MenA, MenC, MenW, and MenY, respectively.

The analyses of the primary endpoints were to be based on the per protocol (PP) population. Additional analyses of the primary endpoints based on the modified intent to treat (MITT) population were to be performed as a test of the results robustness.

The study success criterion

The success criterion for this study was a composite based upon the three co-primary objectives, of which all must be met.

The sample size determination

In the last version of the study protocol, pages 82-86, the applicant estimated that the sample size of 1830 subjects was needed to achieve the overall power 88% for the three combined primary objectives and the powers 96%, 94%, and 98% for objectives #1, #2, and #3, respectively.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Disposition of Subjects

A total of 1630 subjects were enrolled and randomized in 90 study centers. A total of 225 subjects withdrew prematurely from the study, while 1405 completed the study. Of the 225 subjects who withdrew prematurely: 78 were in Group I (MenACWY + MMRV), 88 were in Group II (MenACWY), and 59 in Group III (MMRV).

The disposition of subjects in the study groups is summarized in Table 3.2.2.1.

Table 3.2.2.1: Summary of the disposition of subjects in the study groups

	Group I	Group II	Group III
	ACWY+MMRV	ACWY	MMRV
Enrolled	504	510	616
Completed Study	426 (85%)	422 (83%)	557 (90%)
Premature withdrawals due to	78 (15%)	88 (17%)	59 (10%)
AE	1 (<1%)	0	0
Lost to Follow-up	24 (5%)	23 (5%)	21 (3%)
Withdrew consent	21 (4%)	30 (6%)	29 (5%)
Inappropriate Enrollment	4 (<1%)	3 (<1%)	5 (<1%)
Administrative reason	2 (<1%)	6 (1%)	0
Protocol Deviation/Violation	26 (5%)	26 (5%)	4 (<1%)

Source: Reviewer's table based on Figure 10.1-1; CSR, page 76

Across all groups, premature withdrawals were mainly due to: withdrawal of consent (80 subjects), loss to follow-up (68 subjects), and protocol deviation/violation (56 subjects).

Protocol Deviations

Protocol deviations were reported for 53% (867 subjects) of the enrolled subjects, while 22% (365 subjects) of the enrolled subjects experienced major protocol deviations, with the MenACWY+MMRV subjects exhibiting the highest percentage (28%). A summary of protocol deviations by study group is given in Table 3.2.2.2.

Table 3.2.2.2: Summary of common major protocol deviations

Deviation	Group I ACWY+MMRV	Group II ACWY	Group III MMRV
Enrolled	504	510	616
Any protocol deviations	286 (57%)	354 (69%)	227 (37%)
Any major deviations	139 (28%)	133 (26%)	93 (15%)
No MenACWY immunization	41 (8%)	53 (10%)	0
No MMRV immunization	45 (9%)	0	16 (3%)
No blood draw at any visit	49 (10%)	27 (5%)	19 (3%)
No blood draw at one of visits	54 (11%)	59 (12%)	57 (10%)
Blood draw out of window	10 (2%)	19 (4%)	21 (4%)
Received excluded treatment	17 (3%)	18 (4%)	2 (<1%)

Source: Reviewer's table based on Table 10.2-21; CSR, page 78

The most frequent major deviations were:

(1) No blood draws, especially at Visit 4: altogether 138 subjects, in that 34 (7%), 59 (12%), and 45 (7%) subjects in MenACWY + MMRV, MenACWY, and MMRV groups, respectively
(2) No MMRV immunization: 61 subjects
(3) No MenACWY immunization, especially at injection #2 (visit 3): altogether 87 subjects; 41 (8%) in MenACWY + MMRV group and 46 (9%) subjects in MenACWY groups
(4) Sample available but no ACWY serology results: 50 subjects; 26 (5%) in MenACWY+ MMRV group and 24 (5%) subjects in MenACWY group
(5) Subjects received excluded concomitant treatment or vaccine: altogether 37 subjects; 17 (3%), 18 (4%), and 2 (<1%) subjects in MenACWY + MMRV, MenACWY and MMRV groups, respectively.

Demographic Characteristics

At the commencement of the study, the demographic and other baseline characteristics of the enrolled infants were balanced across the study groups. The majority of the population consisted of Caucasians (59% to 62%), while Asians, Blacks, Hispanics, and

others constituted the rest. Gender ratios were similar across the study groups. The mean age was 8.5 ± 0.8 months in the MenACWY +MMRV and MenACWY groups, and 12.1 ± 0.3 months in the MMRV group (the baseline for this group was at 12 months of age). Weight and height were similar for the MenACWY + MMRV and MenACWY groups, and greater for the MMRV group (the children were older).

3.2.3 Evaluation of Study Immunogenicity Results

Data sets analyzed

The applicant carried out evaluations of all primary and secondary immunogenicity objectives on the per protocol (PP) populations (there were 2 main different PPs). A total of 1630 subjects were enrolled into the study; however, only 1603 subjects were vaccinated, in that 500, 503, and 600 subjects received MenACWY + MMRV, MenACWY, and MMRV, respectively. A summary of the main populations used in the applicant's analyses is given in Table 3.2.3.1.

Table 3.2.3.1: Overview of populations used in the analyses

Population	Group I ACWY+MMRV	Group II ACWY	Group III MMRV
Enrolled	504	510	616
Exposed	500 (99%)	503 (99%)	600 (97%)
Safety	500 (99%)	500 (98%)	597 (97%)
Safety-follow-up	460 (91%)	453 (89%)	556 (90%)
MITTT-MenACWY	455 (90%)	483 (95%)	597 (97%)
MiITT-MMRV	397 (79%)	483 (95%)	536 (87%)
PP-MenACWY	389 (77%)	386 (76%)	544 (88%)
PP-MMRV	388 (77%)	402 (79%)	528 (86%)

Source: Table 11.1-1, CSR; page 79

Reviewer's comments:

In the CSR (page 117 of 9389), it was stated that "no pre-identified immunogenicity subset was used in this study; all subjects were to have blood drawn, which could potentially have been used for analysis." While all available samples were tested for the MMRV antigens and serogroup A, a randomly selected group of subjects was chosen for the analyses of C, W-135, and Y serogroups. However, the applicant did not pre-specify the method used for subject selection for the C, W-135, and Y serogroups analyses.

I. Primary immunogenicity hypotheses

Primary Objective #1 - Non-inferiority Hypothesis #1

Objective #1 (the MMRV primary immunogenicity hypotheses) was to show that the immune response to measles, mumps, rubella, and varicella at six weeks after vaccination with one dose of MMRV (ProQuad™ or MMR™-II/ Varivax™) given concomitantly with MenACWY (Group I) was non-inferior to the immunogenicity of MMRV administered alone (Group III). The criteria for testing the hypothesis related to objective #1 were: the lower limits of the two-sided 95% CIs of the estimated differences of the percentages of subjects with seroconversion for measles, mumps, and rubella, and seroprotection for varicella at 6 weeks after MMRV vaccination were to be greater than or equal to -5% for measles, mumps, and rubella and greater than or equal to –10% for varicella. A summary of the results of the hypothesis testing is presented in Table 3.2.3.2.

Table 3.2.3.2: Seroconversion rates for measles, mumps, and rubella, and seroprotection rate for varicella (PP Population)

Antigen	MenACWY +MMRV			MMRV			Estimation	
	n	Rate	95% CI	n	Rate	95% CI	Difference (%)	95% CI
Measles	350	98 (342)	(96, 99)	467	99 (462)	(98, 100)	-1	(-3.4, 0.5)
Mumps	365	98 (357)	(96, 99)	499	96 (481)	(94, 98)	1	(-1.0, 3.7)
Rubella	370	95 (353)	(93, 97)	515	97 (500)	(95, 98)	-2	(-4.5, 0.8)
Varicella								
Seroconversion	370	96 (325)	(94, 98)	459	98 (448)	(96, 99)	-1	(-3.9, 1.2)
Seroprotection	337	99 (333)	(97, 100)	459	99 (456)	(98, 100)	-1	(-2.4, 0.8)

Source: Table 11.4.1.1-1, CSR, page 83

From Table 3.2.3.2, it can be seen that the seroconversion rates for varicella in the MenACWY +MMRV group were non-inferior to those in the MMRV alone group: the lower limit of the two-sided 95% CI of the difference between the percentage of subjects with seroconversion in the MenACWY + MMRV group and the percentage of subjects with seroconversion in the MMRV group was -3.4%, -1.0%, and -4.5% for measles, mumps, and rubella, respectively. Additionally, the results showed that the seroprotection rates for varicella in the MenACWY + MMRV group were non-inferior to rates in the MMRV alone group: the lower limit of the CI for the difference in percentage of subjects with seroprotection between the two groups was -3.9%.

Reviewer's comments:

- The pre-specified criteria for the primary objective #1 were met. The seroconversion rates for measles, mumps, rubella, and the seroprotection rates for varicella in the MenACWY + MMRV and MMRV groups were similar.
- The groups MenACWY + MMRV (Group I) and MMRV (Group III) were not randomized groups. Therefore, the results should be interpreted with caution.
- Due to a shortage of ProQuad on the US market, M-M-R™ II and Varivax™ (MMR+V) vaccines were given in place of ProQuad. The applicant performed statistical analysis showing that the immune responses to ProQuad and M-M-R-II and Varivax were equivalent and that the groups receiving M-M-R™ II and Varivax™ (MMR+V) or ProQuad could be combined without introducing bias into the statistical analysis. This applicant's statistical analysis was based on an

ANOVA model with center and MMRV types (M-M-R™ II+Varivax™ or ProQuad) as factors. The conclusion related to similarity of these two vaccines was supported by examination of the ratio of GMTs and by showing that the 2-sided 95% CI obtained from the ANOVA was contained within the interval [0.5, 2.0]. However, the applicant's modeling for checking similarity of immune responses to ProQuad and M-M-R-II + Varivax was performed on the dataset combined from two different groups, Groups I and III. The subjects from Groups I and III received MenACWY +MMRV and MMRV, respectively, but interactions between MenACWY and ProQuad and between MenACWY and MMR+V are unknown. Additionally, the applicant did not show that the group of subjects who received M-M-R™II + Varivax™ was statistically similar (with respect to factors like age, gender, etc) to the group of subjects who received ProQuad™. Therefore, it is unknown whether these two groups of subjects were really poolable.

Primary Objective #2 - Non-inferiority Hypothesis #2

Objective #2 (the MenACWY primary immunogenicity hypothesis) was to show that the immune response to MenACWY given concomitantly with MMRV (Group I) can be considered non-inferior to the immunogenicity of MenACWY administered alone (Group II). The criteria for this hypothesis testing were: the lower limit of the two-sided 95% CI of the estimated differences ($P_{MMRV+MenACWY}$ - $P_{MenACWY}$) of the percentages of subjects with hSBA ≥ 1:8 at 6 weeks after the second dose of MenACWY (concomitantly with MMRV or alone) given to 12-month old toddlers were to be greater than or equal to -10% for each serogroup (comparison of Group I vs. Group II at Visit 4). A summary of the results of the MenACWY primary hypothesis testing is presented in Table 3.2.3.3.

Table 3.2.3.3: Percentages of subjects with hSBA ≥1:8 for all four serogroups

Serogroup	ACWY+MMRV			ACWY			Estimation of difference	
	N	≥ 1:8	95% CI	N	≥ 1:8	95% CI	Difference	95% CI
A	384	88%	(84, 91)	379	88%	(84,91)	0%	(-4.7, 4.5)
C	204	100%	(98, 100)	199	100%	(98, 100)	0%	(-1.8, 1.9)
W	205	100%	(97, 100)	199	98%	(96, 100)	1%	(-1.3, 3.9)
Y	201	98%	(95, 99)	198	96%	(93, 99)	2%	(-1.9, 5.3)

Source: Table 11.4.1.2-1, CSR, page 89

Reviewer's comments:

- The pre-specified criteria for the primary objective #2 were met. The percentages of subjects with hSBA ≥1:8 for all four serogroups in MenACWY for the MenACWY+ MMRV and MenACWY groups were similar.
- The applicant did not investigate a possible influence, on the objective #2 results, of using two different vaccines (M-M-RII+Varivax® and ProQuad) in the MenACWY+MMRV group.
- The applicant did not supply information on assignment of sera to the assay runs.

Primary Objective #3

Objective #3 (the MenACWY secondary immunogenicity hypothesis) was to show that two doses of MenACWY administered at 7 to 9 and 12 months of age induce adequate antibody responses. The criteria for this hypothesis testing were: the lower limits of the two-sided 95% CIs of estimated percentages of subjects with hSBA ≥1:8 at 6 weeks after the second dose of MenACWY were to be greater than or equal to 85% for serogroups C, W, or Y, and greater than or equal to 65% for the serogroup A. A summary of the results of this hypothesis testing is presented in Table 3.2.3.4.

Table 3.2.3.4: Percentages of subjects with hSBA ≥1:8 and estimations for GMTs for all four serogroups

Serogroup	ACWY				
	N	≥ 1:8	95% CI	GMT	95% CI
A	379	**88%**	(84,91)	37	(32, 42)
C	199	100%	(98, 100)	180	(158, 205)
W	199	98%	(96, 100)	119	(101, 139)
Y	198	96%	(93, 99)	88	(73, 105)

Source: based on Table 11.4.1.2-2, CSR, page 90

Reviewer's comments:

- The pre-specified criteria for the primary objective #3 were met. In the MenACWY group, the percentages of subjects with hSBA ≥1:8 were 88%, 100%, 98%, and 96%, for serogroups A, C, W, and Y, respectively. After the first dose of MenACWY, the GMTs for the MenACWY group were 8.16, 26, 5.11 and 4.09 for serogroups A, C, W, and Y, respectively, and the GMTs after the second dose increased to 37, 180, 119, and 88, respectively.
- The applicant did not describe methods of subject selection for the analyses of C, W-135, and Y serogroups. Additionally, it is unknown whether each selected sub-group was representative of the relevant whole study group.
- The applicant mentioned in the SAP that another level of sufficiency of immune response for serogroup A (lower limit of the two-sided 95% CI greater than 65%) was based on data from Phase II study V59P9 that was very similar in design to study V59P21. However, higher responses were observed in a separate Phase II study V59P7 in toddlers where the percentages of subjects with hSBA ≥ 1:8 for the serogroup A were 89% and 100% when 2 doses of MenACWY were administered 6 months or 12 months apart, respectively.
- In study P21, the lower limits of the immune responses to 2 doses of MenACWY not only met the pre-specified criteria for sufficiency of response but even met the higher criteria levels, ≥80% for serogroup A and ≥85% for serogroups C, W-135, and Y, i.e., criteria specified for the four-dose infant series study V59P14. Thus, it appears that the immune response to 2 doses of MenACWY is similar to the immune response to the 4-dose infant regimen**.**

II. Secondary immunogenicity objectives

A summary of the results for the secondary objectives are as follows:

1. MenACWY given concomitantly with MMRV at 12 months of age was shown to be non-inferior to MenACWY given alone, as assessed by the difference in the percentages of subjects with hSBA ≥1:4 and by ratios of GMTs for serogroups A, C, W-135, and Y.
2. GMTs for measles, mumps, rubella, and varicella showed that MMRV given concomitantly with MenACWY at 12 months of age had similar immunogenicity as MMRV given alone.
3. The seroconversion rates showed that similar anti-varicella vaccine antibody responses were elicited when MMRV was given concomitantly with MenACWY or alone.
4. A single dose of MenACWY given at 7-9 months of age was immunogenic, as measured by the percentages of subjects with hSBA ≥1:4, hSBA ≥1:8, and GMTs for the four serogroups.

3.2.4 Summary of the Immunogenicity Statistical Results

The primary objectives of the V59P21 Phase III study were assessments of the vaccination safety and the immune responses to the concomitant administration of ProQuad™ with MenACWY to healthy toddlers. However, a supply interruption of ProQuad™ occurred during the course of the study, so M-M-R™II and Varivax™ were used instead of the ProQuad™ vaccine.

The applicant presented an analysis of the comparability of the M-M-R™II + Varivax™ and ProQuad™ vaccines to support pooling of the data from two groups into a single group designated as MMRV. The comparability of these two vaccines was justified only by showing that the immune responses to ProQuad and M-M-R-II + Varivax were statistically equivalent. The applicant's statistical analysis was based on an ANOVA model with center and MMRV types (M-M-R™ II+Varivax™ or ProQuad) as factors. The conclusion related to similarity of these two vaccines was supported by examination of the GMT ratios and by showing that the 2-sided 95% CI obtained from the ANOVA was contained within the interval [0.5, 2.0]. However, the applicant's modeling for checking similarity of immune responses to ProQuad and M-M-R-II + Varivax was performed on the dataset combined from two different groups, Groups I and III. The subjects from Groups I and III received MenACWY +MMRV and MMRV, respectively, but the interactions between MenACWY and ProQuad and between MenACWY and MMR+V are unknown. Additionally, the applicant did not show that the group of subjects who received M-M-R™II + Varivax™ was statistically similar (with respect to factors like age, gender, etc) to the group of subjects who received ProQuad™. Therefore, it is unknown whether these two groups of subjects were really poolable.

Under the assumptions that there was no statistical difference between the M-M-R™II + Varivax™ and ProQuad™ vaccines and that the populations of Groups I and III were not different**,** the criteria for two primary immunogenicity objectives were met:

(1) For the investigated antigens, concomitant administration of MenACWY with MMRV at 12 months of age did not affect the immune response to MMRV.
(2) For the serogroups A, C, W, and Y, concomitant administration of MMRV with MenACWY did not affect the immune response to MenACWY.

The criterion for the third primary objective was met as well: the two-dose series of MenACWY, administered at 7-9 and 12 months of age, induced adequate immune response to all four serogroups, as measured by the percentage of subjects with hSBA≥1:8. The response to 2 doses of MenACWY not only met the pre-specified criteria for sufficiency of response but met even the higher criteria, ≥80% for serogroup A, and ≥85% for serogroups C, W-135, and Y, i.e., levels specified for the four-dose infant series in the V59P14 study.

However, there are some issues related to the testing of these hypotheses.

1. All available samples were tested for the MMRV antigens and serogroup A. However, a randomly selected group of subjects was utilized for the analyses of each serogoup: C, W-135, and Y. The method used for the subject selection for the C, W-135, and Y serogroups analyses was not pre-specified. And, it is unknown whether each selected group was representative of the whole relevant study group.
2. Study P21 was not a "fully" randomized study. Two age groups 7 to 9 months old and 12 months old were enrolled concurrently, but the group of subjects 7 to 9 months of age at enrollment were randomized in a 1:1 ratio to one of two vaccination groups (Group I or II), while subjects 12 months old were all enrolled into the open label Group III. Therefore, a potential bias could be introduced. The first hypothesis was tested based on the combined dataset for subjects from Group I and Group III. It appears that the applicant did not statistically compare populations of Group 1 (MenACWY+MMRV) and Group III (MMRV) at Visit III (vaccination) with respect to: age, sex, race, and titers for antibodies to measles, mumps, rubella, and varicella. The applicant should perform an additional statistical analysis to check for potential bias between Group I and III.

4. Statistical Evaluations of Safety Data

Safety of the MenACWY vaccine in infants and toddlers was evaluated in 3 Phase III trials (V59P14, V59P21, and V59P23) and 3 Phase II trials (V59P5, V59P8, and V59P9).

The applicant assessed the vaccine safety based on the following categories of safety measures:

1) solicited AEs (i.e., local and systemic reactions) and selected indicators of reactogenicity (e.g., use of analgesic/antipyretic medication) on the day of vaccination and each of the following 7 days
2) unsolicited AEs (and related concomitant medications), as predefined in the respective study protocols
3) AEs necessitating a physician's visits
4) medically significant AEs (AEs requiring a physician's visit, Emergency Department visit, or leading to withdrawal, excluding pre-planned visits, medical office visits, or Emergency Room visits for routine medical care and common acute conditions (e.g., upper respiratory tract infection, otitis media, pharyngitis, urinary tract infection, gastroenteritis, superficial skin infection, contact dermatitis))
5) SAEs and AEs leading to premature withdrawal.

Table 4.0.1 (ISS, page 20) summarizes the monitoring periods for AEs in 5 clinical trials conducted with MenACWY in children ages 2 months to 2 years. The monitoring periods were not the same for each study; therefore, it would be difficult to combine safety data from the different studies.

Table 4.0.1: Monitoring periods for safety assessment

Study	Solicited AEs, other indicators of reactogenicity, and all unsolicited AEs	Medically significant AEs	AEs necessitating a physician's visit	SAEs and AEs leading to premature withdrawal
V59P5	Days 1 to 7 after each vaccination	throughout the study	From 2- to 7-month visits and 1 month post-toddler doses	throughout the study
V59P8	Days 1 to 7 after each vaccination	throughout the study	1 month post-vaccination	throughout the study
V59P9	Days 1 to 7 after each vaccination	throughout the study	1 month post-vaccination	throughout the study
V59P14	Days 1 to 7 after each vaccination	throughout the study	From 2- to 7-month visits and 1 month post-toddler doses	throughout the study
V59P23	Days 1 to 7 after each vaccination	throughout the study	throughout the study	throughout the study

Source: ISS, page 20

The applicant presented in tables the numbers and percentages of unsolicited adverse events by time period. The definitions of the time periods (categories) used in these tables are as follows:

1) Infant Vaccination Series: from the first vaccination through 1 month post-infant series vaccination (as applicable)
2) Between infant series: 1 month post-infant series to the first toddler dose
3) Toddler Dose: from the first toddler dose through 1 month post-vaccination

4) 12-18 Months of Age: from 1 month after the last toddler vaccination through 6 months after the last vaccination.

4.1 Evaluation of clinical trial V59P14 safety data

The population in clinical study V59P14 was composed of four main sub-populations:

1. US immunogenicity /safety: US1A, US1B, and US2 groups
2. US safety (only): US 3 and US4 groups
3. LA immunogenicity/safety: LA1, LA2, LA3, and LA4 groups
4. LA safety (only): LA5 and LA6 groups.

There were three countries that enrolled subjects into this trial: US, Argentina (LA1-LA6), and Colombia (LA5 and LA6). Totals of 1508, 1530, and 1507 subjects were enrolled in the US, Argentina, and Colombian sites, respectively. Table 4.1.1 shows the distributions of subjects per vaccine group.

Table 4.1.1: Distribution of LA and US subjects by vaccine groups

Group	Enrolled			Exposed to	Completed Study
	US	Argentina	Colombia		
US1	320			ACWY+Routine	241
US2	159			Routine ACWY (12+15 mths)	110
US3	680			ACWY+Routine	561
US4	349			Routine ACWY after 12 mths	240
LA1		301		ACWY+Routine	289
LA2		148		Routine ACWY (12+15 mths)	121
LA3		301		ACWY+Routine	280
LA4		150		Routine ACWY after 12 mths	135
LA5		420	1006	ACWY+Routine	1270
LA6		210	501	Routine ACWY after 12 mths	607

Source: Reviewer's table

In the following paragraphs, the US and LA safety sub-populations will be first considered separately, but the final safety statistical analyses will be based on the entire study population.

Based on the V59P14 study protocol, the safety data were collected in the following way: First, subjects were observed for 15 minutes after each vaccination to capture immediate hypersensitivity reactions. Next, local and systemic reactions, auxiliary temperature, analgesic/antipyretic medication use, and all adverse events were to be collected for 7 days after each vaccination using diary cards which were given to the subject's parents/legal representatives.

For all groups, information about serious adverse events (SAEs) and AEs requiring a medical office or emergency room (ER) visit and/or resulting in a premature withdrawal of subjects from the study were collected and recorded during each study visit. However, medical office or ER visits for routine medical care and common acute conditions were not collected from the 7-month visit until the next study vaccination, from 28 days after the last MenACWY vaccination until study termination, and, for US4 and LA6, from one month after the 12-month visit up to the 18-month of age preplanned visit,. Additionally, SAEs were collected by phone 6 months after the last MenACWY vaccination.

US safety population

Disposition of Subjects

A total of 1029 subjects were enrolled in the US safety only groups US3 and US4, but only 801 enrolled subjects completed the study. A summary of subject disposition by study group for the US safety population is given in Table 4.1.2.

Table 4.1.2: Disposition of subjects for US safety groups

	Safety Subjects				
	US3	US4			
		US4A	US4B	US4C	Total
Enrolled	680	76	70	203	349
Completed Study	561 (83%)	8 (11%)	54 (77%)	178 (88%)	240 (69%)
Discontinued	119 (18%)	68 (89%)	16 (23%)	25 (12%)	109 (31%)
due to					
AE	4 (<1%)	2 (3%)	1 (1%)	1 (<1%)	4 (1%)
Lost to Follow-up	29 (4%)	11 (14%)	5 (7%)	8 (4%)	24 (7%)
Withdrew consent	52 (8%)	38 (50%)	6 (9%)	12 (6%)	56 (16%)
Administrative reason	20 (3%)	9 (12%)	1 (1%)	1 (<1%)	11 (3%)
Other Reason	13(2%)	6 (8%)	3 (4%)	3 (1%)	12 (5%)

Source: CSR, page 105

As can be concluded from Table 4.1.2, 18% of subjects in the US3 group and 31% subjects in the US4 group withdrew prematurely. The major reason for the premature withdrawal was withdrawal of consent (52 (8%) subjects in US3 group and 56 (16%)

subjects in US4 group). Other reasons included adverse events, inappropriate enrollment, and protocol deviations/violations.

In the US4A group, 50% of subjects withdrew consent, 14% of subjects were lost to follow up, and 12% withdrew due to administrative reasons. The overall withdrawal rate in the US4A group was 89%. Please note that the high rate of withdrawals in the US4A group was partially due to the implementation of protocol Amendment 4. Per the applicant, the enrollment into US4 began in September 2007 and was completed in March 2008. Amendment 4 (which changed the toddler schedule from dosing at 12 and 15 months to dosing at 13 and 15 months) was implemented in May 2008. At this point, most subjects remaining in the study became US4B subjects and subsequently US4C (in August 2008, when Amendment 5 went into effect). The highest drop-out rates occurred in the early stage of the study course, prior to Amendments 4 and 5 being implemented. These early subjects were all assigned, by definition, to US4A subgroup.

Protocol deviations – US safety subjects

A summary of protocol deviations by study group for the US safety population is given in Table 4.1.3.

Table 4.1.3: Number of subjects with protocol deviations – US Safety Subjects

	Safety Subjects				
	US3	**US4**			
Deviation	**680**	**US4A (76)**	**US4B (70)**	**US4C (203)**	**Total (349)**
Any protocol deviations	438 (64%)	76 (100%)	62 (89%)	153 (75%)	291 (83%)
Any major deviations	77 (11%)	43 (57%)	15 (21%)	44 (22%)	102 (29%)
Incomplete Infant Series	54 (8%)	37 (49%)	1 (1%)	0	38 (11%)
Incomplete Toddlers Series	21 (3%)	5 (7%)	12 (17%)	27 (13%)	44 (13%)
Control infants received MenACWY	0	6 (8%)	12 (17%)	12 (6%)	30 (10%)
Control Toddlers received MenACWY	0	0	1 (1%)	8 (4%)	9 (3%)

Source: CSR, page 110, Table 10.1-1B

As shown in Table 4.1.3, for US3 and US4 safety populations, protocol deviations were reported for 64% and 83% of subjects, respectively; in that, major protocol deviations constituted 11% and 29%, respectively.

The main major deviation in US4A was 'Incomplete Infant Series' (49%), i.e., failure to complete the recommended schedule. Some of deviations occurred due to the protocol study changes introduced by Amendment 4.

Reviewer's Comments

The main objective of study V59P14 was to evaluate the immunogenicity and safety of the 4-dose series of MenACWY for the infant population. The V59P14 study was

designed by the applicant without a control group for safety evaluation of the 4 dose series in US subjects. Per protocol specification, US1A and US3 subjects received four doses of MenACWY concomitantly with the routine vaccines, while US1B subjects received only routine vaccination at 12 months of age. US2 and US4A subjects received MenACWY vaccination for the first time at 12 months of age. US4B subjects received the first MenACWY vaccination at 13 months of age while US4C subjects received their first and only MenACWY vaccination at 18 months of age. Subjects in US2, US4A, and US4B also received the second toddler vaccination at 15 months of age.

In the CSR, the applicant presented descriptive results for safety data based on the data for each group separately and for combined US1A + US3 and US2 + US4C groups, and then compared results.

However, the appropriateness of pooling data from the different US groups has limitations because:

1) Methods of safety information collection in the US1 and US2 groups were different from the methods used in the US3 and US4 study groups
2) The US4C group was not created by a randomization process but it was pre-specified by the applicant after the infant series, based on data for the US4 group.

Statistical assessment of V59P14 US safety data

Based on the Clinical Study Report, of 1508 subjects enrolled in the US groups, 1500 subjects were exposed to at least one vaccination and provided safety data; hence, 1500 subjects were included in the safety analysis. The applicant presented (CSR, page 185 of 31591) rates (percentages) of "at least one adverse event occurrence" (any: local, systemic and other) during the 7 days follow-up after any infant vaccination.

Table 4.1.4: Number of subjects with at least one local and/or systemic reaction after any infant vaccination

	Number (%) of Subjects with Solicited Reactions					
Reaction	**US1a N = 153**	**US1b N = 165**	**US1 N = 318**	**US2 N = 159**	**US3 N = 677**	**US4 N = 345**
Any	142 (93%)	159 (96%)	301 (95%)	150 (94%)	632 (93%)	313 (91%)
Severe	18 (12%)	15 (9%)	33 (10%)	22 (14%)	97 (14%)	67 (19%)
Local	101 (66%)	113 (68%)	214 (67%)	120 (75%)	457 (68%)	232 (67%)
Severe	5 (3%)	4 (2%)	9 (3%)	10 (6%)	34 (5%)	32 (9%)
Systemic	130 (85%)	153 (93%)	283 (89%)	140 (88%)	583 (86%)	287 (83%)
Severe	15 (10%)	12 (7%)	27 (8%)	15 (9%)	78 (12%)	45 (13%)
Other	123 (80%)	136 (82%)	259 (81%)	134 (84%)	550 (81%)	276 (80%)

Source: CSR, page 185

From the above table, it can be observed that after the infant series vaccinations, the percentages of subjects with reactogenicity were high and similar across the vaccination groups (range 91% to 96%), with the majority of reactions being systemic reactions (range 85% to 88%). Most of the reactions were mild to moderate in severity. Any severe reactions were reported for 9% to 19% of infants, in that they were reported for 7% to 10% of subjects after the first vaccination, for < 1% to 9% of subjects after the second vaccination, and for < 1% to 6% of subjects after the third vaccination. The distribution of reactions after each vaccination is presented in Table 4.1.5

Table 4.1.5: Numbers of subjects with at least one local and/or systemic reaction after each infant vaccination

	US1A	US1B	US1	US2	US3	US4
Vaccination1	N = 153	N = 165	N = 318	N = 159	N = 677	N = 345
Any	129 (84%)	151 (92%)	280 (88%)	138 (87%)	586 (87%)	289 (84%)
Local	70 (46%)	83 (50%)	153 (48%)	78 (49%)	350 (52%)	179 (52%)
Systemic	112 (73%)	141 (85%)	253 (80%)	122 (77%)	515 (76%)	253 (73%)
Other	105 (69%)	120 (73%)	225 (71%)	110 (69%)	447 (66%)	223 (65%)
Vaccination2	N = 141	N = 150	N = 291	N = 151	N = 646	N = 325
Any	115 (82%)	121 (81%)	236 (81%)	124 (82%)	529 (82%)	263 (81%)
Local	65 (46%)	67 (45%)	132 (45%)	76 (50%)	256 (40%)	153 (47%)
Systemic	100 (71%)	97 (65%)	197 (68%)	100 (66%)	427 (66%)	224 (69%)
Other	94 (67%)	91 (61%)	185 (64%)	96 (64%)	385 (60%)	201 (62%)
Vaccination3	N = 138	N = 146	N = 284	N = 143	N = 629	N = 311
Any	100 (72%)	116 (79%)	216 (76%)	120 (84%)	468 (74%)	228 (73%)
Local	46 (33%)	54 (37%)	100 (35%)	65 (45%)	235 (37%)	124 (40%)
Systemic	72 (52%)	87 (60%)	159 (56%)	86 (60%)	343 (55%)	185 (59%)

Source: CSR, page 217

The proportions of subjects experiencing adverse events within 7 days after vaccination were similar across groups for each vaccination. The percentages of subjects with reactogenicity declined slowly with subsequent infant vaccinations in all vaccination groups except for the US2 group (87% after first vaccination, 82% after second vaccination, and 84% after third vaccination).

Reviewer's Comments

Due to a large amount of missing information (mainly from the diary-cards), it is possible that Tables 4.1.4 and 4.1.5 may not provide fully unbiased results. For example, 12 subjects (US1A group) who withdrew from the study after the first dose and for whom a lot of information was missing, were still included in the safety analyses. Table 4.1.6 shows the influence of 15-minute data inclusion into the analyses by displaying

differences between the applicant and the statistical reviewer results after the first dose of vaccinations.

Table 4.1.6: The influence of 15-minute data on some reactogenicity factors estimated for 7-Day period after the 1st infant series vaccination

		US1A (N=153)		US1B (N=165)		US2 (N=159)	
		Reviewer without 15 min	Applicant with 15 min	Reviewer without 15 min	Applicant with 15 min	Reviewer without 15 min	Applicant with 15 min
Reaction							
Pain	Any	57/144	64/151	70/158	76/164	63/151	69/159
	Severe	2/144	3/151	4/158	4/164	6/151	6/159
Diarrhea	Any	24/144	24/151	45/158	23/164	16/151	17/159
	Severe	2/144	2/151	0/158	0/164	1/151	1/159
Fever($\geq 38^0$)	Any	13/126	13/153	6/147	6/146	7/139	7/157
	Severe	0/126	0/153	0/147	0/146	7/139	1/157

Source: Rewiewer's analysis

Additionally, due to the collection of 15-minute data during a visit, the analyses of reactogenicity data should be carried out on three datasets covering 15 minutes, 6-hour to 3-day, and then 4-day to 7 –day time periods.

The applicant presented an overview of reactogenicity after age 12 months vaccinations. A summary of such reactogenicity data is given in Table 4.1.7 (CSR, page 217, Table 12.2.1-1).

Table 4.1.7: Overview of reactogenicity during the 7 days period after 12-month vaccination - US Subjects

	US1A N = 122	**US1B** N = 124	**US3** N = 583	**US1A+US3** N = 704
Any	84 (69%)	87 (70%)	381 (65%)	465 (66%)
Local	33 (27%)	40 (32%)	188 (32%)	221 (31%)
Systemic	70 (57%)	61 (49%)	267 (46%)	337 (48%)
Other	60 (49%)	56 (45%)	260 (45%)	320 (45%)

Source: CSR, page 217, Table 12.2.1-1

From the previous table it can be observed that after the vaccination at 12 months, subjects receiving MenACWY concomitantly with routine vaccines (US1A,US3) or subjects receiving the routine vaccines alone (US1B) had similar percentages for reactogenicity (65% - 70%). The majority of reactions were systemic reactions (range from 46% to 57%). Most of the reactions after the 12-month vaccination were mild to

moderate in severity. A total of 2%-4% subjects after the 12-month vaccination reported severe reactions.

Adverse Events – US Population

The descriptive analyses were based on data for the study groups: US1, US2, US3, and US4. However, it is important to note that:

(1) Subjects in US1A, US1B (US1 comprises subjects from US1A and US1B) and US3 received three doses of infant series MenACWY concomitantly with the routine infant vaccines at 2, 4, and 6 months of age.
(2) Subjects in US2 and US4 received only the routine infant vaccines at 2, 4, and 6 months of age.
(3) Subjects in US1A and US3 received the toddler MenACWY vaccination at 12 months of age (the fourth MenACWY vaccination) while US4C subjects received only MenACWY vaccination at 18 months of age, thus providing a naïve control group (but not created through the randomization) for US1A and US3 groups.

The overview is presented in Table 4.1.8 (CSR, page 214, Table 12.2.1-17).

Table 4.1.8: Overview of AEs- US subjects

Infants Series					
	US1A 153	**US1B** 165	**US2** 159	**US1+US3** 995	**US2+US4** 504
Any AEs	113 (74%)	113 (68%)	111 (70%)	751 (75%)	385 (76%)
SAEs	3 (2%)	4 (2%)	1 (1%)	29 (3%)	14 (3%)
AEs leading to withdrawals	2 (1%)	0	2 (1%)	5 (<1%)	5 (1%)
Death	0	0	0	0	0
Between Infant Series and Toddler Dose					
	US1A 137	**US1B** 149	**US2** 139	**US1+US3** 887	**US2+US4** 424
Any AEs	48 (35%)	54 (36%)	50 (36%)	288 (32%)	147 (35%)
SAEs	5 (4%)	1 (1%)	4 (3%)	12 (1%)	10 (2%)
AEs leading to withdrawals	0	0	0	1 (<1%)	1 (<1%)
Death	0	0	0	0	0
12-18 Months					
	US1A 121	**US1A+US3** 682	**US4C** 178		
Any AEs	68 (56%)	376 (55%)	110 (62%)		
SAEs	3 (2%)	16 (2%)	3 (2%)		
AEs leading to withdrawals	0	0	0		
Death	0	0	0		

Source: CSR, page 214, Table 12.2.1-17

Based on the CSR, the most commonly reported AEs were upper respiratory tract infections (34% - 36%, similar across the vaccination groups) followed by otitis media (25% - 31%, higher in US4C) and pyrexia (11% - 24%; higher in US4C). The AEs that were at least possibly related were pyrexia, diarrhea, rash, irritability, eating disorder, somnolence, and induration.

Reviewer's Comments

Conclusions that can be made based on the applicant's data, including the summary provided in Table 4.1.8, related to AEs, should consider the following limitations:

(1) The number of participating subjects diminished considerably over the course of the study. Therefore, for instance: claiming that all 153 (US1A) enrolled subjects were followed for one month after the 3rd dose is incorrect (for instance, after the first dose of vaccination 12 subjects dropped out from the study without supplying safety data)
(2) Methods of safety information collection in the US1 and US2 groups were different from the ones used in the US3 and US4 study groups
(3) The US4C group was not created by a randomization process but only due to implementation of Amendment 5. The reason for creation of the US4C group was that the US4 group could not serve as a (safety) control for the 4-dose MenACWY group (control up to 6 months post the final MenACWY dose). Group US4C was initiated in August 2008. Since that time point, most subjects remaining in the study were assigned by the applicant to the US4C group. This means that the US4C group was pre-specified by the applicant after the infant series of vaccination was completed.

Based on the applicant report, a total of 90 US subjects reported SAEs with similar percentages across the study groups. Three SAEs reported in US3 (Kawasaki's Disease, partial complex seizures, and febrile convulsion) were at least possibly related to the vaccination. No deaths were reported in US subjects.

Safety Evaluation - LA Subjects

Of a total of 3037 subjects enrolled in the LA groups, 3033 subjects were exposed to at least one vaccination, provided safety data, and were included in the safety analysis. There were 10 different groups in the LA part of V59P14 study.

Information on vaccinations in the various study groups and throughout the period of study is summarized below:

(1) Infant Vaccination period of study

Subjects in LA3 and LA5 received a series of three doses of infant MenACWY concomitantly with the routine infant vaccines at 2, 4, and 6 months. Subjects in LA1 received two doses of infant series MenACWY concomitantly with the routine infant

vaccines at 2 and 6 months, while subjects in the LA2, LA4, and LA6 groups received only the routine infant vaccines at 2, 4, and 6 months.

(2) MenACWY Toddler Vaccination

Subjects in the LA2, LA4 and LA6A groups and in the LA6B group received the first MenACWY toddler vaccination at age 12 months and13 months, respectively.
LA6C subjects received their only toddler vaccination at 18 months of age. Subjects in LA2, LA4, LA6A, and LA6B groups also received the second MenACWY toddler vaccination at 15 months of age.

(3) 16 Month Vaccination

LA3A subjects received four doses of MenACWY concomitantly with the routine infant vaccines at age 2, 4, 6, and 16 months. LA3B subjects received three doses of infant series MenACWY concomitantly with the routine infant vaccines at age 2, 4, and 6 months and received only routine vaccines at age 16 months.

Table 4.1.9: Overview of reactogenicity during 7 days period after each vaccination- LA Subjects

	Number (%) of Subjects With Solicited Reactions					
Infant Vaccination						
Vaccination: 1	**LA1 N = 301**	**LA2 N = 148**	**LA3 N = 301**	**LA4 N = 150**	**LA5 N = 1424**	**LA6 N = 709**
Any	246 (82%)	130 (88%)	244 (81%)	126 (84%)	1325 (93%)	668 (94%)
Local	188 (62%)	114 (77%)	197 (65%)	112 (75%)	1085 (76%)	568 (80%)
Systemic	187 (62%)	96 (65%)	179 (59%)	95 (63%)	1102 (77%)	540 (76%)
Other	155 (51%)	75 (51%)	159 (53%)	80 (53%)	996 (70%)	510 (72%)
Vaccination: 2			**N = 292**	**N = 148**	**N = 1381**	**N = 683**
Any			209 (72%)	96 (65%)	1178 (85%)	598 (88%)
Local			154 (53%)	81 (55%)	968 (70%)	523 (77%)
Systemic			140 (48%)	65 (44%)	863 (62%)	440 (64%)
Other			131 (45%)	61 (41%)	857 (62%)	430 (63%)
Vaccination: 3	**N = 297**	**N = 131**	**N = 290**	**N = 147**	**N = 1358**	**N = 679**
Any	166 (56%)	68 (52%)	169 (58%)	83 (56%)	1018 (75%)	542 (80%)
Local	119 (40%)	54 (41%)	121 (42%)	67 (46%)	773 (57%)	442 (65%)
Systemic	102 (34%)	41 (31%)	108 (37%)	48 (33%)	666 (49%)	353 (52%)
Other	93 (31%)	38 (29%)	90 (31%)	51 (35%)	592 (44%)	342 (50%)
12 Month Vaccination						
	LA1A N = 145		**LA1B N = 143**		**LA5 N = 1275**	
Any	72 (50%)		70 (49%)		845 (66%)	
Local	47 (32%)		46 (32%)		569 (45%)	
Systemic	46 (32%)		40 (28%)		577 (45%)	
Other	48 (33%)		43 (30%)		406 (32%)	
MenACWY Toddler Vaccination						
Vaccination: 1	**LA2+4+6A N = 564**		**LA6B N = 160**		**LA6C N = 175**	
Any	365 (65%)		76 (48%)		91 (52%)	
Local	272 (48%)		51 (32%)		75 (43%)	
Systemic	236 (42%)		40 (25%)		43 (25%)	
Other	204 (36%)		14 (9%)		34 (19%)	
Vaccination: 2	**N = 539**		**N = 153**			
Any	270 (50%)		83 (54%)			
Local	213 (40%)		52 (34%)			
Systemic	137 (25%)		52 (34%)			
Other	85 (16%)		21 (14%)			

Source: CSR, page 230, Table 12.2.1-9

As can be observed in Table 4.1.9, the percentages of subjects with local and systemic reactions decreased after each subsequent vaccination. After each infant vaccination, the percentages of subjects with local reactions were slightly lower, and systemic reactions were similar in subjects with concomitant MenACWY vaccination (LA3+LA5) when compared with those with routine vaccination only (LA4+LA6). After the vaccination at 12 months of age, the percentages for solicited local and systemic reactions ranged from 50% - 66% in subjects who received the concomitant vaccinations.

Based on the CSR (page 253-255), 71% of subjects reported at least one AE. The most commonly reported AEs were nasopharyngitis (15% - 23%, higher in LA2+4+6A+B) followed by bronchiolitis (8% - 21%, higher in LA6C), pyrexia (7% - 13%, higher in LA6C) and bronchitis (9% - 12%). About 6% of AEs were considered to be possibly related to the study vaccination. For more detailed discussion on AEs and SAEs please refer to the review of clinical reviewer Dr. Meghan Ferris.

Interpretation of the Latin America safety data and comparison of these data to US safety data should keep the following information in mind. Amendments 5 and 6 to the study protocol allowed, according to local practice, for administration of a second dose of hepatitis A vaccine in Latin American subjects. However, the timing of the second dose administration was not specified in the protocol. It is unknown whether this additional vaccination had any influence on the safety results.

Summary of Safety Analysis – Study V59P14

The applicant stated that "After over 4500 infants vaccinated, MenACWY appeared to be well tolerated and without any obvious adverse events disproportionately associated with the additional MenACWY administration." However, there are several limitations to the safety data that need to be considered in drawing conclusions regarding the safety profile of this vaccine.

It is unclear how reliably the diary card data were collected and, additionally, how systematic the collection of data for unsolicited adverse events, serious adverse events, and medically attended adverse events was. In the "comments.xpt" dataset, there are some comments related to the procedure for recording the diary card (1480 comments on diary cards related to 1098 patients) data in the relevant CRF. As per certain comments, it appears that reactogenicity data for some subjects were reconstructed based on the parent's memory. The applicant should clarify the procedure for reconstructing the reactogenicity data, e.g., at which time point in the study course the reconstruction occurred. According to the study protocol, a phone call was scheduled at 7 days after each vaccination; the applicant did not describe whether safety data were reconstructed at that time point or whether this reconstruction occurred at the next study visit, or later. Additionally, a diary card consisted of two parts: Diary Card-A and Diary Card-B. Some diary card comments (comments.xpt) specified the card part they were related to, but the statement "Diary cards not returned" does not specify whether the term *diary card* means Diary Card-A or -B or both. Therefore, there is some degree of uncertainty regarding how systematic the collections of safety data from days 8 – 28 were.

Additionally, rates of solicited and specific unsolicited AEs reactions were meaningfully different for US subjects and Latin American subjects. For example (CSR Table 12.2.1-21 and 12.2.1-22, page 256-259), otitis media was reported in 25% - 30% of US subjects while only 1% - 2% of Latin American subjects reported otitis media. Upper respiratory tract infections were reported in about 34% - 36% and <1% - 1% in US and Latin America subjects, respectively.

Such disparities suggest that the safety data from US and Latin America would be better not pooled but presented separately.

In summary: In the case of uncertain reliability of data and large amounts of missing information related to safety data, drawing inferences on safety endpoints is more difficult than usual. For instance, it remains unknown how many discontinuations in reality were connected to possible AEs and whether subjects who discontinued were different from those who remained in the study, with regard to both safety and immunogenicity.

The submitted safety data have limitations and uncertain reliability. Verification of the results presented in the CSR by statistical analyses based on the submitted V59P14 datasets is problematic. Therefore, the statistical reviewer cannot make a firm assessment of the safety of the MenACWY vaccine used for infants and toddlers.

4.2 Evaluation of Clinical Trial V59P23 Safety Data

Title: "A Phase 3b, Open-Label, Randomized, Parallel-Group, Multi-Center Study to Evaluate the Safety of Novartis MenACWY Conjugate Vaccine when Administered with Routine Infant Vaccinations to Healthy Infants"

Date of the first enrollment: 05 December 2008
Date of the enrollment closing: 31 July 10
Date of the last visit: N/A

General Information

Originally, this clinical trial was intended to collect additional safety data after vaccination with the Novartis MenACWY conjugate vaccine (MenACWY) in infant populations in terms of serious adverse events (SAEs) and medically attended adverse events (AEs). However, due to some issues related to the safety data of study V59P14, the clinical trial V59P23 protocol was subsequently amended to expand the overall sample size and to include specific assessments of solicited local and systemic reactogenicity in a large subset of the overall cohort. Subjects who contributed reactogenicity data to the statistical analyses constituted the detailed safety (DS) groups whereas subjects who only provided SAE and medically attended AE data constituted the non-detailed safety groups (NDS). Necessarily, DS subjects also provided data for the

NDS analyses, since, in terms of data collection, what distinguished the DS from NDS subjects was the addition of a diary card for collection of local and systemic post-vaccination reactions. All other data collection procedures were identical.

History of Study Protocol

The original study protocol was submitted on Aug 18th, 2008, and was followed by two amendments in February 2009 and May 2009. Enrollment started under the original protocol. Initially, this trial was designed to include 4,300 infants that would be randomized in a ratio 3:1 to receive MenACWY concomitantly with standard routine infant vaccines or standard routine infant vaccines alone at 2, 4, 6, and 12 months of age with follow-up through 18 months of age. Medically significant AEs and SAEs (non-detailed safety) were to be collected in all subjects. Following discussions with CBER, the applicant submitted (on Feb 16th, 2009) Amendment 1 to the study protocol, which included several major changes to the clinical trial design. The key changes were as follows:

(1) Detailed Safety Arms (Groups 3 and 4), that comprised 1250 controlled subjects who received MenACWY at 2, 4, 6, and 12 months with routine vaccinations and were to be followed through 18 months, were added.
(2) Numbers of subjects in the non-detailed safety arms were increased
(3) The safety hypothesis was stated
(4) A standard set of core vaccines for all groups, that included DTaP, IPV, Hib, and pneumococcal conjugate vaccines administered at 2, 4, and 6 months of age with MMR and pneumococcal conjugate vaccines administered at 12 months of age, was established and the administration of such vaccines was set as a requirement.
(5) A 15-month visit to administer DTaP and Hib vaccines was added/ required.

To include additional changes requested by CBER, the second amendment was submitted on May 14th, 2009. Major changes, related to adverse events, were incorporated into this version of the protocol and an independent Data Monitoring Committee was established. The statistical analysis plan (SAP) submitted on May 27th, 2010 took into account all changes introduced in Amendment 2.

The applicant stated that the 6-month post-dose-4 safety data (Groups 1 to 4) will be submitted for a labeling supplement.

Study design

Study V59P23 was a multicenter clinical trial conducted in the US, Taiwan, and Latin America (Guatemala, Panama, Costa Rica, and Peru) to evaluate the safety of MenACWY when administered at the 2, 4, 6, and 12 month schedule with routine infant vaccines to healthy infants. The plan was to enroll approximately 7700 infants at approximately 2 months of age and to randomize them in a ratio 3:1 into two groups. Subjects in these two treatment groups would receive either MenACWY with concomitant routine vaccines or routine vaccines alone.

Approximately 1840 infants were planned to be enrolled into the detailed safety arm (Groups 3 and 4) and approximately 5860 infants were to be enrolled into the non-detailed safety arms (Groups 1 and 2). Routine infant vaccines (RIV) given in the detailed safety arm were administered according to the US ACIP recommendations. Infants enrolled into the non-detailed safety study arms would receive a core set of concomitant vaccines that would include a DTaP-IPV-Hib vaccine, pneumococcal conjugate, and MMR at a minimum. Other country-specific vaccinations were permitted per local guidelines. The list of routine vaccines could not include other meningococcal vaccines (e.g., serogroup C meningococcal conjugate vaccine). MenACWY would be administered at 2, 4, 6, and 12 months of age to subjects in Groups 1 and 3 in all countries. One third of the subjects in the non-detailed safety arm (Groups 1 and 2) were to be enrolled in the United States (US). At least 80% of the infants in the detailed safety arms (Groups 3 and 4) were to be enrolled in the US.

The outline of the study design is presented in Table 4.2.1.

Table 4.2.1: Outline of the study design

	Months of Age						
	2 months	4 months	6 months	9 Months	12 Months	15 Months	18 Months
	Visit 1	Visit 2	Visit 3	Phone Call	Visit 4	Visit 5	Phone Call
Group 1 ACWY-ND	ACWY+ RIV	ACWY+ RIV	ACWY+ RIV	Safety Follow-up	ACWY+ RIV	RIV	Safety Follow-up
Group 2 RVAX-ND	RIV	RIV	RIV	Safety Follow-up	RIV	RIV	Safety Follow-up
Group 3 ACWY-D	ACWY+ RIV	ACWY+ RIV	ACWY+ RIV	Safety Follow-up	ACWY+ RIV	RIV	Safety Follow-up
Group 4 RVAX-D	RIV	RIV	RIV	Safety Follow-up	RIV	RIV	Safety Follow-up

Source: CSR V59P23 Table 9.1-1
ACWY = MenACWY conjugate vaccine; RIV= Routine Infant Vaccines; ND= Non-detailed safety group; D= Detailed safety group

Enrollment into the study was closed on 31 July 2010, at which time 7,744 subjects had been enrolled in 6 countries. Of these subjects, 1898 subjects, all from the USA, were enrolled in the detailed safety groups (Groups 3 and 4). The remaining 5,846 subjects were enrolled into the non-detailed safety groups (Groups 1 and 2) in the following countries: US (1956 subjects), Taiwan (795 subjects), Costa Rica (1301 subjects), Guatemala (1096 subjects), Peru (396 subjects), and Panama (302 subjects).

It is worth noting that although the study enrolled subjects from multiple countries, the interim study report considered only subjects from U.S. sites.

Collection of safety data

After each vaccination, each subject's parent(s)/legal guardian(s) were given a worksheet and were instructed on how to record all medically attended AEs (i.e., AEs necessitating a medical office or emergency room (ER) visit and/or resulting in the premature withdrawal of subjects from the study), SAEs, and the prescription medications used to treat these events. Each worksheet was to be returned at the next study visit and the information obtained was to be appropriately reported in the CRF. Safety data (serious adverse events, medically attended adverse events) one month post the fourth dose of MenACWY were recorded on the worksheet handed out at the 12-month visit (Visit 4) and returned to the site at the 15-month visit (Visit 5) for all subjects. Information from the worksheet handed out to the subject's parent(s)/guardian(s) at the last clinical study visit (Visit 5) was collected verbally during the last follow-up phone call.

Parents were instructed to call the study site immediately if the subject experienced a SAE.

In addition to the worksheet, parents/legal representatives of the DS (detailed safety) subjects belonging to Groups 3 and 4 received diary cards and were instructed how to complete the cards. However, reactions occurring during the first 15 minutes after vaccination were captured on the clinic case report forms. The first information on the diary card should be entered, at the earliest, 6 hours after the injection. Then, entries were to be continued for another six days to record local reactions and systemic reactions. Telephone calls were to be made 2 and 7 days after each study vaccination to remind the subject's parent(s)/legal representative(s) about completion of the diary card. Diary cards given at Visits 1, 2, and 3 were collected at Visits 2, 3, and 4 and reviewed with the subject's parent(s)/legal representative(s). Then, the collected information was recorded on the appropriate CRFs. The diary card handed out at Visit 4 was to be returned at Visit 5 or mailed back to the study site after completion. No diary card was handed out at Visit 5. The final follow-up phone call was to be performed at approximately 18 months of age (3 months after the last office visit or 6 months after the last study vaccination) to assess the health status of the subject and to collect the safety information. If a subject was terminated early from the study but had not withdrawn consent for further contacts, a phone call was attempted 6 months after the subject's last injection to review the 6-month safety.

Safety endpoints

Serious adverse events and medically attended adverse events were collected throughout the study for the study population. However, in Groups 3 and 4 (DS groups), local and systemic reactions along with all AEs were also collected for the 7-day post-study-vaccination period.

Objectives of the study

Primary Safety Objective

To compare the percentage of subjects presenting, during Days 1-7 after any vaccination, with at least one severe systemic reaction after administration of MenACWY plus routine vaccines, with the percentage of subjects presenting with at least one severe systemic reaction after routine vaccines alone when vaccines were given at 2, 4, 6 and 12 months of age (Group 3 vs. Group 4).

Secondary Safety Objective

To compare the percentage of subjects presenting at least one serious adverse event (SAE) after administration of MenACWY plus routine vaccines with the percentage of subjects presenting at least one SAE after routine vaccines alone in periods: up to age 12 months and 12 to 18 months of age (Groups 1+3 vs. Groups 2+4).

Hypotheses

The primary objective of this study was to show that the rate of severe systemic reactions in subjects receiving MenACWY plus routine vaccines is less than 6% higher than the rate for subjects receiving routine vaccines only. The non-inferiority primary safety hypothesis was defined for Groups 3 and 4 (DS groups) as follows:

$$H_0: (P_{\text{MenACWY+Routine Vaccines}} - P_{\text{Routine Vaccines}}) \geq 6\%$$
$$H_a: (P_{\text{MenACWY+Routine Vaccines}} - P_{\text{Routine Vaccines}}) < 6\%,$$

where $P_{\text{MenACWY+Routine Vaccines}}$ and $P_{\text{Routine Vaccines}}$ are proportions for Groups 3 and 4, respectively, of subjects experiencing at least one severe solicited systemic reaction during the first 7 days after any vaccination.

Study success

The study will be considered a success if the rate of severe systemic reactions for MenACWY given concomitantly with routine vaccines is shown to be non-inferior to the rate for routine vaccines only.

Interim analysis

The applicant planned to perform an interim safety analysis after information about the 6-month follow-up post-third-vaccination period or information about patient withdrawal from the study was available for all enrolled infants. The data included in this analysis would consist of data for the primary safety objective (post-injection reactions after vaccination at 2, 4, 6 and 12 months of age) for subjects in Groups 3 and 4 and interim data for all other safety objectives for subjects in all groups with follow-up at least one month after the fourth dose of vaccination.

The results of the interim analysis would be used to support a regulatory filing in an infant population but would not alter the course of the trial. The applicant stated (CSR, page 43) that "*the result of this analysis will not alter the course of the trial and will be governed by the procedures specified in the Novartis BCDM document entitled Interim Analysis in a Clinical Trial.*"

Specifically, the interim analysis was to be performed when the adverse events and local and systemic reactions collected for 7 days after the 12-months-of-age vaccination are available for the subjects in Groups 3 and 4. Subjects in Groups 1 and 2 were to be included in the interim analysis to the extent of the available data.

The objectives of the pre-specified interim safety analysis were to assess the primary objective of this clinical trial and, for all study groups (US subjects only), to evaluate safety data collected up to 15 months of age.

Sample size consideration

In the section 'Determination of Sample Size,' the sponsor stated that "*the FDA has specifically requested that an additional 3000 subjects be followed for a filing in infants with no more than a 3:1 ratio of MenACWY to control subjects. In order to meet this requirement, 4000 subjects are needed in this trial. To account for an estimated 7% early withdrawal rate, a total of 4300 subjects will be enrolled. The sample size determination is therefore based on a regulatory, rather than statistical rationale.*"

Moreover, the sponsor estimated chances for detecting AEs and calculated probabilities of observing at least one subject with a given possible event for several underlying event rates (1/100, 1/200, 1/500, and 1/1000). Additionally, in Table 6.9.2-2 (page 44), the sponsor presented 95% confidence intervals for several possible observed adverse event rates from 0% to 60% in the case of 1000, 2000, or 3000 subjects receiving MenACWY during the study.

Patient Disposition, Demographic and Baseline Characteristics

Interim Analysis

The objectives of the pre-specified interim safety analysis was to assess the primary objective of this clinical trial and, for all study groups, to evaluate safety data collected up to 15 months of age. The following data were utilized in the interim analysis:

(1) For the primary safety objective (rates of post-injection severe systemic reactions following vaccinations at 2, 4, 6, and 12 months of age), data for detailed safety subjects (Groups 3 and 4), all of whom were enrolled in the US.
(2) AE and SAE data in US subjects from all groups (Groups 1 through 4) with onset up to the 15-month visit (Visit 5); for those US subjects who did not have the 15-month visit, AE and SAE data with event onset up to the 15-month birthday or study termination date, whichever was earlier.

Table 4.2.2 shows the number of US subjects who provided data up to 15 months of age for the safety analyses included in the interim analysis.

Table 4.2.2: Summary of subjects planned, enrolled, and analyzed

	Planned	Enrolled	Analyzed
Groups 3 and 4 (primary analysis)	1840	1898	1810
Groups 3 and 4[a] (secondary analysis)	1840	1898	1890
Groups 1 and 2[b] (US data up to 15 months)	1954	1956	1956
Groups 1 and 2 rest of World)	3906	3890	0

Source: CRS, page 67

[a]Eifty subjects provided no follow-up solicited systemic reaction data for the primary endpoint analysis, but were considered at risk in the analyses of AEs and SAEs. Eight additional subjects were enrolled but were not vaccinated.

[b]Six subjects were enrolled but were not vaccinated

Disposition of Subjects

A total of 2855 US subjects enrolled in the MenACWY non-detailed (ACWY-ND) and MenACWY detailed (ACWY-D) groups and 999 subjects enrolled in the routine vaccine non-detailed (RVAX-ND) and routine vaccine detailed (RVAX-D) groups were included in the interim analysis.

Of the subset of enrolled subjects included in the interim analysis, 473 subjects in the ACWY-All group and 188 subjects in the RVAX-All group withdrew from the study prior to the 15 months of age cut-off.

The disposition of subjects in the study groups is summarized in Table 4.2.3.

Table 4.2.3: Disposition of subjects in the study groups

	ACWY-ND	RVAX-ND	ACWY-D	RVAX-D
Enrolled	1446	510	1409	489
Completed Study	1200 (83%)	414 (81%)	1182 (84%)	489 (81%)
Premature withdrawals	246 (17%)	96 (19%)	227 (16%)	92 (19%)
Death	1	0	1	0
AE	13(<1%)	1 (<1%)	10(<1%)	1(<1%)
Lost to Follow-up	81 (6%)	25 (5%)	66 (5%)	28 (6%)
Withdrew consent	67 (5%)	25 (5%)	71 (5%)	31 (6%)
Inappropriate Enrollment	0	1 (<1%)	0	0
Administrative reason	68 (5%)	23 (5%)	57 (4%)	23 (5%)
Protocol Deviation/Violation	16 (1%)	11 (2%)	22 (2%)	9 (2%)

Source: CRS, Table 10.1-2, page 64

By examining Table 4.2.3, it can be observed that across all groups, premature withdrawals were mainly due to: withdrawal of consent (194 subjects), and loss to follow-up (200 subjects).

Protocol Deviations

Protocol deviations were reported for 65% (2490 subjects) of the US enrolled subjects (ACWY-D subjects exhibiting the highest percentage), while 1% (14 subjects) of them were classified as major protocol deviations.

Demographic Characteristics

At baseline, demographic and other characteristics of subjects included in the interim analysis were balanced across the study groups. The majority of the population consisted of Caucasians (62% to 65%), while Asians, Blacks, Hispanics, and others constituted the rest. Gender ratios were similar across the study groups. The mean age was 65.3 ± 6.7 days in all study populations included in the analysis. Weight and height were similar for all study groups (on average 5.427±0.669 kg and 58.5±2.5cm).

Evaluation of Study Safety Results

Quality of Datasets Analyzed

A total of 7744 subjects were enrolled into the P23 study, but only 5500 subjects were exposed to MenACWY. A subset of the enrolled study population consisting of 3854 subjects was included in the interim analysis, with 2855 and 999 subjects enrolled in the MenACWY and only routine vaccines groups, respectively. The number, per group, of subjects included in the interim safety analyses is given in Table 4.2.4.

Table 4.2.4: Number of subjects analyzed per study group

	Enrolled	Vaccinated	Safety Analysis	At last Visit (5)
MenACWY + Routine (ND)	1446	1440	1440	1172
Routine only (ND)	510	510	510	403
Total (ND groups)	***1956***	***1950***	***1950***	***1575***
MenACWY + Routine (D)	1409	1403	1403	1156
Routine only (D)	489	487	487	386
Total (D groups)	***1898***	***1890***	***1890***	***1542***

Source: Reviewer's table

Table 4.2.4 demonstrates that similar numbers of subjects belonging to ND and D groups were considered in the interim analyses. .

Reviewer's Comments:

There are major concerns related to the completeness and reliability of the interim safety data, used for the statistical analyses. Some of the issues are listed below:

- As per the applicant, "The majority of vaccination noncompliance at several sites occurred due to poor labeling of the study subject charts causing MenACWY vaccination to be missed altogether or to be given days after routine vaccines." In the submitted datasets (e.g., immune.xpt, injuct.xpt), there is no variable which indicates whether MenACWY was given on the same day as routine vaccines. Therefore, it is unknown:
  - how many subjects received MenACWY and routine childhood vaccines on different days instead on the same visit day
  - how diary cards were distributed/filled out in the case when MenACWY and routine vaccines were not given on the same day
  - how subjects who received wrong study vaccines at one or more visits or who received routine vaccines and Menveo on different days were handled in the analyses.
- Based on the CSR, 75 subjects withdrew from the study but were still followed and were included in the safety analysis. This is appropriate. However, there was no information provided within the CSR on: (1) the procedure for safety data collection for these subjects, (2) how long they were followed, and (3) what information was collected for them.
- In the submitted datasets, there are no identifier-variables that would permit assessment of how reactogenicity and AE data were collected during the course of study P23 with respect to timing (i.e., if they were collected based on the diary card or if the data were recalled from memory).

Primary Safety Analysis

The primary safety objective of this study was to compare the percentage of subjects experiencing, during days 1-7 after any vaccination, at least one severe systemic reaction to MenACWY plus routine vaccines (ACWY-D group) to the relevant percentage observed in the routine vaccines alone group (RVAX-D). The ACWY-D group was to be considered non-inferior to the RVAX-D group with respect to the frequency of AEs if the upper limit of the two-sided 95% CI of the difference in the percentages of subjects experiencing at least one severe systemic reaction was less than 6%. A summary of the results of the primary safety hypothesis testing is presented in Table 4.2.5.

Table 4.2.5: Results of the primary safety hypothesis testing

Systemic Reaction	Number (%) of Subjects with Systemic Reaction		Estimated % Diff. (95% CI)
	ACWY-D N=1349	RVAX-D N=461	
Severe	213 (16%)	59 (13%)	**3% (-0.8, 6.4)**

Source: CSR, Table 12.2-1; page 77

Reviewer's comments:

(1) The pre-specified criterion for the primary safety hypothesis was narrowly missed. The upper limit (6.4%) of the two-sided 95% CI of the estimated difference in the percentage of subjects experiencing at least one severe systemic reaction was slightly above the pre-specified criterion set for non-inferiority (i.e., < 6%).

(2) The applicant performed an additional post-hoc adjusted statistical analysis, taking into account center and vaccination group by center differences, and showed that the criterion of non-inferiority was met. This analysis, however, has the following limitations:
   a. numbers of subjects per center were small (on average only 16 subjects (median 11) per center; 4 centers had only one subject)
   b. a statistical justification of appropriateness (e.g., how well the model describes the data) of the selected model was not provided.

(3) A summary of results of an additional post-hoc analysis, which explored group differences in the rate of any severe systemic reaction after each vaccination, is given in the CSR, Table 12.2-3 page 92. By examining this table, it can be observed that rates of any severe systemic reaction during days 1 through 7 after each vaccination were low. The upper limit of the unadjusted Miettinen and Nurminen two-sided 95% confidence interval for the risk difference was ≤ 4.3% for severe systemic reactions during days 1 through 7 after each of the four individual vaccinations, i.e., below the 6% non-inferiority criterion limit for the upper two-sided 95% CI for the overall ACWY-D minus RVAX-D rate difference.

(4) Severe reactions were reported for a total of 8% of subjects after the first vaccination, 6% -7% of subjects after the second vaccination, 4% - 5% of subjects after the third vaccination, and 7% - 8% of subjects after the fourth vaccination.

Summary of safety profile of the P23 clinical study

The percentages of subjects with solicited local and systemic reactions declined from 89% after the first vaccination to 79% after the fourth vaccination in the concomitant MenACWY vaccine group, and from 88% after the first vaccination to 81% after the fourth vaccination in the routine vaccine only group, and were the lowest after the third infant vaccination. A summary of the percentages of subjects with at least one solicited local and systemic reaction after any injection is presented in Table 4.2.6.

Table 4.2.6: The percentages of subjects with at least one reactogenicity reaction during 7-day period after any injection

	Any Injection	
	ACWY-D	**RVAX-D**
	1350	462
Any	1301 (96%)	446 (97%)
Local	1009 (75%)	375 (81%)
Systemic	1218 (90%)	411 (89%)
Other	1110 (82%)	368 (80%)

Source: CSR, Table 12.2.1-1; page 83

Considering several tables included in the CSR (pages 95-100), the profile of systemic reactions to MenACWY vaccine given along with routine vaccines appears to be similar to the profile of systemic reactions for routine vaccines given alone, except for a higher percentage of subjects developing diarrhea in the MenACWY vaccine plus routine vaccines group. The majority of the local and systemic reactions were mild to moderate in severity, and the percentage of subjects reporting local and systemic reactions decreased after the first vaccination in both vaccination groups.

As per study P23 CSR, the percentages of subjects reporting any unsolicited AEs or SAEs were similar in all vaccination groups. SAEs that were possibly or probably related to MenACWY and AEs leading to premature withdrawal were slightly more frequent in subjects receiving MenACWY vaccine plus routine vaccines than in subjects receiving only routine vaccines.

Four SAEs possibly related to MenACWY [febrile convulsion, inguinal abscess, epilepsy, and ADEM (acute disseminated encephalomyelitis)] were reported during the study. Additionally, there were two deaths in US subjects randomized to MenACWY prior to 15 months of age, but both deaths, as per the applicant's knowledge, were not related to the study vaccine.

The rates of SAEs were higher in the ACWY vaccine groups during the period from day 1 up to 7 months of age (3% vs. 1%), while the SAE rate was slightly higher in the

RVAX group during the period 7 months to 12 months of age (2% vs. 3%). From 12 months to 13 months and from 13 months to 15 months of age, SAE rates in the ACWY and RVAX groups were similar.

Information on SAEs is summarized in Tables 4.2.7 and 4.2.8.

Table 4.2.7 (CSR, page 101): Overview of total numbers of AEs and SAEs after any vaccination (note: subjects can have more than one AE or SAE)

	Number (%) of Subjects with Adverse Events	
	ACWY- All	**RVAX-All**
	2843	**997**
Any AEs	1301 (96%)	446 (97%)
Any SAE up to 15 months of age	152 (5%)	42 (4%)
Any SAE up to 12 months of age	127 (4%)	35 (4%)

Source: CSR, Tabel 12.2.1-4; page 90

Table 4.2.8: Number of SAEs after each injection

	Injection Number				Total
	#1	#2	#3	#4	
ACWY-ND	28	32	54	25	139
RVAX-ND	4	2	17	10	33
ACWY-D	25	16	43	5	89
RVAX-D	3	1	26	5	35
Total	60	51	140	45	296

Source: Reviewer's analysis

Based on the ADVERSE.xpt data set, there were 297 SAEs during the 13-months study period. It appears that one infant (067004) experienced an SAE before visit one while she/he was enrolled into the study. Some infants had more than one SAE during the participation in the study (until 15 months of age). The rates of SAE occurrences in the study safety population were higher in the ACWY vaccine groups during the period Visit 1 to Visit 5 (about 7% vs. 5%), while the rate was slightly higher in the RVAX group during the period Visit 4 to Visit 5 (4% vs. 5%).

For details related to the P23 safety data issues, please refer to the clinical review of Dr. Anuja Rastogi.

In summary, the V59P23 clinical safety data submitted by the applicant has uncertain reliability. Verification of the results presented in the CSR by statistical analyses based on the submitted datasets is challenging, rendering it difficult for the statistical reviewer

to make a firm assessment of the safety of the MenACWY vaccine used for infants and toddlers.

The statistical concerns are:

1) Inconsistencies between the CSR and the results drawn from the relevant datasets. For example: (a) numbers of subjects seen at each study visit and (b) numbers of subjects with premature study discontinuation due to adverse events are not consistent.
2) Identifier-variables, in the relevant datasets, which would make possible to assess how and when reactogenicity and AEs data were collected, are missing. Therefore, it is not possible to perform adequate statistical analyses
3) Variables, in the relevant datasets, that identify which vaccines were given to the enrolled subjects during each study visit are missing.

Based on the applicant's CSR, an important vaccination noncompliance (protocol deviation) occurred related to co-administration of routine childhood vaccinations. MenACWY vaccine was sometimes given days after the routine vaccines. However, in the submitted datasets (e.g., immune.xpt, inject.xpt), there is no variable that would show whether MenACWY was given on the same day as routine vaccines. Thus, it is not possible to

(1) identify subjects who received four doses of MenACWY with routine vaccines or routine vaccines alone as specified in the protocol, or
(2) to evaluate safety endpoints.

All the above mentioned issues compromised the statistical reviewer's ability to assess adequately the safety data and study results of clinical trial V59P23.

4.3 Evaluation of Clinical Trial V59P21 Safety Data

Title of the study: "A Phase 3, Open-Label, Randomized, Multi-Center Study to Evaluate the Safety and Immunogenicity of ProQuad™ Vaccine when Administered Concomitantly with Novartis Meningococcal ACWY Conjugate Vaccine to Healthy Toddlers."

Brief Overview of the Study

The main objectives of this Phase III study were assessments of the safety and immune responses to the concomitant administration of ProQuad™ with MenACWY to healthy infants/toddlers. ProQuad™ (Merck & Co., Inc.) is a measles, mumps, rubella, and varicella vaccine licensed in the U.S. in 2005 for children 12 months to 12 years of age.

The study design, data collection, subject disposition for this study, and immunogenicity evaluation results are discussed in Section 3.2. However, for the sake of completeness, some important characteristics of trial V59P21 are repeated below from Section 3.2.

Study V59P21 was a Phase 3, open-label, randomized, multi-center study to evaluate the safety and immunogenicity of ProQuad™ and MenACWY vaccines when administered concomitantly with each other to healthy toddlers.

Two age groups of subjects, 7 to 9 months of age and 12 months of age, were enrolled concurrently. In the group of subjects 7 to 9 months of age at enrollment, approximately 1014 subjects were randomized in a 1:1 ratio to one of two vaccination groups, Group I or II. At the same time, 616 subjects who were 12 months old at the time of enrollment entered the open label Group III. The general study design is shown in Table 4.3.1.

Table 4.3.1: The overview of study design

Visit	Visit 1	Visit 2	Visit 3	Visit 4
Age	**7 to 9 Months**	**8 to 10 Months**	**12 Months**	**13.5 Months**
Group 1 N=504	Enrollment MenACWY	N/A	Blood Draw MenACWY MMRV	Blood Draw
Group II N=510	Enrollment MenACWY	Blood Draw	MenACWY	Blood Draw MMRV
Group III N=616	N/A	N/A	Enrolment Blood Draw MMRV	Blood Draw

Source: Clinical Study Protocol (Am 3), Table 6.1.1-1; page 38

The above table provides a summary of the timing of vaccines administration and blood draws throughout the duration of the study.

Safety objectives:

The primary safety objective was to describe the safety profile of subjects in each vaccine group in terms of:

5. Immediate (within 15 minutes) hypersensitivity reactions following vaccination
6. Local and systemic reactions during day 1 to day 7 after each vaccination
7. Adverse events (AEs) that required medical visits and took place between day 8 to day 28 after each vaccination
8. Medically significant AEs and SAEs throughout the study.

Evaluation of Study Safety Results

Safety was evaluated in terms of the number of subjects with reported local and systemic reactions as well as the number of subjects with reported AEs and SAEs per vaccination group. All AEs were to be reported for the first 7 days after each vaccination. From day 8

to day 28, AEs requiring a medical office or ER visit and/or resulting in premature withdrawal from the study were to be recorded. Throughout the study, all SAEs and medically significant AEs were to be reported.

Overview of Datasets Analyzed

In study P21, a total of 1630 subjects were enrolled and randomized; 1603 were exposed to the study vaccines, 500 in the MenACWY + MMRV group (Group 1_, 503 in the MenACWY group (Group 2), and 600 in the MMRV group (Group 3). Twenty seven subjects were not vaccinated (14 due to withdrawal of consent, 12 due to inappropriate enrollment, and 1 due to protocol deviation). These subjects were excluded from the safety analysis. Four subjects in the MenACWY group and 3 subjects in the MMRV group who received the incorrect vaccines per their treatment assignment were also excluded from the safety summaries.

Evaluation of Safety Data

An overview of the reactogenicity recorded during the 7-day period after each vaccination is presented in Table 4.3.2 (CSR, page 123). It is important to note that the possibility of developing solicited reactions differed between the groups due to different numbers of vaccinations received in each group at each study visit.

Table 4.3.2: Overview of the reactogenicity recorded during the 7-day period after each vaccination

	Visit 1 (study vaccination 1)			
	MenACWY+MMRV (Group 1)		MenACWY (Group 2)	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Days 1 to 7	N=500		N=500	
Any reaction	335	0.67	351	0.7
Local reaction	159	0.32	170	0.34
Systemic reaction	270	0.54	271	0.54
Other reaction	118	0.24	165	0.33

	Visit 3 (study vaccination 2)					
	MenACWY+MMRV (Group 1)		MenACWY (Group 2)		MMRV (Group 3)	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
Days 1 to 7	N=459		N=456		N=597	
Any reaction	337	0.73	275	0.6	478	0.8
Local reaction	227	0.49	141	0.31	316	0.53
Systemic reaction	263	0.57	195	0.43	281	0.54
Other reaction	143	0.43	105	0.23	203	0.34

	Visit 4 (study vaccination 3)			
			MenACWY (Group 2)	
			# of subjects	Estimated Ratio
Days 1 to 7			N=429	
Any reaction			281	0.66
Local reaction			188	0.44
Systemic reaction			195	0.45
Other reaction			108	0.25

Source: CSR, page 123

Treatment at Visit 1 was MenACWY for both groups; at Visit 3, vaccines administered were as described after the group number in the column headings; at Visit 4, subjects in the ACWY group (Group II) received MMRV

From Table 4.3.2,, it can be observed that at least one local or systemic or other reaction was reported in 67-80% of subjects throughout the study.

The applicant (CSR, page 126) presented a summary of the rates of systemic reactions (including fever and use of analgesic medication) during the 7- day period following each vaccination. It appears that, across the study groups, the most frequently reported systemic reactions were: irritability (reported by 29% to 50% of the subjects), sleepiness (17% to 33%), change in eating habits (11% to 19%), and diarrhea (9% to 18%). Other systemic solicited reactions were reported by less than 10% of the subjects. The differences between the rates of any reaction, any local, and any systemic (post injection 2/Visit 3) reaction were not different between Groups I and II when ProQuad™ vaccine was used as compared to when MMR+V vaccine was used.

An overview of the unsolicited AEs is presented in Table 4.3.3 (CSR, page 132).

Table 4.3.3: Overview of AEs per the study group

	Number of Subjects with Adverse Events					
	MenACWY+MMRV (Group 1)		MenACWY (Group 2)		MMRV (Group 3)	
	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio	# of subjects	Estimated Ratio
	N=500		N=500		N=597	
Any AEs	335	0.67	353	0.71	311	0.52
Possibly related AEs	70	0.14	63	0.13	2	<0.01
Serious Aes	18	0.04	19	0.04	9	0.02

Source: CSR, page 132

As per Table 4.3.3, the percentages of subjects reporting at least 1 AE in the MenACWY+MMRV and MenACWY alone groups were comparable, i.e., 67% and 71%, respectively. Percentage of subjects in the MMRV group reporting any AEs was 52%. However, it is important to note that subjects in the MenACWY + MMRV and MenACWY groups received two doses of MenACWY vaccines and were on-study nearly twice as long as the subjects in the MMRV group.

It appears that the group receiving MenACWY concomitantly with MMRV experienced slightly higher rates of severe systemic reactions (including fever) than the subjects who received MenACWY alone, but the rates were similar or lower than for those receiving MMRV alone.

About 4 % of the subjects (68 subjects) reported SAEs (e.g., febrile seizure, pneumonia, asthma, wheezing respiratory infection). As per the applicant, all these SAEs were unrelated to the study vaccination. Most of the SAEs were moderate or severe in intensity.
Please refer to Dr. Meghan Ferris's clinical review for more safety details.

Summary of safety results

It appears, based on the results presented by the applicant, that the group receiving MenACWY concomitantly with MMRV did not show increased reactogenicity as compared to the group receiving MMRV alone, while they experienced slightly higher rates of severe systemic reactions (including fever) as compared to the subjects who received MenACWY alone. The later rates of any systemic/local reactions were similar or lower than for the MMRV alone group.

There are some concerns related to the quality of the spplicant's submitted datasets:

1. Study P21 was not a fully randomized clinical trial. Subjects 7 to 9 months of age at enrollment were randomized in a 1:1 ratio to one of two vaccination groups (Group I or II), but subjects 12 months old were all enrolled into the open label Group III. Therefore, a potential bias could have been introduced.
2. Collection of data was not fully reliable (e.g., in comment.xpt dataset, there were about 648 comments related to the diary card collection that raised concerns).
3. During the course of the study, a supply interruption of ProQuad™ occurred and M-M-R™II and Varivax™ were used instead of the ProQuad™ vaccine. It is known that safety data of ProQuad™ vaccine and M-M-R™II + Varivax™ are not fully comparable. Thus, interpretation of study results may be limited.

Additionally, the P21 study was intended to be a supplemental not a pivotal trial for the 2-dose schedule. Therefore, this study was rather small with approximately 500 subjects per study group.

5. Final Conclusions

5.1 Summary of Statistical Results

The statistical evaluation of the safety and immunogenicity of the four- dose regimen of MENVEO administered to infants/toddlers at 2, 4, 6, and 12-16 months of age, was based mainly on the data collected within the Phase III safety and immunogenicity clinical trial

V59P14 (conducted in the US and Latin America) and from safety clinical trial V59P23 (conducted in the US and other countries). The pivotal clinical trial V59P21, submitted in this sBLA, provided data allowing characterization of the immune response to a 2-dose catch-up series (two injections administered at least 2 months apart, with the second dose of MENVEO vaccine administered in the second year of life) in older infants and toddlers.

There are numerous important concerns related to the data integrity in clinical trial V59P14 that have been discussed extensively within this review. A significant amount of missing data is one of the major issues encountered in evaluation of data based on the V59P14 clinical trial. More than 45% of enrolled subjects were not included in the PP immunogenicity populations due to a variety of reasons. Thus, the primary endpoint was assessed on data comprising only about 55% of the enrolled subjects. Therefore, interpretation of the study results is challenging from the statistical perspective, and an adequate statistical assessment of the vaccines immunogenicity data cannot be performed on the currently submitted data/datasets from study V59P14. In addition, it is not possible to determine from the material provided by the applicant, including datasets, whether the safety data were collected in a systematic manner. The V59P23 clinical safety data submitted by the applicant are not sufficient and verification, by statistical analyses based on the submitted datasets, of the results presented in the CSR is problematic.

Data generated by these three pivotal clinical trials and submitted by the applicant are not fully reliable, verifiable, and sufficient to provide apparent evidence for supporting the applicant's claims that MENVEO is safe and immunogenic in infant and toddler populations.

5.2. Recommendations

As a result of the review of the up-to-date submitted materials, the statistical reviewer recommends sending a CR letter that would address the statistical concerns. Please refer to the CR letter for a comprehensive list of recommendations/questions to the applicant.