1 Title and General Information

1.1 Medical Officer's (MO) Review Identifiers and Dates

1.1.1 BLA/NDA #: 125300/226

1.1.2 Related IND #(s): IND 11278

1.1.3 Clinical Reviewers:

Meghan Ferris, MD, MPH; Anuja Rastogi, MD, MHS; Melisse S. Baylor, MD.
Medical Officers
Vaccine Clinical Trials Branch 1, HFM-485
Division of Vaccines and Related Product Applications (DVRPA)
Office of Vaccines Research and Review (OVRR)
Center for Biologics Evaluations and Research (CBER)
Food and Drug Administration (FDA)

Through:

Lucia Lee, MD
Team Leader, Vaccine Clinical Trials Branch 1, HFM-485
DVRPA/OVRR/CBER/FDA

1.1.4 Submission Received by FDA:

April 13, 2011

1.1.5 Review Completed: February 6, 2012

1.2 Product

1.2.1 Proper Name or Established Name (as applicable):

Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine

1.2.2 Proposed Trade Name:

Menveo

1.2.3 Product Formulation:

Each 0.5 mL dose contains 10 mcg MenA oligosaccharide, 5 mcg each of MenC, MenY, and MenW-135 oligosaccharides, and a total of 32.7 to 64.1 mcg of CRM197 protein. The vaccine contains no preservative or adjuvant.

1.3 Applicant:

Novartis Vaccines and Diagnostics, Inc.

1.4 Pharmacologic Class or Category

Vaccine

1.5 Proposed Indication(s):

Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135.

1.6 Proposed Population(s):

Individuals 2 months through 55 years of age.

1.7 Dosage Form(s) and Route(s) of Administration:

Solution supplied as a lyophilized vaccine component that is combined through reconstitution with a liquid vaccine component, both in single dose vials. Intramuscular injection.

2 Table of Contents

1 TITLE AND GENERAL INFORMATION 1

1.1 MEDICAL OFFICER'S (MO) REVIEW IDENTIFIERS AND DATES 1
1.1.1 BLA/NDA #: *125300/226* *1*
1.1.2 Related IND #(s): *IND 11278* *1*
1.1.3 Clinical Reviewers: *1*
1.1.4 Submission Received by FDA: *1*
1.1.5 Review Completed: February 6, 2012 ..... *1*
1.2 PRODUCT 1
1.2.1 Proper Name or Established Name (as applicable): *1*
1.2.2 Proposed Trade Name: *1*
1.2.3 Product Formulation: *1*
1.3 APPLICANT: 1
1.4 PHARMACOLOGIC CLASS OR CATEGORY 1
1.5 PROPOSED INDICATION(S): 2
1.6 PROPOSED POPULATION(S): 2
1.7 DOSAGE FORM(S) AND ROUTE(S) OF ADMINISTRATION: 2

2 TABLE OF CONTENTS 2

3 EXECUTIVE SUMMARY 4

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES 6

4.1 STATISTICAL 6

5 CLINICAL AND REGULATORY BACKGROUND 6

5.1 EPIDEMIOLOGY 6
5.2 RATIONALE FOR SELECTED VACCINE FORMULATION 6
5.3 PREVIOUS HUMAN EXPERIENCE WITH THE PRODUCT INCLUDING FOREIGN EXPERIENCE 6
5.4 REGULATORY BACKGROUND 6

6 CLINICAL DATA SOURCES (BOTH IND AND NON-IND), REVIEW STRATEGY AND DATA INTEGRITY 7

6.1 MATERIAL REVIEWED 7
6.1.1 BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review *7*
6.1.2 Post-Marketing Experience *8*
6.2 TABLE 1: SUMMARY OF CLINICAL STUDIES 8
6.3 REVIEW STRATEGY 9
6.4 GOOD CLINICAL PRACTICES (GCP) AND DATA INTEGRITY 9

6.5 FINANCIAL DISCLOSURES 9

7 CLINICAL STUDIES 10

7.1 TRIAL #1: V59P14 10
7.1.1 NCT# 00474526 ..... *10*
7.1.1.1 Title 10
7.1.1.1.1 Objective/Rationale 10
7.1.1.1.2 Design Overview 11
7.1.1.1.3 Population 11
7.1.1.1.4 Products mandated by the protocol 13
7.1.1.1.5 Endpoints 15
7.1.1.1.6 Surveillance/Monitoring 18
7.1.1.1.7 Statistical Analysis Plan 19
7.1.1.2 Results 19
7.1.1.2.1 Populations 19
7.1.1.2.2 Immunogenicity Outcomes 23
7.1.1.2.3 Safety outcomes 30
7.1.1.3 Reviewer Summary & Conclusions 58
7.1.2 Trial #2: V59P23 ..... *60*
7.1.2.1 Title 60
7.1.2.1.1 Objective 60
7.1.2.1.2 Design Overview 60
7.1.2.1.3 Population 62
7.1.2.1.4 Study Products 63
7.1.2.1.5 Safety Endpoints and Monitoring 63
7.1.2.1.6 Statistical considerations including plan for analysis 65
7.1.2.2 Results 67
7.1.2.2.1 Populations enrolled/analyzed 67
7.1.2.2.2 Efficacy outcomes 73
7.1.2.2.3 Safety outcomes 73
7.1.3 Trial 3: V59P21 ..... *85*
NCT# 00626327 ..... *85*
7.1.3.1 Title 85
7.1.3.1.1 Objective/Rationale: 85
7.1.3.1.2 Design Overview 86
7.1.3.1.3 Population 86
7.1.3.1.4 Products mandated by the protocol 87
7.1.3.1.5 Endpoints 87
7.1.3.1.6 Surveillance/Monitoring 88
7.1.3.1.7 Changes in the Conduct of the Study: 89
7.1.3.1.7.2 Protocol Amendments 90
7.1.3.1.7.3 Changes in the analysis plan 90
7.1.3.1.8 Statistical considerations including plan for analysis 90
7.1.3.2 Results 90
7.1.3.2.1 Populations enrolled/analyzed 90
7.1.3.2.1.1 Demographics: 91
7.1.3.2.2 Efficacy endpoints/outcomes 93
7.1.3.3 Reviewer Summary and Conclusions 102
7.1.4 Trial #4: V59P9 ..... *103*
7.1.4.1 Title 103
7.1.4.1.1 Objectives 103
7.1.4.1.2 Design Overview 104
7.1.4.1.3 Population 105
7.1.4.1.4 Products mandated by the protocol 105
7.1.4.1.5 Endpoints 105
7.1.4.1.6 Statistical considerations including plan for analysis 105
7.1.4.2 Populations enrolled/analyzed 106
7.1.4.2.1 Immunogenicity outcomes 106
7.1.4.2.2 Safety outcomes 107
7.1.4.3 Comments & Conclusions 108
7.1.5 Trial #5: V59P5 ..... *109*

7.1.5.1 Title ... 109
7.1.5.1.1 Objectives ... 109
7.1.5.1.2 Design Overview ... 109
7.1.5.1.3 Population ... 110
7.1.5.1.4 Products mandated by the protocol ... 111
7.1.5.1.5 Endpoints ... 111
7.1.5.1.6 Statistical considerations including plan for analysis ... 111
7.1.5.2 Results ... 112
7.1.5.2.1 Populations enrolled/analyzed ... 112
7.1.5.2.2 Immunogenicity outcomes ... 112
7.1.5.2.3 Safety outcomes ... 114
7.1.5.3 Comments & Conclusions ... 116
7.1.6 Trial #6: V59P7 ... *117*
7.1.6.1 Title ... 117
7.1.6.1.1 Objective/Rationale ... 117
7.1.6.1.2 Design Overview ... 117
7.1.6.1.3 Population ... 119
7.1.6.1.4 Products mandated by the protocol ... 119
7.1.6.1.5 Endpoints ... 119
7.1.6.1.6 Statistical considerations including plan for analysis ... 120
7.1.6.2 Results ... 120
7.1.6.2.1 Populations enrolled/analyzed ... 120
7.1.6.2.2 Immunogenicity outcomes ... 121
7.1.6.2.3 Safety outcomes ... 121
7.1.6.3 Comments & Conclusions ... 123
7.1.7 Trial #7: V59P8 ... *123*
7.1.7.1 Applicant's Protocol # V59P8 and Protocol Title ... 123

8 OVERVIEW OF EFFICACY ACROSS TRIALS ... **124**

8.1.1 Efficacy Findings ... *125*
8.1.2 Efficacy Conclusions ... *126*

9 OVERVIEW OF SAFETY ACROSS TRIALS ... **127**

9.1.1 Product-Product Interactions ... *131*
9.1.2 Post-Marketing Experience ... *131*
9.2 SAFETY CONCLUSIONS ... 131

10 ADDITIONAL CLINICAL ISSUES ... **132**

10.1 DIRECTIONS FOR USE ... 132
10.2 DOSE REGIMENS AND ADMINISTRATION ... 132
10.3 SPECIAL POPULATIONS ... 132
10.4 PEDIATRICS ... 132
11.5 OTHER ... 132

12 CONCLUSIONS - OVERALL ... **132**

13 RECOMMENDATIONS ... **133**

13.1 APPROVAL OR NON-APPROVAL RECOMMENDATION ... 133
13.2 RECOMMENDATIONS ON POSTMARKETING ACTIONS ... 133
13.3 LABELING ... 133

3 Executive Summary

Menveo (MenACWY) is currently approved for use in individuals 2 – 55 years of age. Menveo is indicated for the prevention of invasive disease caused by *Neisseria meningitidis* serogroups contained in the vaccine. The immunogenicity and safety data included in this supplemental BLA application was intended to support extended use of Menveo in infants and toddlers.

Studies V59P14 and V5923 were the pivotal trials to evaluate Menveo administered as a primary 4-dose series at 2, 4, 6 and 12 months. Study V59P21 was the main study to evaluate Menveo as a 2-dose catch-up vaccination series given three months apart. Serum bactericidal activity with human complement (hSBA) was used as an immune measure to infer effectiveness of Menveo in children aged 6 to 23 months. Menveo contains CRM_{197} carrier protein.

The safety and immunogenicity data submitted in this supplemental application are not adequate to support extending the use of Menveo to children less than 2 years of age, primarily due to concerns regarding the completeness, reliability, and verifiability of the clinical data. The main deficiencies/concerns are as follows:
`

Safety

- For all three pivotal studies, it was not possible to ascertain if safety information (solicited local and systemic adverse events [AEs], any AEs, medically-attended AEs and serious AEs) was collected in a systematic manner. In particular, the extent to which AEs were reported on diary cards/worksheets collected at the time of the visit/mailed to site, by verbal recall, and/or by review of clinical charts could not be determined. The frequencies of certain solicited local and systemic AEs, particularly fever, in the MenACWY groups and corresponding control groups were unexpectedly low, which could be attributed to underreported adverse events, methods of temperature measurement, and significant proportions of missing data.
- In study V59P23, the safety data for the subjects who received all 4 doses and had follow-up for one month after the 4th dose, and the timing of adverse events onset relative to vaccination could not be determined from the datasets provided. Also, there were numerous discrepancies between the Clinical Study Report (CSR), the datasets, and the Integrated Safety Summary (ISS). These discrepancies were for the number of subjects vaccinated at each visit and for the number of subjects with premature study discontinuation due to adverse events. Without the appropriate datasets, there was no mechanism to verify, analyze independently, and resolve discrepancies in reported safety information.

Immunogenicity:

- In study V59P14, approximately 45% (n=68-70 of 154 US1a subjects, depending on the serogroup) were excluded from the immunogenicity per-protocol population for the primary analysis.
- Retested sera for hSBA antibody responses were suboptimal due to potential introduction of bias introducted by correcting visit numbers, and, missing data. The original hSBA assay results were generated in an unblinded manner.
- During the review of this supplement, the agency became aware that translucent particles were observed in liquid CWY component packaged in ----------(b)(4)---------- Information submitted to the IND indicated that the particles in part consisted of ----------(b)(4)----------. The pivotal safety and immunogenicity data were generated using MenACWY doses in this presentation. No information regarding the investigation of particulates was provided in this sBLA.

Concomitant vaccine evaluation

- Immunogenicity evaluation of a 7-valent pneumococcal CRM_{197} conjugate vaccine (Prevnar) co-administered with MenACWY was confounded by the control group (US1b) used for 4th dose comparisons. Routine vaccinations recommended by the ACIP at age 12 months were administered to US1b, but these subjects had received three doses of MenACWY in infancy (2, 4, and 6 months of age). Pneumococcal IgG GMCs in the control group might also have been reduced.

We recommend that a complete response letter be issued and that the applicant address the deficiencies described above.

4 Significant Findings from Other Review Disciplines

4.1 Statistical

Please see statistical review memo.

5 Clinical and Regulatory Background

5.1 Epidemiology

Neisseria meningitidis is a primary cause of bacterial meningitis, especially in young children. Other important clinical presentations include pneumonia and occult bacteremia.

In the U.S., the highest incidence of meningococcal disease occurs in children younger than one year of age. During 1999-2008, the average annual incidence of meningococcal disease in children <1 years old was 5.65 cases/per 100,000 population; serogroups Y, C and W-135/other serogroups accounted for approximately 25%, 10% and 5% of meningococcal disease[i]. Also, the largest disease burden occurred among children ages 0 to 8 months of age. In 2009, preliminary data indicated that the incidence of meningococcal serogroup Y, C, W-135 disease in children <1 year old was 0.58. 0.19, and 0.19/ per 100,000 population, respectively [ii].

For meningococcal disease overall, the overall mortality rate is 3.8% - 14%, and is up to 21.2% of children in specific age groups[iii]. Despite broad antibiotic susceptibility, 11 – 19 % of survivors of meningococcal disease experience long-term sequelae[iv].

5.2 Rationale for selected vaccine formulation

Selection of the antigen dosage and ---(b)(4)--------- formulation was based on clinical studies conducted in adults (V59P1, V59P3), children 12 – 35 months old (V59P4, V59P7, V59P8) and infants as young as 2 months of age (V59P5, V59P9). Please see sections 7.1.4 to 7.1.7 for further details.

5.3 Previous Human Experience with the Product including Foreign Experience

Menveo is approved for use in individuals 2 – 55 years of age in the United States, and in individuals 11 years of age and older in Europe, Canada, Australia, Asia and Latin America.

5.4 Regulatory Background

5.4.1. Immunologic Marker of Protection: serum bactericidal antibody

Demonstration of effectiveness, inferred from immunogenicity data, was an approach used as a basis for licensing a tetravalent polysaccharide (Menomune; Sanofi Pasteur, Inc.) vaccine. In September 1999, use of an serological marker to infer effectiveness of new meningococcal conjugate vaccines was discussed at a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting [v]. The committee concurred that this approach could be used for children 2 years of age and older.

Use of serum bactericidal antibody to inferr effectiveness of meningococcal conjugate vaccines in young children was discussed at a VRBPAC meeting held April 6-7, 2011. At the time, a meningococcal conjugate vaccine for use in children younger than 2 years old had not been licensed in the U.S. In individuals 2 years of age and older, clinical trials had been designed to demonstrate non-inferiority of serum bactericidal antibody responses of a new meningococcal vaccine to responses in a randomized, control group who received a U.S. licensed meningococcal vaccine. The committee concurred that serum bactericidal activity with human complement (hSBA) could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children <2 years old. Also, seroresponses achieved at or above a pre-defined hSBA titer indicated that the meningococcal-specific functional antibodies

measured post-vaccination were considered protective against systemic infection [vi].

5.4.2 Previous vaccine approvals

Please see section 5.3.

5.4.3 Pertinent regulatory communications

5.4.3.1 November 25, 2008

CBER requested clarification from the applicant regarding the blinding of immunogenicity evaluations in study V59P14. As these evaluations were not performed in a blinded fashion, it was possible that bias was introduced into the immunogenicity evaluations. Novartis retested remaining serum samples from group US1 for all serogroups as well as the control group samples (US2), while maintaining blinding to subject ID, visit, and group allocation. The applicant found concordance in the results. Please see the portion of the clinical review related to study V59P14 for additional details.

5.4.3.2 December 18, 2008

CBER reiterated its End of Phase 2 guidance on the requirement to provide adequate infant safety data for licensure: a) that detailed safety data be collected from 3000 randomized controlled subjects receiving the intended infant schedule with US licensed vaccines; b) that safety be assessed for 6 months following the final dose in the series; c) that 50% or more of the safety database be from US infants; d) that additional extended safety data (SAEs and medically significant events) be collected from an additional 3000 infants. Due to the fact that V59P14 would not have provided sufficient safety data alone, study V59P23 was planned to supplement the safety database in infants.

5.4.3.3 November 30, 2010

The applicant submitted sBLA to support the infant indication. CBER determined the application deficient in information critical to performing a meaningful review and issued a Refuse-to-File letter on January 27, 2011.

6 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review

The following modules of the sBLA were reviewed:
M1.2
M1.3
M1.9
M1.14
M2.5
M2.7
M5.3.5.1

Amendment 2 (July 1, 2011): request for waiver of the requirement to conduct studies with Menveo to infants from birth to 2 months of age. Confirmation that there were inconsistencies related to the headers of V59P14 Amendment 7, dated November 16, 2009 but that the corresponding CSR submitted in this sBLA is authentic and was the one reviewed and signed by the investigators and that the final versions of the protocol and associated amendments included in the CSR have the same word-for-word content as those used in the study, submitted

to the investigators, and reviewed and approved by the Institutional Review Boards/Ethics Committees.

6.1.2 Post-Marketing Experience

Please see package insert.

6.2 Table 1: Summary of Clinical Studies

Study Number Country/ Population	Description (relevance to US licensure)	Vaccination schedule	Vaccines	Number of subjects: Total Cohort receiving any dose of final formulation
V59P14 United States Argentina Colombia Infants	P3 immunogenicity (4-dose primary series) and safety; open label, randomized, controlled Com vx: diphtheria, tetanus, IPV, PT, FHA, PRN, hepatitis B, PCV7 (post-3rd and post-4th)	US: 2, 4, 6, 12 months of age Latin America (additional schedules relevant to US licensure): 2-dose series (12 and 15 months of age)	MenACWY + US routine vx US routine vx alone followed by MenACWY	3022 1511
V59P21 United States Infants	P3 safety and immunogenicity; open label; 2 Menveo treatment arms randomized Com vx: MMRV or MMR and V	7 - 9 mos, 12 mos	MenACWY + MMRV MenACWY at 7 -9 mos, 13.5 mos, MMRV at 12 mos MMRV	500 503
V59P23 United States Taiwan Costa Rica Guatemala Peru Panama Infants	P3 safety; open label, randomized, controlled	2, 4, 6, 12 months	MenACWY + US routine vx US routine vx alone	5771 1973
V59P5 UK Canada Infants	P2 safety and immunogenicity of MenACWY ---(b)(4)------- as a 1, 3, or 4 dose series; open label, randomized, controlled	2, 4, 12 months	MenACWY + Canadian or UK routine vx	135

V59P7 Finland Poland Children 12-59 months of age	P2 safety and immunogenicity of MenACWY ---(b)(4)------; observer-blind, randomized, controlled	12 – 35 months of age, second dose 1 month later, 6 months later, or 12 months later	MenACWY	206
V59P8 US Children 12-23 months of age, 2-10 years of age	P2 safety and immunogenicity; single blind, randomized, controlled	Single dose at either 12 – 15 months or at 16 – 23 months	MenACWY at 12 – 15 months MenACWY at 16 – 23 months MenACWY + PCV7 at 12 – 15 months MenACWY + DTaP at 16 – 23 months	74 71 71 73
V59P9 Canada Infants 6-12 months	P2 safety and immunogenicity of 1 or 2 doses of MenACWY; open label, partially randomized, controlled	Either single dose at 12 months or 2 doses at 6, 12 months	MenACWY + Canadian routine vx at 12 months MenACWY + routine vx at 6 months and 12 months	61 164

6.3 Review Strategy

The clinical review was shared by Drs. Rastogi and Baylor (studies V59P23, V59P5, V59P7, V59P8, V59P9, and the Integrated Summary of Safety) and Dr, Ferris (studies V59P14, V59P21, Integrated Summary of Efficacy)

6.4 Good Clinical Practices (GCP) and Data Integrity

The applicant states in the sBLA that Good Clinical Practices were applied throughout the trials included in the sBLA. However, it appears that safety data were reconstructed in some cases. Please see the individual study reviews for additional details. The sites selected for BIMO inspection included V59P14, V59P23: Dr. William Johnston, Jr.: inspection revealed no deviations from applicable regulations.

6.5 Financial Disclosures

One investigator from study V59P14 and two investigators who participated in both studies V59P21 and V59P23 received > -(b)(4)(b)(6)- in payments from the applicant. The investigators were at sites 1, 38; sites 90, 76, V59P21 sites 76, 90 V59P23 sites 16, 25 and 76). Sub-investigators at V59P14 sites 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 33; V59P21 sites 82, 83 and 76; V59P23 sites 5, 109, 110, 112, 113, 118, 134. These sites accounted for the following numbers of subjects enrolled or randomized, by study: V59P14: 361 (of 1508 US subjects, i.e., 24% of US subjects); V59P21: 89 (of 1630 subjects, i.e.,5%); V59P23: 209.

7 Clinical Studies

7.1 Trial #1: V59P14

7.1.1 NCT# 00474526

7.1.1.1 Title
V59P14: 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

7.1.1.1.1 Objective/Rationale
Evaluation of the safety of and immune response to MenACWY when administered to healthy infants at 2, 4, 6, and 12 months of age. Secondary objectives were to assess an alternative primary immunization schedule at 2 and 6 months of age with another dose at 16 months of age.

Immunogenicity Objectives:
Primary:

1. To assess the immunogenicity of 4 doses of MenACWY administered at 2, 4, 6, and 12 months of age as measured by the percentage of subjects with serum bactericidal activity using human complement (hSBA) $\geq$ 1:8 against each serogroup (US subjects)
2. To compare the immunogenicity of the 4th dose of MenACWY administered at 12 months of age in subjects who previously received 3 doses of MenACWY 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, as measured by the ratio of geometric mean titers (GMTs) against each serogroup (US subjects)

Secondary:

1. To assess the immunogenicity of 3 doses of MenACWY administered at 2, 4, and 6 months of age as measured by hSBA GMTs and by the percentage of subjects with hSBA $\geq$ 1:8 and $\geq$ 1:4 against each serogroup (US subjects)
2. To compare the immunogenicity of 2 doses of MenACWY administered at 2 and 6 months of age to 3 doses of MenACWYadministered at 2, 4, and 6 months of age as measured by hSBA GMTs and by the percentage of subjects with hSBA $\geq$ 1:8 and $\geq$ 1:4 against each serogroup (Latin American 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 that of routine infant vaccines given without MenACWY (US and Latin American subjects, assessed separately)
4. To assess the persistence of bactericidal antibodies at 12 or 16 months of age in subjects who previously received 2 or 3 doses of MenACWY at 2 and 6 or 2, 4, and 6 months of age, as measured by hSBA GMT, hSBA $\geq$ 1:8 and $\geq$ 1:4 against each serogroup (US and Latin American subjects, assessed separately)
5. To assess the immunogenicity of the 3rd or 4th dose of MenACWY at 12 or 16 months of age in subjects who previously received 2 or 3 doses of MenACWY at 2 and 6 or 2, 4, and 6 months of age, measured by hSBA GMT, hSBA $\geq$ 1:16, $\geq$ 1:8 and $\geq$ 1:4 against each serogroup (US and Latin American subjects, assessed separately)
6. To demonstrate the immunogenicity of routine booster vaccinations administered during the second year of life (i.e., pneumococcal conjugate booster, Hib) when given concomitantly with MenACWY in subjects who previously received 2 or 3 doses of MenACWY at 2 and 6 or 2, 4, and 6 months of age is non-inferior to that of routine booster

vaccines given alone (US and Latin American subjects, assessed separately)

7. To assess the immunogenicity of 1 or 2 doses of MenACWY administered at 12 months or at 12 and 15 months of age as measured by hSBA GMTs, hSBA ≥ 1:8 and ≥ 1:4 against each serogroup (US and Latin American subjects, assessed separately)

Safety Objective:
To assess the safety and tolerability of MenACWY when given concomitantly with routine infant vaccines at 2 and 6 or 2, 4, and 6 months of age and in the second year of life

7.1.1.1.2 Design Overview

V59P14 was a Phase 3, randomized, open-label, multi-center, parallel group study in healthy infants in the US and Latin America (LA; Argentina, Columbia). Overall, subjects were randomized in a 2:1 ratio, stratified by geographic region, to receive either MenACWY + routine childhood vaccines (as recommended by the US Advisory Committee on Immunization Practices) or routine childhood vaccines alone. Subjects at all US sites and pre-specified LA sites were enrolled in the immunogenicity subset; once enrollment for immunogenicity was completed, all US sites continued to enroll subjects in the safety subset only. LA subjects in the safety only subset were enrolled at separate sites.

U.S. subjects in the immunogenicity subset received MenACWY + routine infant vaccines at 2,4, and 6 months of age (US1) or routine infant vaccines alone (US2). At 12 months of age, US1 subjects received either MenACWY + routine toddler vaccines (US1a) or routine toddler vaccines alone (US1b). US2 subjects (previously meningococcal vaccine naïve) received 1 dose of MenACWY at 12 months of age. Subsequent to immunogenicity evaluation, subjects in US1b and US 2 received 1 dose of MenACWY.

U.S. subjects in the safety only subset received MenACWY + routine infant vaccines at 2, 4, and 6 months of age (US3) or routine infant vaccines alone (US4a-c). At 12 months of age, subjects received MenACWY + routine toddler vaccines (US3 and US4a) or routine toddler vaccines alone (US4b and c). US4 subjects received 1 or 2 doses of MenACWY, depending on the subset (a-c).

Subjects were at varying stages in the study when protocol amendments were implemented.

7.1.1.1.3 Population

Inclusion criteria:

- Healthy, full-term, 2 month old infants (55 – 89 days, inclusive), birth weight ≥ 2.5 kg.
- Written informed consent
- Available for all scheduled study visits
- In good health as determined by medical history, physical assessment, and investigator judgment

Exclusion criteria:

- No written informed consent obtained
- Previously received any meningococcal vaccine
- Received prior vaccination with D, T, P, IPV or OPV, Hib, or pneumococcal vaccines
- Previous confirmed or suspected disease caused by *N. meningitidis*, *C. diphtheriae*, *C. tetani*, poliovirus, hepatitis B, Hib, pneumococcus, or *B. pertussis*
- Household contact with and/or intimate exposure to an individual with laboratory confirmed N. meningitidis (serogroups A, C, W, or Y), B. pertussis, Hib, C. diphtheriae, polio, or pneumococcal infection at any time since birth
- History of anaphylactic shock, asthma, urticaria, or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component

- Significant acute or chronic infection within the previous 7 days or fever within the previous 3 days
- Any present or suspected serious acute (e.g., leukemia, lymphomas), or chronic disease (e.g., with signs of cardiac disease, renal failure, severe malnutrition, or insulin dependent diabetes), or progressive neurological disease, or a genetic anomaly/known cytogenic disorders
- Known or suspected autoimmune disease or persistent impairment of immune function
- Known or suspected HIV infection or HIV related disease
- Received blood, blood products, and/or plasma derivatives or any parenteral immunoglobulin preparation
- Known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time
- History of seizure (exception: one febrile seizure)
- Planning to leave the study area before the end of the study
- Any condition which, in the investigator's opinion, may interfere with evaluating the study objectives
- Any antipyretic medication use in the previous 6 hours
- Any investigational agents or vaccines since birth or anticipated receipt prior to study completion

Reasons for delaying subsequent vaccinations:

- Acute, chronic, or febrile illness within the previous 7 days
- Use of antipyretics within 6 hours
- Use of systemic corticosteroids administered during the study for $\leq$ 5 days would delay further vaccinations 15 days or for > 5 days would delay further vaccinations 21 days
- Receipt of any licensed vaccines within 28 days prior to any study visit or for whom receipt of a licensed vaccine was anticipated within 28 days post-vaccination, except for influenza vaccine, which could be administered within 15 days of vaccination. All concomitant vaccines required by local practice but not part of the study could be administered in the study visits.

Reason for delaying subsequent blood draws (and vaccination for the second year of life only):

- Received oral or parenteral antibiotic treatment in the 7 days prior to the scheduled blood draw

Procedures allowed (concomitant products and timing).

7.1.1.1.4 Products mandated by the protocol

Table 2. V59P14. Vaccination Schedule

US Safety and Immunogencity									
Group	2 mos	4 mos	6 mos	12 mos	13 mos	15 mos	16 mos	17 mos	18 mos
US 1A	ACWY + routine	ACWY + routine	ACWY + routine	ACWY + routine					
US 1B	ACWY + routine	ACWY + routine	ACWY + routine	Routine	ACWY*				
US 2	Routine	Routine	Routine	ACWY + routine		ACWY*			
US Safety only									
US 3	ACWY + routine	ACWY + routine	ACWY + routine	ACWY + routine					
US 4A	Routine	Routine	Routine	ACWY + routine		ACWY* + routine			
US 4B	Routine	Routine	Routine	Routine	ACWY	ACWY* + routine			
US 4C	Routine	Routine	Routine	Routine					ACWY*
LA Safety and Immunogenicity									
LA 1A	ACWY + routine	Routine	ACWY + routine	ACWY + routine					
LA 1B	ACWY + routine	Routine	ACWY + routine	Routine	ACWY*				
LA 2	Routine	Routine	Routine	ACWY + routine		ACWY*			
LA 3A	ACWY + routine	ACWY + routine	ACWY + routine	Routine			ACWY DTaP Hib		
LA 3B	ACWY + routine	ACWY + routine	ACWY + routine	Routine			DTaP Hib	ACWY*	
LA 4	Routine	Routine	Routine	ACWY + routine		ACWY* DTaP Hib			

Table 2 (continued). V59P14. Vaccination Schedule

LA Safety only									
Group	2 mos	4 mos	6 mos	12 mos	13 mos	15 mos	16 mos	17 mos	18 mos
LA 5	ACWY + routine	ACWY + routine	ACWY + routine	ACWY + routine					
LA 6A	Routine	Routine	Routine	ACWY + routine		ACWY			
LA 6B	Routine	Routine	Routine	Routine	ACWY	ACWY			
LA 6C	Routine	Routine	Routine	Routine					ACWY* + routine

*No blood drawn one month after MenACWY vaccination
ACWY= MenACWY. US routine = concomitant vaccines, which were Pediarix® (DTaP-HepB-IPV), ActHIB® (Hib), and Prevnar® (PCV7), and Rotateq® (rotavirus) at 2, 4, 6 months of age; ProQuad™ MMRV [or MMR®II (MMR) + Varivax® (V)] and Havrix® (HepA) at 12 months of age. For LA subjects: Hib + Infanrix® (DTaP) or DTaP-Hib given at >15 months of age, as per national recommendations.

Vaccine dose, route of administration, and composition:

MenACWY: Each 0.5 mL dose contains 10 mcg MenA conjugated to ---(b)(4)---- mcg CRM_{197}, 5 mcg MenC conjugated to ---(b)(4)---- mcg CRM_{197}, 5 mcg MenW conjugated to ---(b)(4)---- mcg CRM_{197}, and 5 mcg MenY conjugated to ---(b)(4)---- mcg CRM_{197}. The lyophilized MenA (single dose vial) was reconsitituted with the liquid MenCWY component (single dose ---(b)(4)----------). Given intramuscularly (IM). Lot Z009011 (vial) /Z79P42I1 ---(b)(4)- .

Concomitant Vaccines: supplied as as study vaccines

Pediarix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant), and Inactivated Poliovirus Vaccine Combined; GSK Biologicals, Inc.): Each 0.5 mL dose contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 mg pertussis toxoid, 8 mg pertactin (PRN), 25 mg filamentous hemagglutinin (FHA), 10 mg recombinant Hepatitis B surface antigen, 40 D-antigen units poliovirus type 1 (Mahoney strain), 8 D-antigen units poliovirus type 2 (MEF-1 strain), 32 D-antigen units poliovirus type 3 (Saukett strain). Given IM.

ActHIB (*Haemophilus influenzae* type b Conjugate Vaccine; Sanofi Pasteur, Inc.): Each 0.5 mL dose contains 10 mcg Hib capsular polysaccharide conjugated to 24 mcg of tetanus toxoid. Given IM.

Prevnar/Prevenar (Pneumococcal 7-valent Conjugate Vaccine; Pfizer, Inc.): Each 0.5 mL IM injection contains 2 mg each of saccharide (serotypes 4, 9V, 14, 18C, 19F, 23F), except for serotype 6B (4 mg) individually conjugated to CRM_{197} carrier protein (~20ug total), and (b)(4) mg aluminum phosphate.

RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent; Merck & Co, Inc.): Each 2 mL dose contains 5 live reassortant rotaviruses containing G1, G2, G3, G4 and P1A[8] which contains a minimum of 2.0 – 2.8 x 10^6 infectious units (IU) per individual reassortant dose, depending on the serotype, and not greater than 116 x 10^6 IU per aggregate dose. Given orally.

ProQuad (Measles, Mumps, Rubella, and Varicella Vaccine; Merck & Co, Inc.): Each 0.5 mL dose contains $\geq$ 3.00 log10 TCID50 measles virus Enders' Edmonston strain (live, attenuated), $\geq$ 4.30 log10 TCID50 mumps virus (Jeryl Lynn Level B strain (live attenuated), $\geq$ 3.00 log10 TCID50 rubella virus Wistar RA 27/3 strain (live attenuated), $\geq$ 3.99 log10 PFU varicella virus Oka/Merck strain (live attenuated). Refrigerator formulation. Given subcutaneously (SC).

M-M-R II (Measles, Mumps, and Rubella Vaccine; Merck & Co, Inc.): Each 0.5 mL dose contains ≥ 1000 TCID50 measles virus Enders' Edmonston strain (live, attenuated), ≥ 12500 TCID50 mumps virus (Jeryl Lynn Level B strain (live attenuated), ≥ 1000 TCID50 rubella virus Wistar RA 27/3 strain (live attenuated). Given SC.

Varivax (Varicella Vaccine; Merck & Co, Inc.): Each 0.5 mL dose contains > 1350 PFU varicella virus Oka/Merck strain (live attenuated). Given SC.

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; GSK Biologicals): Each 0.5 mL dose contains 25 Lf diphtheria toxoid, 10 Lf tetanus toxoid, 25 mcg inactivated PT, 25 mcg FHA, 8 mcg pertactin, 2.5 mg 2-phenoxyethanol ≤ 0.625 mg aluminum. Given IM.

Havrix (Hepatitis A; GSK Biologicals): Each 0.5 mL dose contains 720 ELISA Units of viral antigen, adsorbed on 0.5 mg of aluminum hydroxide. Given IM.

Permitted vaccines: Routine childhood vaccines that were required per local practice, but not part of the study, could be administered at the study visits.

7.1.1.1.5 Endpoints

Primary Endpoints and success criteria:

- Lower limit of the 95% CI for the proportion of subjects with hSBA ≥ 1:8 at 1 month following the 4th dose of MenACWY ≥ 80% for serogroup A and ≥ 85% for serogroups C, W, and Y
- Lower limit of the 95% CI for the ratio of the GMT post-4th dose at 12 months after receiving MenACWY at 2, 4, and 6 months of age compared to the GMT after a single dose at 12 months of age is ≥ 2.0

Secondary Endpoints:

- Proportions of subjects achieving hSBA ≥ 1:4, hSBA ≥ 1:8, and GMTs for each serogroup
- Proportions of subjects with antibody responses above the pre-specified levels at one month post-3rd vaccination as follows: diphtheria > 0.1 IU/mL; tetanus > 0.1 IU/mL; PT, FHA, pertactin GMCs and 4-fold increase over baseline if baseline ≥ LLQ and ≥ 4 LLQ if baseline < LLQ; poliovirus types 1, 2, and 3 ≥ 1:8; hepatitis B ≥ 10 mIU/mL; pneumococcal vaccine serotypes ≥ 0.35 mcg/mL and ≥ 1.0 mcg/mL (and one month after 4th dose); PRP ≥ 0.15 mcg/mL
- Non-inferiority of responses to routine infant vaccines when given concomitantly with MenACWY at 2 and 6 or 2, 4, and 6 months of age to responses to those vaccines given alone as demonstrated by a lower limit of the two-sided 95% CI for [Proportion$_{\text{concomitant vaccine + MenACWY}}$ minus P$_{\text{concomitant vaccine}}$] > -10%.
- Non-inferiority of concomitantly administered pertussis antigens as demonstrated if the GMC ratio [GMC$_{\text{Pediarix + MenACWY}}$/ GMC$_{\text{Pediarix}}$] is ≥ 0.67 after vaccination at 2, 4, and 6 months of age
- Non-inferiority of concomitantly administered pneumococcal antigens as demonstrated by a GMC [GMC$_{\text{PCV7 + MenACWY}}$/ GMC$_{\text{PCV7}}$] ≥ 0.50 after vaccination at 2, 4, 6, and 12 months of age

Retesting of sera tested by hSBA assay:

When sera from the US subjects were initially tested, samples from the control group were not

tested for hSBA antibody responses to meningococcal vaccine antigens since MenACWY was not administered to the control group. Due to subject numbering and labeling conventions, it was possible that the laboratory personnel could anticipate samples might have had higher titers, which could potentially introduce reporting bias. As per CBER recommendations, a blinded retest of all remaining sera from US subjects was performed.

Changes to the Protocol*:*
Protocol Amendment 1, 3 April 2007: re-stated primary objectives and success criteria to be consistent with final selected infant dosing regimen (2-4-6m primary series, 12m booster dose), increased the number of subjects in the Safety Groups, expanded the collection of detailed safety data (immediate AEs, solicited AEs, unsolicited AEs, SAEs, and medically significant AEs) to include all subjects in the Safety Groups, included pneumococcal non-inferiority comparison of GMC ratio post-dose 4, pneumococcal analyses of %≥1.0ug/mL post-dose 4 and GMC post-dose 3, included pertussis non-inferiority comparison of GMT ratio (1.5 fold differences), DTaP schedule revised to be consistent with product labeling, modified the inclusion criteria to allow children with history of up to one febrile seizure to be eligible for study participation.

Protocol Amendment 2, 3 December 2007: revised the blood draw for "comparator" groups US2 and LA2 scheduled for one month after the 2nd dose of MenACWY to one month after the 1st dose of MenACWY to assess the fourth dose of MenACWY as either a "booster" dose or the final dose in a 4-dose primary series (i.e. immune response following a single dose at 12 months of age [US2] vs. immune response measured after 4 doses [US1a]), revised primary endpoint for booster response from seroresponse to GMT, included endpoints for D, T, aP booster response, removed testing for MMR-V antigens and moved the blood draw scheduled at 13.5 months to 13 months.

Protocol Amendment 3, 13 March 2008: 4th dose of DTaP and Hib vaccines, given at 15 months of age, were deleted as concomitantly administered vaccines from control group US2 and LA2 to allow flexibility in administering the two vaccines in the second year of life, 4th DTaP and Hib were provided as study vaccines for LA3a, LA3b, and LA4, allowed the option for administering MMR-V (ProQuad) as the separate components (MMR and varicella vaccines).

Protocol Amendment 4, 27 May 2008: revised the primary objective and timepoint to reflect evaluation of a 4-dose MenACWY primary series, revised primary criteria for serogroup-specific seroresponse, deferred the MenACWY vaccination schedule in groups US4 and LA6 from 12 months to 13 months of age to provide a "control" group (i.e., receives routine childhood vaccinations only) for safety evaluations at the 4th dose, included additional secondary endpoints: (hSBA seroresponse ≥1:8 and GMT after MenACWY dose 3, pneumococcal IgG seroresponse ≥1.0mcg/mL post-dose 3 and ≥0.35 mcg/mL post-dose 4), clarify that preliminary analysis applied only to U.S. immunogenicity cohort.

Protocol Amendment 5, 7 August 2008: revised MenACWY vaccination schedule in groups US4 and LA6 from a 2-dose series (13m, 18m) to a single dose at 18 months to enable these groups to serve as a "control" group for the 6m safety follow-up (i.e., US3 up to 18 months of age vs. US4c). As a result, US4c and LA6c were initiated.

> *Reviewer comment: Amendments 4 and 5 affected groups US4 and LA6, and subjects were at different stages in the study when these amendments were implemented. Thus, 3 subsets of subjects within each group received MenACWY at different times from 12 months of age forward.*

Protocol Amendment 6, 15 June 2009: provided an additional concomitant vaccine (2nd dose of Hepatitis A vaccine) in the study.

Protocol Amendment 7, 16 November 2009: clarified the collection of adverse events for US4 and LA6 subjects during the period between 12 and 13 months of age, changed criteria for seroresponse to pertussis antigens based on revised cut-off value, changed the non-inferiority criteria for polio antigens to be consistent with CBER recommendations.

Changes in the conduct of the study*:*
The applicant performed a routine audit of site 34. Site-specific Good Clinical Practice (GCP) concerns were identified, including inadequate documentation of informed consent process and collection of diary card information. Novartis notified CBER of its concerns in a letter submitted to the MenACWY IND on March 17, 2010. In the study report, the applicant indicates that the investigator took some corrective steps to address the GCP efficiencies. However, in the March 2010 letter, the applicant states that the investigator provided no assurance of compliance with corrective actions within the suggested timeline. In this communication, Novartis informed CBER's OCBQ of the related issues and stated that:

> *The study documentation [for study V59P14] allowed sites, in the event that parents lost a diary card, to ask the parent to reconstruct as much of the information as they could from memory regarding adverse events and concomitant medications given during the period between study visits. Sites were to clearly document [sic] on the source documentation that this was verbal data, the identity of the person who provided that data, who collected the data, and the date/time the data was verbally collected [sic]….for study cards that were not originally completed at the subjects' homes, these steps were not routinely followed in reconstructing data from memory concerning subjects' temperatures, adverse events, concomitant medications, and solicited local/systemic reactions.*
>
> *Reviewer comment: Data reconstruction is a less optimal method of collecting safety information in a clinical trial, and can lead to underreporting of adverse events. The study design included a telephone call 7 days after each vaccination to remind the parent to complete the diary card(s), clarify questions about study procedures and respond to any parental concerns. Another diary card was provided to parents to record medically attended adverse events [MAEs] and serious adverse events [SAEs]. See section 7.1.1.1.6 (Surveillance/Montoring) for details. Depending on the study group, a diary card(s) was collected and reviewed with parent at the next visit, which could occur up to 6 months after the diary card was issued. The extent to which information about solicited adverse events [AEs], any AEs, MAEs and SAEs were reported by this method is unclear. The proportion of safety data which was reconstructed, as well as the timepoints at which reconstruction occurred are factors that can significantly affect systematic collection of safety infomation, lead to introduction of biases and affect the accuracy of reported adverse events. Accurate assessment of MenACWY safety in infants would thus be difficult.*

(b)(4) IRB had ethical oversight for 19 US sites but received a warning letter from the FDA citing serious concerns about its ability to protect human subjects on ---------(b)(4)----. Enrollment had already been completed at these sites; the IRB ceased operations on June 30, 2009. The applicant identified an alternative central IRB which performed a de novo review of the trial, reviewed and approved the protocol in June 2009. The applicant reports that there were no

indications that ethical oversight of the study sites by (b)(4) IRB was compromised during its tenure and that there were no lapses in IRB coverage during the transfer of the trial to the new IRB. Documents pertaining to these events were not provided in the application.

In Latin America, the applicant performed an audit on August 13 – 15 2008 of the 2 ethics committees responsible for oversight of 3 sites in Cali Colombia (sites 81, 82, and 83). Serious concerns about the qualifications of both ethics committees were identified. IRB duties and responsibilities were transfered to another ethics committee in October 2009. Consequently, there was a significant delay in the approval and implementation of protocol amendment 5 at the Colombian sites. In this protocol amendment, the number of MenACWY doses administered to group LA6 decreased from 2 doses at 13 and 15 months (group LA6B) to a single dose at 18 months (group LA6C). The amendment was implemented in a timely fashion at the Argentinian sites, creating a disproportionate representation of subjects from Argentina in group LA6C and from Colombia in group LA6B. In addition, study enrollment at site 44 was placed on hold on September 12, 2007 and terminated on January 2, 2008, due to major protocol deviations which occurred during the conduct of an unrelated vaccine study.

Changes in the Analysis Plan:
Version 2.0 dated April 2, 2010, was revised 5 months after study completion. The updated analysis plan incorporated changes made in protocol amendments 6 and 7. Also, per CBER recommendations, the analysis plan was revised to include 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 blood draw intervals for subjects included in the per-protocol population were lengthened from 28-42 days to 23-55 days.

7.1.1.1.6 Surveillance/Monitoring

Safety:
Subjects were observed for 15 minutes after each vaccination to capture immediate hypersensitivity reactions. Local and systemic reactions, axillary temperature, analgesic/antipyretic medication use, and all adverse events were collected for 7 days after each vaccination on diary cards (diary card A), which were to be returned at the next study visit. According to the protocol, serious Adverse Events (SAEs) and AEs requiring a medical office or Emergency Room (ER) visit and/or resulting in premature withdrawal of subjects from the study were collected throughout the study and recorded at the next study visit, although where parents recorded this information beyond days 1 – 7 is not specified. 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 (subjects followed under Amendment 5) from one month after the 12 month visit up to the 18 month of age visit, pre-planned visits, medical office or ER visits for routine medical care, and common acute conditions were not collected. Whole-limb swelling after 4th dose of DTaP; and rash, encephalitis, and parotid/salivary gland swelling after MMR vaccination were elicited specifically. SAEs were collected in a phone call 6 months after the last MenACWY vaccination; the source document was diary card B, which was intended to capture SAEs, medically attended AEs, and concomitant medications and was distributed at whichever visit preceded the 6 month follow up period and varied by group.

Immunogenicity:
Subjects in the immunogenicity cohorts had blood drawn pre-vaccination, and 1 month after the last infant vaccination (after the doses at 2, 4, and 6 months of age in the U.S. and after either 2 doses or 3 doses in Latin America), pre-final dose vaccination, and 1 month post-final dose vaccination. The immunogenicity cohorts were: US1a, US1b, US2, LA1a, LA1b, LA2, LA3a,

LA3b, LA4.
(b)(4): diphtheria, tetanus, pertussis, Hib, HBsAg, and pneumococcal antibody titers (all but pneumococcal performed by ----------(b)(4)----------; pneumococcal antibody titers performed by -------(b)(4)----------
Neutralization test: poliovirus antibody titers (performed by ----------(b)(4)----------
hSBA: MenA, MenC, MenW, MenY (performed by Novartis Vaccines, Germany)

7.1.1.1.7 Statistical Analysis Plan

The study's overall power to achieve its primary objectives was 86%, assuming 120 subjects were available for immunogenicity analyses.

Interim analyses were permitted according to page 4527/31591, but no further information was provided.

Within each region (US and Latin America), 2 randomization lists were used. Each of the 4 randomization lists was stratified by site. In the US, the immunogenicity group list randomly assigned subjects to either US1a, US1b, or US2 groups, and the safety group list randomly assigned subjects to either US3 or US4. In Latin America, the immunogenicity group list randomly assigned subjects to either LA1a, LA1b, LA2, LA3z, LA3b, or LA4, and the safety group list randomly assigned subjects to LA5 or LA6. After the immunogenicity subgroups were enrolled, randomization switched over to the safety group randomization lists.

> *Reviewer comment: There were 4 different randomization schemes, which complicates the interpretation of the results, as it is unclear whether bias was introduced randomly and to a similar extent in all 4 study groups. For instance, the reviewer's analyses compare the safety of the 4 dose series of Menveo in US1a and US3 with the safety of the 4 dose series in US4b and US4c. The 203 subjects in US4c comprised 58% of the 349 subjects enrolled at study start in US4. While there were no formal criteria for pooling, the subjects in these groups were combined to increase the numbers of subjects for whom any data were available for evaluation of the safety of the 4 dose series. However, since subjects' randomization to group US1a or US3 was performed separately, the combined groups may not be separately balanced with respect to bias.*

7.1.1.2 Results

7.1.1.2.1 Populations

Safety Population: All subjects who received a study vaccination and provided post-baseline safety data

The proportion of subjects in the safety population 28 days after the 1st MenACWY toddler vaccination (i.e., after the dose administered when the subjects were ≥ 12 months of age) ranged from 72% - 80% of the immunogenicity subjects, with numbers shown in the table below. The proportion of subjects in the safety cohorts who were defined as belonging to the safety population at the same timepoint is not provided by the applicant. Approximately 89% of subjects in group US3 (safety cohort) were defined as not having major protocol deviations. More subjects in the groups US4a, US4b, and US4c were defined as having major protocol deviations (21% - 57%).

> *Reviewer comment: It appears that the applicant may not have collected detailed*

safety data through one month after the final dose in the safety cohorts (in the US, groups US3 and US4a, 4b, and 4c). The applicant should clarify this point.

Immunogenicity Modified Intention-to-treat (MITT): Population: all subjects who received a study vaccination and provided at least one evaluable serum sample post-baseline.

Immunogenicity Per Protocol Population: all subjects who received all relevant doses of vaccine correctly, provided evaluable serum samples at relevant time points, and had no major protocol deviations as defined prior to database lock.

Table 3. V59P14. Subject Disposition

Vaccine group	Planned Enroll	Actual Enroll	Vaccinated	Vaccine group	Completed	Safety	Safety through 1 month after final dose	MITT (Infant)	MITT (Toddler)	PP (MenACWY Infant)	PP (Concomitant Infant)	PP (Pertussis Infant)	PP (MenAC Toddler
US1a	150	154	153	US1a	121	153	127	115	107	108	106	81	91
US1b	150	166	165	US1b	120	165	133	121	105	115	111	93	92
US2	150	159	159	US2	110	159	116	106	99	100	103	83	84
US3	700	680	678	US3	561								
US4	350	349	345	US4a[1]	8								
				US4b[2]	54								
				US4c[3]*	178								
LA1a	150	151	151	LA1a	145	151	151	145	144	141	144	143	106
LA1b	150	150	150	LA1b	144	150	150	146	143	143	143	143	106
LA2	150	148	148	LA2	121	148	124	130	120	124	123	123	80
LA3a	150	151	151	LA3a	141	151	149	142	141	138	140	139	123
LA3b	150	150	150	LA3b	139	150	149	140	139	139	143	142	110
LA4	150	150	150	LA4	135	150	138	143	138	139	138	135	106
LA5	1400	1426	1424	LA5	1270								
LA6	700	711	709	LA6a	281								
				LA6b	152								
				LA6c*	183								

1: Enrollment in US4 began in September 2007 and was completed in March 2008
2: US4b implemented in May 2008 by protocol amendment 4
3: US4c implemented in August 2008 by protocol amendment 5
* No 6 month post-last dose follow-up; One month post-vaccination follow-up phone call; diary card to be returned via mail or dropped off in clinic

Immunogenicity Per Protocol Population (US subjects): A total of 479 subjects were enrolled in the US immunogenicity cohorts US1 and US2. Out of these 479 enrollees, 351 subjects completed the study (79% of US1a subjects, 72% of US1b subjects, and 69% of US2 subjects). The proportion of US immunogenicity subjects for whom protocol deviations were reported was 84% - 94%, and the proportion of subjects for whom major protocol deviations were reported ranged from 52% - 65%, resulting in the exclusion of a large proportion of subjects from the per protocol immunogenicity population. For the per protocol infant MenACWY population, 30% - 37% of subjects were excluded. **The per protocol populations included 323 subjects from the infant series and 267 subjects after the toddler vaccination. The MITT and PP populations for the infant series differed by $\leq$ 5%, and the MITT and PP populations differed by $\leq$ 10% for the toddler vaccination; *i.e., a substantial proportion of subjects was missing from the MITT population.*** The most common protocol violations, their distribution by treatment group, and the potential biases they may introduce are provided below:

Deviations: exclusion of subjects from the per protocol immunogenicity population for any of the reasons below could have biased the immunogenicity results either in favor of or against MenACWY's immunogenicity in the infant population. Discussion of the potential biases introduced is presented below in the context of the most conservative estimate of MenACWY's immunogenicity.

- *No baseline blood draw*. US1a: 34 subjects (22%), US1b: 24 subjects (14%), US2: 29 subjects (18%). Lack of a baseline serum sample may not influence the results with respect to the immunogenicity endpoints of proportion of subjects with hSBA titers $\geq$ 1:8 for each meningococcal serogroup contained in the vaccine. However, there is no way to know whether exclusion of these subjects results in overestimation or underestimation of the proportion of subjects achieving the final endpoints. A conservative estimate would be that, if these subjects would have gone on to have lower immune responses to the MenACWY vaccine, the proportion of subjects achieving hSBA $\geq$ 1:8 was overestimated in study V59P14. The converse may produce an underestimation of this proportion.
- *Incomplete infant series*. US 1a: 16 subjects (10%), US1b: 21 subjects (13%), US2: 16 subjects (10%). This protocol violation would have caused the exclusion of a slightly greater proportion of subjects who received MenACWY doses 1 – 3 (12%) compared with those who received only concomitant vaccinations (10%) through age 7 months. It is possible that subjects did not complete the infant series due to reactions to previous vaccinations, although the proportions are close enough that a major safety concern is not raised. However, exclusion of these subjects may bias the assessment of the immune response to MenACWY; in which direction the bias would occur is subject to speculation.
- *No blood draw Visit 4*: US1a: 12 subjects (8%), US1b: 14 subjects (8%), US2: 17 subjects (11%). It is possible that the applicant elected not to draw blood from subjects who did not complete the infant series. However, this is not mentioned in the CSR. Exclusion of these subjects may bias the assessment of the immune response to MenACWY in either direction. However, a conservative estimate may be that the immune response to MenACWY may be overestimated due to this deviation.
- *Incomplete toddler series*: US1a: 9 subjects (6%), US1b: 5 subjects (3%), US2: 0 subjects. A conservative estimate would be that, if these subjects would have

gone on to have lower immune responses to the MenACWY vaccine, the proportion of subjects achieving hSBA ≥ 1:8 was overestimated in study V59P14. The converse may produce an underestimation of this proportion.

- *No blood draw Visit 6*: US1a: 7 subjects (5%), US1b: 8 subjects (5%), US2: 12 subjects (8%). It is possible that the applicant evaluated the immune responses to the first 3 doses and did not draw blood on subjects for whom the immune responses after doses 1 – 3 were deemed insufficient. This would result in the exclusion of subjects who were poor responders to MenACWY, resulting in overestimation of the immune response to the vaccine.

Reviewer comment: Since a large proportion of subjects were excluded from the per protocol population (52% - 65%), primary analyses of MenACWY immunogenicity may not have been performed on a randomized population.

Demographics: US immunogenicity subjects (Groups US1a, US1b, and US2) were similar with respect to ethnic origin and gender. Males comprised 55 – 57% and Caucasians were 52 – 61% of the populations in these groups. US safety subjects (Groups US3, US4a, US4b, and US4c) were generally similar to each other in terms of gender (49 – 59% males) and ethnic origin (55 – 76% Caucasian). Excluding Group US4a, the proportion of Caucasian subjects was 69 – 76%. Comparing the US safety subjects to the US immunogenicity subjects, fewer African American subjects were included in the US safety groups (7 – 9%) compared with the US immunogenicity groups (11 – 17%). Latin American immunogenicity subjects (Groups LA1a, LA1b, LA2, LA3a, LA3b, and LA4) were balanced with respect to gender and ethnic origin, although they included only 1 subject who was not Caucasian (65 – 66% across groups) or Hispanic (33 – 35% across groups). Males comprised 45 – 52% of subjects across these groups. Latin American safety subjects (Groups LA5, LA6a, LA6b, and LA6c) were mostly balanced (with the exception of a higher proportion of Caucasians in group LA6c) in terms of gender (48 – 52% male) and ethnic origin (79 – 85% Hispanic, except group LA6c which was 66% Hispanic) but differed in comparison to the Latin American immunogenicity subjects in that the safety population had a much higher proportion of Hispanic subjects. Mean weights and heights at enrollment were similar across all groups.

Of the 3037 subjects enrolled in Latin America, 1530 subjects were enrolled in Argentina, and 1507 were enrolled in Columbia. While this suggests 50% of Latin American subjects were enrolled in each of the two countries, distribution among treatment groups was disproportionate, so that 100% of subjects in groups LA1a, LA1b, LA2, LA3a, LA3b, and LA4 were from Argentina.

7.1.1.2.2 Immunogenicity Outcomes

Primary Endpoints:

Post-MenACWY dose 4 hSBA antibody responses

Of note, there is no direct comparator for the 4 dose series in US subjects.

Primary objectives for meningococcal hSBA antibody responses were achieved. The lower bound of the 95% CI for was ≥ 80% for serogroup A and ≥ 85% for serogroups C, W, and Y at one month after the 4th dose in US subjects who received 4 doses.

Table 4. V59P14. Percentage of Subjects [95% CI] with hSBA ≥ 1:8 one month after the 4th MenACWY dose, Study Groups US1a and US1b* (Per-Protocol Population)

	Timepoint hSBA drawn	US1a	US1b
		MenACWY at 2,4,6,12 mos	MenACWY at 2,4,6 mos
MenA		N = 84	N = 83
	12 mos	8 (10%) [4-18]	12 (14%) [8-24]
	13 mos	79 (94%) [87-98]	N/A
MenC		N = 86	N = 83
	12 mos	43 (50%) [39-61]	45 (54%) [43-65]
	13 mos	84 (98%) [92-100]	N/A
MenW		N = 85	N = 81
	12 mos	60 (71%) [60-80]	55 (68%) [57-78]
	13 mos	85 (100%) [96-100]	N/A
MenY		N = 84	N = 70
	12 mos	51 (61%) [49-71]	42 (60%) [48-72]
	13 mos	84 (100%) [96-100]	N/A

*US1b subjects received MenACWY at 2,4,6 months of age
Source: V59P14 CSR, Table 11.4.1-1, page 164/31591.

Secondary Endpoints:

hSBA GMTs

Table 5. V59P14. hSBA GMTs one month after the 4th MenACWY vaccination, Study Groups US1a and US1b* (Per-Protocol Population)

	Timepoint hSBA drawn	US1a	US1b
		MenACWY at 2,4,6,12 mos	MenACWY at 2,4,6 mos
MenA		N = 84	N = 83
	12 mos	2.51 (2.14 - 2.96)	3.08 (2.61 – 3.62)
	13 mos	77 (55 - 109)	N/A
MenC		N = 86	N = 83
	12 mos	7.72 (5.9 - 10)	8.45 (6.43 – 11)
	13 mos	227 (155 - 332)	N/A
MenW		N = 85	N = 81
	12 mos	14 (11 - 18)	14 (11 – 18)
	13 mos	516 (288 - 602)	N/A
MenY		N = 84	N = 70
	12 mos	11 (8.76 – 15)	10 (7.77 – 14)
	13 mos	395 (269 – 580)	N/A

*US1b subjects received MenACWY at 2,4,6 months of age
Source: V59P14 CSR, Table 11.4.1-2, page 165/31591.

Antibody persistence between the 3rd and 4th MenACWY dose:

The percentage of subjects (US1a and US1b) with hSBA titers were 12% for serogroup A [LL 95% CI = 7] and 52% - 69% for serogroups C, W-135, and Y [LL 95% CI range 44 – 62]. Antibody persistence following the 4th dose in the 4 dose series is not provided in this sBLA.

<u>Reviewer comment</u>: the number of participants s presented in these tables as being the PP population are lower than the numbers presented by the applicant elsewhere as being in the PP population at the Toddler MenACWY blood draw. No explanation is provided by the applicant, and this should be clarified to ensure that results presented are accurate.

<u>Post-MenACWY dose 3 hSBA antibody responses</u>

Table 6. V59P14. Percentage of subjects in the per protocol population achieving hSBA ≥ 1:8 and GMTs, Study Group US1 vs. US2 (Per-protocol Population)

	Timept hSBA drawn	**US1**	**US2**	**US1**	**US2**
		3 doses of MenACWY by 6 mos	0 doses MenACWY by 6 mos	3 doses of MenACWY by 6 mos	0 doses MenACWY by 6 mos
		% ≥ 1:8 (95% CI)		**GMT by hSBA (95% CI)**	
MenA	Pre	**N = 212**	**N = 80**	**N = 212**	**N = 80**
		2 (0 – 5)	3 (0 – 11)	2.11 (2 – 2.23)	2.1 (1.92 – 2.29)
	Post 3rd	**N = 177**	**N = 65**	**N = 177**	**N = 65**
		67 (61 – 74)	1 (0.032 – 7)	13 (11 – 16)	2.03 (1.53 – 2.7)
MenC	Pre	**N = 204**	**N = 84**	**N = 204**	**N = 84**
		7 (3 – 11)	5 (1 – 13)	2.48 (2.23 – 2.75)	2.17 (1.83 – 2.57)
	Post 3rd	**N = 168**	**N = 64**	**N = 168**	**N = 64**
		97 (93 – 99)	1 (0.03 – 6)	108 (92 – 127)	2.12 (1.64 – 2.74)
MenW	Pre	**N = 197**	**N = 90**	**N = 197**	**N = 90**
		17 (12 – 24)	11 (4 – 21)	3.07 (2.7 – 3.5)	2.71 (2.2 – 3.33)
	Post 3rd	**N = 165**	**N = 66**	**N = 165**	**N = 66**
		96 (93 – 99)	2 (0 – 8)	100 (86 – 116)	2.08 (1.67 – 2.6)
MenY	Pre	**N = 182**	**N = 84**	**N = 182**	**N = 84**
		5 (2 – 10)	3 (0 – 11)	2.53 (2.31 – 2.77)	2.13 (1.85 – 2.45)
	Post 3rd	**N = 150**	**N = 62**	**N = 73**	**N = 62**
		96 (92 – 98)	0 (0 – 4)	73 (62 – 86)	2.03 (1.6 – 2.57)

Source: V59P14 CSR, Tables 11.4.1-3A and 11.4.1-3B, pages 167 – 168/31591.

<u>Retesting of subset of US subjects' sera for hSBA results</u>:
Please see section 7.1.1.1.5 for additional details.

The original complement source and many of the reagents were no longer available in sufficient quantities for sera retesting. Thus, the applicant stated that observed difference between the original results and retest results might be attributed to 1) new reagents (exogenous complement, control sera and/or media) or 2) conscious or unconscious bias in the original testing. The techniques used in the analyses presented by the applicant in the "Retest Report" could not differentiate the source of the differences, and the applicant emphasized this limitation *a priori*.

The goals of retesting were: 1) to determine the representativeness of the subgroup with sera left to be sampled compared to the entire original cohort; 2) to assess how well the

retest titer results agreed with the original test titers; 3) to compare the study endpoints derived using the original test results and the retest results.

The demographic characteristics betweent the subset and overall population were similar. Some of the retest data represented fewer than half the subjects who contributed to the original dataset, but proportions of subjects with hSBA titers of $\geq$ 1:8 were similar using the original test results and the retest results for each serogroup at the Visit 1, Visit 4, Visit 5, and Visit 6 timepoints (agreement for 82% or more of the subjects in the analyses). The hSBA GMTs were similar but consistently lower in the retest samples.

The CBER statistical assay reviewer identified two issues for clarification:
- Reason for correcting the variable “VISIT” for 100 observations in the “concort.txt” file, which is a SAS code file to create the dataset “DEMOG”. Correction of the visit number which might introduce potential for bias , i.e., that the visit numbers associated with low hSBA titers were not corrected to associate them with Visit 1, the baseline value, rather than the post-vaccination timepoint.
- 549 observations were missing results in the “RETEST” data file.

Concomitant vaccination:
Except for pneumococcal serotype 6B, primary endpoints for each co-administered vaccine were met. For serotype 6B, the lower 95% confidence limit for the percentage of subjects with an IgG antibody level ≥0.35 mcg/mL was -14%; the 95%CIs did not include zero.

Table 7. V59P14. Post-dose 3 Antibody Responses to Co-administered Infant Vaccines, Study Groups US1 vs.US2 (Per-Protocol Population)

	GMCs or GMTs (95% CI) of concomitant antigens 1 month after infant series in US subjects (PP population)				Seroresponse Rates* (95% CI) of concomitant antigens 1 month after infant series in US subjects (PP population)			
	US1	US2	US1:US2 ratio (95% CI)	Non-inferiority criteria met?	US1	US2	US1 – US2 (95% CI)	Non-inferiority criteria met?
	N = 214	**N = 102**			**N = 214**	**N = 102**		
Diphtheria	2.52 (2.28 – 2.78)	2.88 (2.5 – 3.32)	0.87 (0.74 – 1.04)	--	100% (97 – 100)	100% (96 – 100)	0% (-3 – 3)	Yes
Tetanus	2.5 (2.28 – 2.74)	2.31 (2.01 – 2.64)	1.08 (0.92 – 1.28)	--	100% (98 – 100)	100% (96 – 100)	0% (-2 – 4)	Yes
Pertussis Ags	**N = 174**	**N = 83**			**N = 174**	**N = 83**		
PT	54 (48 – 62)	54 (44 – 66)	1 (0.79 – 1.26)	Yes	87% (81 – 92)	86% (76 – 92)	2% (-7 – 12)	Yes
FHA	118 (106 – 132)	114 (97 – 134)	1.03 (0.85 – 1.25)	Yes	85% (79 – 90)	80% (69 – 88)	6% (-4 – 17)	Yes
Pertactin	114 (100 – 130)	110 (90 – 134)	1.04 (0.83 – 1.32)	Yes	76% (69 – 83)	78% (68 – 87)	-2% (-12 – 10)	Yes
Polio Ags	**N = 176**	**N = 98**			**N = 176**	**N = 98**		
Polio type1	422 (363 – 491)	441 (361 – 540)	0.96 (0.75 – 1.23)	--	99% (97 – 100)	100% (96 – 100)	-1% (-3 – 3)	Yes
Polio type 2	348 (297 – 408)	290 (235 – 358)	1.2 (0.93 – 1.55)	--	100% (98 – 100) [N=175]	100% (96 – 100)	0% (-2 – 4)	Yes
Polio type 3	733 (607 – 885)	635 (493 – 818)	1.15 (0.85 – 1.56)	--	99% (97 – 100)	100% (96 – 100)	-1% (-3 – 3)	Yes

Table 7 (continued). V59P14. Post-dose 3 Antibody Responses to Co-administered Infant Vaccines, Study Groups US1 vs.US2 (Per-Protocol Population)

	GMCs or GMTs (95% CI) of concomitant antigens 1 month after infant series in US subjects (PP population)					Seroresponse Rates* (95% CI) of concomitant antigens 1 month after infant series in US subjects (PP population)			
	US1	US2	US1:US2 ratio (95% CI)	Non-inferiority criteria met?		US1	US2	US1 – US2 (95% CI)	Non-inferiority criteria met?
	N = 148	**N = 98**				**N = 148**	**N = 98**		
Hepatitis B	1863 (1538 – 2257)	2112 (1668 – 2674)	0.88 (0.65 – 1.2)	--		99% (96 – 100)	100% (96 – 100)	-1% (-4 – 3)	Yes
	N = 213	**N = 101**				**N = 213**	**N = 101**		
Hib	4.64 (3.9 – 5.53)	3.56 (2.77 – 4.58)	1.31 (0.97 – 1.77)	--		≥ 0.15: 99% (97 – 100)	100% (96 – 100)	-1% (-3 – 3)	Yes
						≥ 1.0: 89% (84 – 93)	84% (76 – 91)	5% (-3 – 14)	Yes
Pneumococcal	**N = 181**	**N = 102**				**N = 181**	**N = 102**		
PnC 4	1.67 (1.5 – 1.86)	2 (1.73 – 2.3)	0.84 (0.7 – 1)			98% (95 – 100)	100% (96 – 100%)	-2% (-5 – 2)	Yes
PnC 6B	1.94 (1.61 – 2.34)	2.55 (1.99 – 3.27)	0.76 (0.56 – 1.03)			88% (83 – 93)	96% (90 – 99)	-8% (-14 – -1)	No
PnC 9V	1.83 (1.62 – 2.06)	2.15 (1.83 – 2.53)	0.85 (0.7 – 1.04)			98% (94 – 99)	98% (93 – 100)	0% (-4 – 5)	Yes
PnC 14	6.97 (6.18 – 7.86)	6.79 (5.78 – 7.96)	1.03 (0.84 – 1.26)			100% (98 – 100)	99% (95 – 100)	1% (-1 – 5)	Yes
PnC 18C	1.96 (1.75 – 2.19)	2.54 (2.18 – 2.95)	0.77 (0.64 – 0.93)			97% (94 – 99)	100% (96 – 100)	-3% (-6 – 1)	Yes
PnC 19F	2.24 (2.02 – 2.48)	2.73 (2.39 – 3.13)	0.82 (0.69 – 0.97)			99% (96 – 100)	100% (96 – 100)	-1% (-4 – 3)	Yes
PnC 23F	1.71 (1.47 – 1.98)	2.15 (1.76 – 2.62)	0.79 (0.62 – 1.02)			92% (87 – 95)	94% (88 – 98)	-2% (-8 – 5)	Yes

* Seroresponse was defined as follows: Diphtheria ≥ 0.1 IU/mL, Tetanus ≥ 0.1 IU/mL, [PT, FHA, pertactin: if baseline is < LLQ, ≥ 4LLQ; if baseline is ≥ LLQ, 4-fold increase over baseline], polio 1 ≥ 1:8, polio 2 ≥ 1:8, polio 3 ≥ 1:8, HBV ≥ 10 mIU/mL, Hib ≥ 0.15 mcg/mL, Hib ≥ 1.0 mcg/mL, PnC ≥ 0.35 mcg/mL

Source: V59P14 CSR pages 173-4/31591 Tables 11.4.1-5A and 11.4.1-5B

Post-dose 4 Pneumococcal Antibody Responses

Due to the study design, there are no subjects in the immunogenicity subset who completed a routine chidhood vaccination series without co-administered MenACWY. The study group used for pneumococcal IgG GMC comparisons was US1b; these subjects had received MenACWY at 2, 4, and 6 months of age and no 4th MenACWY dose in the second year of life.

Table 8. V59P14. Pneumococcal IgG GMCs (95% CI) one month after the 4th dose, Study Groups US1a and US1b* (Per-Protocol Population)

	US1A	US1B	US1A:US1B ratio (95% CI)
	N = 86	N = 99	
PnC 4	2.9 (2.33 – 3.61)	3.24 (2.64 – 3.97)	0.9 (0.67 – 1.2)
	N = 86	N = 99	
PnC 6B	6.82 (5.67 – 8.21)	8.58 (7.22 – 10)	0.8 (0.62 – 1.02)
	N = 86	N = 99	
PnC 9V	2.8 (2.26 – 3.47)	3.13 (2.56 – 3.82)	0.89 (0.67 – 1.2)
	N = 86	N = 99	
PnC 14	12 (9.74 – 14)	15 (12 – 17)	0.8 (0.63 – 1.03)
	N = 87	N = 98	
PnC 18C	2.76 (2.26 – 3.38)	2.71 (2.24 – 3.27)	1.02 (0.78 – 1.34)
	N = 86	N = 99	
PnC 19F	3.63 (3 – 4.39)	3.48 (2.92 – 4.16)	1.04 (0.81 – 1.34)
	N = 87	N = 99	
PnC 23F	5.31 (4.2 – 6.71)	5.63 (4.52 – 7.01)	0.94 (0.69 – 1.29)

*US1b received MenACWY at 2,4 and 6 months of age but no 4th MenACWY dose at age 12 months.
Source: V59P14 CSR, Table 11.4.1-8A, page 190/31591.

Reviewer Comment: PCV7 and MenACWY contain the same carrier protein, CRM_{197}. Interpretation of pneumococcal IgG GMC comparisons is limited by (a) large proportion of subjects (> 40%) excluded from the per-protocol population (b) a control group that received three MenACWY doses in infancy. Immunological interference might not be observed if IgG GMCs in the control group (US1b) had also been reduced, due to prior receipt of MenACWY.

For most serotypes, GMCs among subjects who received PCV7 alone were higher than GMCs among subjects who received MenACWY with PCV7. Non-inferiority criteria were met for all serotypes; however, the lower limit of the GMC ratio ranged from 0.62 to 0.81, indicating a trend towards lower pneumococcal IgG antibody responses when PCV7 is co-administered with MenACWY.

Concomitant Evaluation of MMRV and MenACWY

Evaluated in V59P21. Please see section 7.1.3.

Other Immunogenicity analyses

Proportion of subjects with 4-fold rise one month after toddler vaccination at 12 months:

In the US PP population, 100% of subjects (group US1A) had at least a 4-fold rise in the hSBA titers against serogroup W, while 94 – 99% achieved at least a 4-fold rise for the other serogroups. Analyses were based on ~ N = 85.

7.1.1.2.3 Safety outcomes

Overall safety profile:

Significant study design changes occurrred during the course of the trial. The study groups used for safety comparisons in infancy differed from the study groups used for 4th MenACWY dose comparisons. For MenACWY doses given in infancy, the groups most relevant for safety comparisons are US1 + US3 vs US4 and LA5 vs LA6. Comparative safety data for the 4th dose (through 6 month after the last vaccination) were available in a very limited number of subjects, which included: US1a + US3 vs US4c for US subjects and LA5 vs LA6c for Latin American subjects. For US4b and LA4c subjects, safety data was available through one month after the 12 month vaccination visit.

In addition, interpretation of the incidence rates for solicited AEs, any AEs, MAEs and SAEs was limited by the following:

- Potential for reporting bias introduced by safety data reconstruction
- The Exposed Safety Population was used to calculate frequencies of AEs. For some participants, only data at 15 minutes after vaccination was available; safety information for local and systemic adverse events through the remainder of the 7-day post-vaccination safety assessment was not done.

Immediate reactions:

There were no immediate reactions reported.

Solicited reactions:

Doses 1 – 3 (given at 2,4,6 months)

The percentage of subjects reporting adverse events within 7 days of vaccination was generally similar across groups for each of the 3 infant vaccinations. If groups US1 + US3 and US4 were compared, the proportions were similar, as well. Safety data describing local and systemic reactogenicity during Days 1 – 7 were missing in $\leq$ 1% of subjects in each group. Overall, most AEs were mild or moderate, with proportions of subjects with severe AEs after any of the first 3 doses ranging from 9% in US1b to 19% in US4 for any AE, from 2% in US1b to 9% in US4 for local AEs, from 7% in US1b to 13% in US4 for systemic AEs. AEs reported as severe occurred most frequently after the first MenACWY dose compared to subsequent doses. Overall, there was no dose-dependent increase in severity of local and systemic reactions. In general, most of the subjects who reported the solicited AEs reported on Days 1 – 4, with the exception of irritability, which occurred in $\geq$ 10% of subjects during Days 5 – 7.

Table 9. V59P14. Overview of Local and Systemic Reactions Occurring 7 Days After Vaccination, Study Groups US 1-4 (Safety Population)

Number (%) of Subjects with Solicited Reactions						
	US1a	US1b	US1	US2	US3	US4
After any of doses 1 – 3	N = 153	N = 165	N = 318	N = 159	N = 677	N = 345
Any	142 (93%)	159 (96%)	301 (95%)	150 (94%)	632 (93%)	313 (91%)
Local	101 (66%)	113 (68%)	214 (67%)	120 (75%)	457 (68%)	232 (67%)
Systemic	130 (85%)	153 (93%)	283 (89%)	140 (88%)	583 (86%)	287 (83%)
Other	123 (80%)	136 (82%)	259 (81%)	134 (84%)	550 (81%)	276 (80%)
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%)
Other	75 (54%)	82 (56%)	157 (55%)	96 (67%)	349 (55%)	178 (57%)

Source: V59P14 CSR, Tables 12.2.1-1 and 14.3.1.1.2.1, pages page 217 and 785 of 31591.

The most commonly reported local AE was tenderness, which was reported in 42% - 48% of subjects across groups. Fever was reported in 4% - 8% of subjects across groups. The incidence of fever after dose 1 provided in the PCV13 Package Insert (PI) is 22.1% for the group receiving PCV7 + concomitant infant vaccines, the same vaccines as were administered to the control groups in study V59P14. Irritability after dose 1 was reported in 54% - 65% of subjects in this trial, whereas it is reported as 83.6% in the group receiving PCV7 + concomitant infant vaccines in the PCV13 PI.

Table 10. V59P14 Overview of Solicited Reactions Within 7 Days of the First Vaccination, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 1							
Local		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Tenderness	Any	64/151 (42%)	76/164 (46%)	140/315 (44%)	69 (44%)	324 (48%)	161 (47%)
	Cried inj. Limb moved	3/151 (2%)	4/164 (2%)	7/315 (2%)	6 (4%)	25 (4%)	19 (6%)
Erythema	Any	10 (7%)	17 (10%)	27 (8%)	23 (15%)	66 (10%)	54/344 (16%)
	> 50 mm	0	0	0	2 (1%)	0	4/344 (1%)
Induration	Any	10 (7%)	14 (8%)	24 (8%)	25 (16%)	61 (9%)	44/344 (13%)
	> 50 mm	0	0	0	0	0	1/344 (< 1%)
Systemic							
Rash	Any	6/151 (4%)	9/164 (5%)	15/315 (5%)	5 (3%)	16/670 (2%)	11 (3%)
	Urticarial	3/151 (2%)	4/164 (2%)	7/315 (2%)	3 (2%)	4/670 (1%)	3 (1%)
Change in eating habits	Any	42/151 (28%)	46/164 (28%)	88/315 (28%)	34 (22%)	171 (25%)	96 (28%)
	Severe	1/151 (1%)	1/164 (1%)	2/315 (1%)	1 (1%)	8 (1%)	2 (1%)
Sleepiness	Any	83/151 (55%)	104/164 (63%)	187/315 (59%)	76 (48%)	354 (53%)	173 (50%)
	Severe	2/151 (1%)	3/164 (2%)	5/315 (2%)	0	14 (2%)	3 (1%)
Persistent crying	Any	43/151 (28%)	74/164 (45%)	117/315 (37%)	49 (31%)	252/670 (38%)	125 (36%)
	Severe	1/151 (1%)	2/164 (1%)	3/315 (1%)	5 (3%)	11/670 (2%)	8 (2%)

Table 10 (continued). V59P14 Overview of Solicited Reactions Within 7 Days of the First Vaccination, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 1							
Systemic (continued)		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Irritability	Any	82/151 (54%)	107/164 (65%)	189/315 (60%)	96 (61%)	419 (62%)	211 (61%)
	Severe	6/151 (4%)	2/164 (1%)	8/315 (3%)	4 (3%)	24 (4%)	12 (3%)
Vomiting	Any	15/151 (10%)	18/164 (11%)	33/315 (10%)	14 (9%)	67/670 (10%)	36 (10%)
	Severe	0	0	0	0	0	1 (< 1%)
Diarrhea	Any	24/151 (16%)	23/164 (14%)	47/315 (15%)	17 (11%)	107 (16%0	46 (13%)
	Severe	2/151 (1%)	0	2/315 (1%)	1 (1%)	3 (< 1%)	1 (< 1%)
Fever (> 38C)	Yes	13 (8%)	6/164 (4%)	19/317 (6%)	7/157 (4%)	32/665 (5%)	21/340 (6%)
Temperature (C)	< 38 C	140 (92%)	158/164 (96%)	298/317 (94%)	150/157 (96%)	633/665 (95%)	319/340 (94%)
	> 40.0C	0	0	0	1/157 (1%)	0	0
Analgesic or antipyretic medications used	Yes	105/152 (69%)	120 (73%)	225/317 (71%)	110 (70%)	447 (67%)	223/343 (65%)

Source: (Table 12.2.1-3, page 220/31591 of the V59P14 CSR)

After dose 2, the most commonly reported systemic AEs were irritability and sleepiness. Fever was reported in 4% - 12% of subjects; one subject in group US2 reported temperature $\geq$ 40C. A total of 65% - 73% of subjects received analgesic and/or antipyretic medication after the first vaccination. Fever was reported in 32.8% of subjects receiving dose 2 of PCV7 + concomitant infant vaccines in the PCV13 PI, with over 80% of subjects using antipyretics. Irritability was reported in 53% - 59% of subjects in study V59P14 after dose 2; comparable data from the PCV13 PI give 80.4% of subjects with irritability post-dose 2.

Table 11. V59P14. Overview of Solicited Adverse Events Within 7 Days of Vaccination 2, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 2							
Local		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Tenderness	Any	59/141 (42%)	59/150 (39%)	118/291 (41%)	56/151 (37%)	230/645 (36%)	137/325 (42%)
	Cried inj. Limb moved	1/141 (1%)	0	1/291 (< 1%)	2/151 (1%)	13/645 (2%)	11/325 (3%)
Erythema	Any	14/141 (10%)	19/150 (13%)	33/291 (11%)	35/151 (23%)	75/645 (12%)	60/325 (18%)
	> 50 mm	0	0	0	0	0	2/325 (1%)
Induration	Any	16/141 (11%)	16/150 (11%)	32/291 (11%)	27/151 (18%)	45/645 (7%)	48/325 (15%)
	> 50 mm	1/141 (1%)	0	1/291 (< 1%)	0	0	3/325 (1%)
Systemic							
Rash	Any	3/141 (2%)	5/150 (3%)	8/291 (3%)	4/151 (3%)	24/645 (4%)	13/325 (4%)
	Urticarial	3/141 (2%)	1/150 (1%)	4/291 (1%)	1/151 (1%)	6/645 (1%)	4/325 (1%)
Change in eating habits	Any	25/141 (18%)	21/150 (14%)	46/291 (16%)	20/151 (13%)	122/645 (19%)	64/325 (20%)
	Severe	0	0	0	0	3/645 (< 1%)	0
Sleepiness	Any	69/141 (49%)	56/150 (37%)	125/291 (43%)	47/151 (23%)	178/645 (28%)	107/325 (33%)
	Severe	0	0	0	1/151 (1%)	3/645 (1%)	4/325 (1%)
Persistent crying	Any	42/141 (30%)	41/150 (27%)	83/291 (29%)	34/151 (23%)	178/645 (28%)	107/325 (33%)
	Severe	0	0	0	0	5/645 (1%)	4/325 (1%)
Irritability	Any	83/141 (59%)	80/150 (53%)	163/291 (56%)	83/151 (55%)	342/645 (53%)	182/325 (56%)
	Severe	2/141 (1%)	0	2/291 (1%)	3/151 (2%)	14/645 (2%)	9/325 (3%)
Vomiting	Any	8/141 (11%)	9/150 (7%)	17/291 (6%)	7/151 (5%)	49/645 (8%)	27/325 (8%)
	Severe	0	0	0	0	0	1/325 (< 1%)

Table 11 (continued). V59P14. Overview of Solicited Adverse Events Within 7 Days of Vaccination 2, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 2							
Systemic (continued)		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Diarrhea	Any	16/141 (11%)	10/150 (7%)	26/291 (9%)	11/151 (7%)	53/645 (8%)	35/325 (11%)
	Severe	0	1/150 (1%)	1/291 (< 1%)	1/151 (1%)	1/645 (< 1%)	2/325 (1%)
Fever (≥ 38C)	Yes	17/141 (12%)	6/150 (4%)	23/291 (8%)	15/150 (10%)	49/642 (8%)	28/320 (9%)
Temperature (C)	< 38 C	124/141 (88%)	144/150 (96%)	268/291 (92%)	135/150 (90%)	593/642 (92%)	292/320 (91%)
	≥ 40.0C	0	0	0	0	2/642 (< 1%)	0
Analgesic or antipyretic medications used	Yes	94/141 (67%)	91/150 (61%)	185/291 (64%)	96/151 (64%)	385/645 (60%)	201/325 (62%)

Source: Table 12.2.1-4, page 222/31591 of the V59P14 CSR)

Table 12. V59P14 Overview of Solicited Adverse Events Within 7 Days of Vaccination 3, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 3							
Local		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Tenderness	Any	37/138 (27%)	45/145 (31%)	82/283 (29%)	45/143 (31%)	189/627 (30%0	92/311 (30%)
	Cried inj. Limb moved	0	0	0	1/143 (1%)	1/627 (< 1%)	7/311 (2%)
Erythema	Any	16/138 (12%)	18/145 (12%)	34/283 (12%)	28/143 (20%)	92/627 (15%)	67/310 (22%)
	> 50 mm	0	0	0	1/143 (1%)	0	1/310 (< 1%)
Induration	Any	15/138 (11%)	15/145 (10%)	30/283 (11%)	29/143 (20%)	59/627 (9%)	53/310 (17%)
	> 50 mm	0	0	0	2/143 (1%)	0	1/310 (< 1%)
Systemic							
Rash	Any	2/138 (1%)	9/145 (6%)	11/283 (4%)	4/143 (3%)	14/627 (2%)	8/311 (3%)
	Urticarial	1/138 (1%)	4/145 (3%)	5/283 (2%)	3/143 (2%)	2/627 (< 1%)	1/311 (< 1%)
Change in eating habits	Any	19/138 (14%)	22/145 (15%)	41/283 (14%)	18/143 (13%)	94/627 (15%)	39/311 (13%)
	Severe	0	0	0	1/143 (1%)	3/627 (< 1%)	2/311 (1%)
Sleepiness	Any	37/138 (27%)	41/145 (28%)	78/283 (28%)	39/143 (27%)	179/627 (29%)	91/311 (29%)
	Severe	0	0	0	0	6/627 (1%)	1/311 (< 1%)
Persistent crying	Any	28/138 (20%)	26/145 (18%)	54/283 (19%)	24/143 (17%)	135/627 (22%)	74/311 (24%)
	Severe	0	0	0	0	4/627 (1%)	4/311 (1%)
Irritability	Any	58/138 (42%)	73/145 (50%)	131/283 (46%)	70/143 (49%)	285/627 (45%)	157/311 (50%)
	Severe	1/138 (1%)	1/145 (1%)	2/283 (1%)	0	4/627 (1%)	6/311 (2%)

Table 12 (continued). V59P14 Overview of Solicited Adverse Events Within 7 Days of Vaccination 3, Study Groups US1 – US4

Number (%) of Subjects with Injection Site Reactions after dose 3							
Systemic (continued)		US1a	US1b	US1	US2	US3	US4
		N = 153	N = 165	N = 318	N = 158	N = 671	N = 345
Vomiting	Any	6/138 (4%)	6/145 (4%)	12/283 (4%)	9/143 (6%)	31/627 (5%)	20/311 (6%)
	Severe	0	0	0	0	0	1/311 (< 1%)
Diarrhea	Any	13/138 (9%)	9/145 (6%)	22/283 (8%)	9/143 (6%)	41/627 (7%)	26/311 (8%)
	Severe	0	0	0	0	2/627 (< 1%)	1/311 (< 1%)
Fever (≥ 38C)	Yes	4/138 (3%)	9/145 (6%)	13/283 (5%)	14/142 (10%)	33/615 (5%)	20/296 (7%)
Temperature (C)	< 38 C	134/138 (97%)	136/145 (94%)	270/283 (95%)	128/142 (90%)	582/615 (95%)	276/296 (93%)
	≥ 40.0C	0	1/145 (1%)	1/283 (< 1%)	0	1/615 (< 1%)	0
Analgesic or antipyretic medications used	Yes	75/138 (54%)	82/145 (57%)	157/283 (55%)	96/143 (67%)	349/626 (56%)	178/310 (57%)

Source: Table 12.2.1-5, page 224/31591 of the V59P14 CSR)

Table 13. V59P14. Overview of Solicited Adverse Events Reported After Vaccinations 1 – 3, Study Groups US1 – US4

Comparison between MenACWY (US1 + US3) and Hib (US2 + US4) Vaccines After Each Infant Vaccination – US Subjects							
Number (%) of subjects with reactions							
		Vaccination 1		Vaccination 2		Vaccination 3	
		US1 + US3	US2 + US4	US1 + US3	US2 + US4	US1 + US3	US2 + US4
		N = 989	N = 503	N = 936	N = 476	N = 910	N = 454
Local							
Tenderness	Any	464/986 (47%)	230 (46%)	348 (37%)	193 (41%)	271 (30%)	137 (30%)
	Cried inj. Limb moved	32/986 (3%)	25 (5%)	14 (1%)	13 (3%)	1 (< 1%)	8 (2%)
Erythema	Any	93 (9%)	77/502 (15%)	108 (12%0	95 (20%)	126 (14%)	95/453 (21%)
	> 50 mm	0	6/502 (1%)	0	2 (< 1%)	0	2/453 (< 1%)
Induration	Any	85 (9%)	69/502 (14%)	77 (8%)	75 (16%)	89 (10%)	82/453 (18%)
	> 50 mm	0	1/502 (< 1%)	1 (< 1%)	3 (1%)	0	3/453 (1%)
Systemic							
Rash	Any	31/985 (3%)	16 (3%)	32 (3%)	17 (4%)	25 (3%)	12 (3%)
	Urticarial	11/985 (1%)	6 (1%)	10 (1%)	5 (1%)	7 (1%)	4 (1%)
Change in eating habits	Any	259/986 (26%)	130 (26%)	168 (18%)	84 (18%)	135 (15%)	57 (13%)
	Severe	10/986 (1%)	3 (1%)	3 (< 1%)	0	3 (< 1%)	3 (1%)
Sleepiness	Any	541/986 (55%)	249 (50%)	363 (39%)	178 (37%)	257 (28%)	130 (29%)
	Severe	19/986 (2%)	3 (1%)	3 (< 1%)	3 (1%)	6 (1%)	1 (< 1%)
Persistent crying	Any	369/985 (37%)	174 (35%)	261 (28%)	141 (30%)	189 (21%)	98 (22%)
	Severe	14/985 (1%)	13 (3%)	5 (1%)	4 (1%)	4 (< 1%)	4 (1%)

Table 13 (continued). V59P14. Overview of Solicited Adverse Events Reported After Vaccinations 1 – 3, Study Groups US1 – US4

Comparison between MenACWY (US1 + US3) and Hib (US2 + US4) Vaccines After Each Infant Vaccination – US Subjects							
Number (%) of subjects with reactions							
		Vaccination 1		Vaccination 2		Vaccination 3	
		US1 + US3	US2 + US4	US1 + US3	US2 + US4	US1 + US3	US2 + US4
		N = 989	N = 503	N = 936	N = 476	N = 910	N = 454
Irritability	Any	608/986 (62%)	307 (61%)	505 (54%)	265 (56%)	416 (46%0	227 (50%)
	Severe	32/986 (3%)	16 (3%)	16 (2%)	12 (3%)	6 (1%)	6 (1%)
Vomiting	Any	100/985 (10%0	50 (10%)	66 (7%)	34 (7%)	43 (5%0	29 (6%)
	Severe	0	1 (< 1%)	0	1 (< 1%)	0	1 (<1%)
Diarrhea	Any	154/986 (16%)	63 (13%)	79 (8%)	46 (10%)	63 (7%)	35 (8%)
	Severe	5/986 (1%)	2 (< 1%)	2 (< 1%)	3 (1%)	2 (< 1%)	1 (< 1%)
Fever (≥ 38C)	Yes	51/982 (5%)	28/497 (6%)	72/933 (8%)	43/470 (9%)	46/898 (5%)	34/438 (8%)
Temperature (C)	< 38 C	931/982 (95%)	469/497 (94%)	861/933 (92%)	427/470 (91%)	852/898 (95%)	404/438 (92%)
	≥ 40.0C	0	1/497 (< 1%)	2/933 (< 1%)	0	2/898 (< 1%)	0
Analgesic or antipyretic medications used	Yes	672/988 (68%)	333/501 (66%)	570 (61%)	297 (62%)	506/909 (56%)	274/453 (60%)

Source: Table 12.2.1-6, page 225/31591 of the V59P14 CSR

Dose 4:
The occurrences of AEs during the 7 days following vaccination at 12 months were similar between groups receiving the 4th dose of MenACWY and groups not receiving MenACWY at any timepoint through 12 months of age. Most AEs were mild or moderate, with severe AEs reported in ≤ 8% of subjects in any group.

Table 14. V59P14. Overview of Adverse Events Within 7 Days of Vaccination 4, Study Groups US1 – US4

Number (%) of Subjects with Solicited Reactions					
	US1a	US1b	US3	US1a + US3	US4b + US4c
	N = 122	N = 124	N = 582	N = 704	N = 261
Any	84 (69%)	87 (70%)	381 (65%)	465 (66%)	173 (66%)
Local	33 (27%)	40 (32%)	188 (32%)	221 (31%)	102 (39%)
Systemic	70 (57%)	61 (49%)	267 (46%)	337 (48%)	124 (48%)
Other	60 (49%)	56 (45%)	260 (45%)	320 (45%)	120 (46%)

Source: Table 14.3.1.1.2.5, page 793/31591 of the V59P14 CSR)

Of 704 subjects in US1a + US3, 66% reported any, 31% reported local, 48% reported systemic, and 45% reported other AEs within 7 days of the 4th dose.

Table 15. V59P14. Overview of Solicited Adverse Events Within 7 Days After Dose 4, Study Groups US1 – US4

Number (%) of subjects with solicited adverse events							
		US1a	US3	US4b	US4c	US1a + US3	US4b + US4c
Local		N = 121	N = 567	N = 59	N = 179	N = 688	N = 238
Tenderness	Any	28 (23%)	149/566 (26%)	10 (17%)	38 (22%)	177/687 (26%)	48 (20%)
	Cried inj limb moved	0	2/566 (< 1%)	1 (2%)	1 (1%)	2/687 (< 1%)	2 (< 1%)
Erythema	Any	11 (9%)	70 (12%)	9 (16%)	28 (16%)	81 (12%)	37 (16%)
	> 50 mm	0	2 (< 1%)	0	1 (1%)	2 (< 1%)	1 (< 1%)

Table 15 (continued). V59P14. Overview of Solicited Adverse Events Within 7 Days After Dose 4, Study Groups US1 – US4

		US1a	US3	US4b	US4c	US1a + US3	US4b + US4c
Local (continued)		N = 121	N = 567	N = 59	N = 179	N = 688	N = 238
		US1a	US3	US4b	US4c	US1a + US3	US4b + US4c
Induration	Any	10 (8%)	34 (6%)	3 (5%)	14 (8%)	44 (6%)	17 (7%)
	> 50 mm	0	0	0	0	0	0
Systemic							
Rash	Any	8 (7%)	23/566 (4%)	2 (3%)	5 (3%)	31/687 (5%)	7 (3%)
	Urticarial	1 (1%)	2/566 (< 1%)	0	2 (1%)	3/687 (< 1%)	2 (< 1%)
Change in eating habits	Any	21 (17%)	80 (14%)	5 (9%)	14 (8%)	101 (15%)	19 (8%)
	Severe	1 (1%)	6 (1%)	0	1 (1%)	7 (1%)	1 (< 1%)
Sleepiness	Any	38 (31%)	111 (20%)	6 (10%)	21 (12%)	149 (22%)	27 (11%)
	Severe	0	3 (1%)	0	0	3 (< 1%)	0
Persistent crying	Any	21 (17%)	99 (17%)	10 (17%)	17 (10%)	120 (17%)	27 (11%)
	Severe	0	6 (1%)	1 (2%)	1 (1%)	6 (1%)	2 (< 1%)
Irritability	Any	53 (44%)	218 (38%)	17 (29%)	52 (30%)	271 (39%)	69 (29%)
	Severe	2 (2%)	6 (1%)	1 (2%)	1 (1%)	8 (1%)	2 (< 1%)
Vomiting	Any	6 (5%)	21 (4%)	2 (3%)	6 (3%)	27 (4%)	8 (3%)
	Severe	0	1 (< 1%)	0	0	1 (< 1%)	0
Diarrhea	Any	5 (4%)	56 (10%)	5 (9%)	13 (8%)	61 (9%)	18 (8%)
	Severe	0	4 (1%)	2 (3%)	1 (1%)	4 (1%)	3 (1%)
Fever $\geq$ 38°C	Yes	14/116 (12%)	35/550 (6%)	0	5 (3%)	49/666 (7%)	5 (2%)
Temperature (C)	< 38°C	102/116 (88%)	515/550 (94%)	0	3 (2%)	617/666 (93%)	3 (1%)
	$\geq$ 40°C	0	0	0	0	0	0
Analgesic and/or antipyretic meds	Yes	28 (23%)	149/566 (26%)	16 (28%)	45 (26%)	177/687 (26%)	61 (26%)

Source: Table 12.2.1.-7, page 227/31591 of the V59P14 CSR combined with data from Table 14.3.1.1.3.7, page 864/31591 of the V59P14 CSR

Unsolicited AEs at any timepoint from initiation of trial through completion:

Table 16. V59P14 Overview of Adverse Events of Interest, Study Groups US1 – US4 subjects exposed to the 4th dose

AE	US1a	US1b	US1	US2	US3	US1a + US3 N = 704	US4b + US4c	US4a	US4b	US4c
						N = 704	N = 261			
Bronchiolitis	15	10	25	12	70	85 (12%)	32 (12%)	8	13	19
Bronchitis	1	1	2	3	8	9 (1%)	6 (2%)	1	2	4
Asthma/RAD	9	7	16	9	30	39 (6%)	17 (7%)	1	3	14
Pneumonia	8	7	15	7	23	31 (4%)	12 (5%)	1	4	8
Vasculitis	0	0	0	0	2	2 (<1%)	0	0	0	0
Otitis media	41	29	70	29	123	164 (23%)	65 (25%)	18	20	45
Gastroenteritis	7	8	15	14	35	42 (6%)	13 (5%)	1	4	9
Diarrhea	11	13	24	16	48	59 (8%)	26 (10%)	3	9	17
Seizure	1	0	1	0	9	10 (1%)	2 (<1%)	2	0	2
Febrile	1	0	1	2	5	6 (<1%)	2 (<1%)	1	0	2

Source: CBER-generated analysis

Serious adverse events (SAEs):

At any timepont from study initiation through study completion, which ranged from 1 month after the last vaccination to 6 months after the last vaccination, depending on the study group:
A total of 90 US subjects reported SAEs (4% - 7% across study groups US1-4). A total of 269 Latin American subjects (LA1-4) reported SAEs with percentages (7% - 10%) similar across groups. Pertinent case narratives are described below.

In a CBER-generated analysis, among recipients of the 4 dose MenACWY series, there were 308 SAEs; among recipients of the 2 dose series with and without routine vaccines, there were 100 SAEs. Among subjects receiving only routine vaccinations, there were 44 SAEs. Among subjects receiving routine vaccines and 2 doses MenACWY, there were 40 SAEs.

Table 17. V59P14 Serious Adverse Events of Special Interest

SAE	US1a	US1b	US1	US2	US3	US4a	US4b	US4c	LA1a	LA1b	LA2	LA3a	LA3b	LA4	LA5	LA6a	LA6b	LA6c
Kawasaki Disease and/or possible vasculitis	1	1	2	1	2	0	0	0	0	0	0	1	1***	0	0	0	0	0
Seizures	0	0	0	0	6	2****	0	1	1	0	0	4	1	1	16	3	3	1
Meningitis																		
Pneumonia	2	0	2	*	2	0	2	1	1	1	1	2	2	2	43	6	3*	2
Bacteremia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0
Sepsis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Source: CBER-generated analysis
* RSV pneumonia = 1 case
*** more information is necessary to determine
**** one child with seizure in US4a is listed in the case narrative as having the seizure following MenACWY administration

Onset within 28 days after visit at 12 months of age:
In the US, there were 7 subjects reporting 9 SAEs reported with onset within 28 days of the visit at 12 months of age. Four subjects reported 5 SAEs were reported in the 706 subjects in groups US1a + US3 (1%), while 3 subjects reported 4 SAEs were reported among the 266 subjects in groups US4b + US4c (1%). During this period, there was one febrile seizure reported among each of the two groups US1a + US3 and US4b + US4c. There was one episode of pneumonia in the group US4b + US4c.

In Latin America, there were 13 subjects reporting 15 SAEs with onset within 28 days of the visit at 12 months of age. The 2 reported episodes of febrile seizure occurred in subjects in group LA5 (n = 1275), while no cases were reported in LA6b or LA6c (n = 160 and n = 174, respectively). One LA6b subject did report seizure within 28 days of the first MenACWY toddler vaccination, and one LA6b subject reported seizure within 28 days after the 2nd MenACWY toddler vaccination.

> *Reviewer comment: Only subjects in US4c and LA4c constitute a control group for the entire 4 dose series complicates interpretation of these events (through 6 months after the 4th dose). The control groups used for safety comparisons for MenACWY dose 1-3 and for dose 4 were not the same subset of participants, since MenACWY was administered at time points (in the second year of life) to study groups that had previously served as the infant dose control groups. Therefore, the treatment group is provided in parentheses, but the events are grouped according to whether the subjects received MenACWY at any timepoint prior to the SAE.*

***Kawasaki Disease and/or vasculitis*:**
Received MenACWY at any timepoint prior to the SAE:
US:

1. Subject 16/5002 (US1b) was a Caucasian male who was 61 days old at enrollment and was hospitalized for pyrexia 78 days after his **4th dose of MenACWY**, which was administered at 13 months of age. At the time of hospitalization, he had a history of intermittent fever of unknown etiology for 5 months. Each febrile episode lasted 5 days and occurred monthly. The first episode was reported 13 days after his 1st vaccination with MenACWY, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. During the hospitalization, his erythrocyte sedimentation rate was elevated at 85 mm/h. He was reported as having otitis media during the hospitalization. He was discharged from the hospital after one day and was treated with a 10 day course of oral antibiotics.

   > *Reviewer comment: In this reviewer's opinion, insufficient details were provided to rule out vasculitis as an etiology of the intermittent, recurrent fevers without a source.*

2. Subject 28/7010 (US3) was a Caucasian male who was 68 days old at enrollment and was hospitalized for Kawasaki Disease 29 days after his **third vaccination with MenACWY**, DTaP-HBV-IPV, PCV7, and rotavirus vaccine. He developed vomiting, fever, and rash 26 days post-vaccination. His initial presentation included red eyes without exudates, mildly red lips, and a fine maculopapular rash scattered over his trunk and back with easy blanching, no petechiae or vesicles, and no apparent pruritis. His white blood cell count was

19, 700 cells/uL, platelets were 518,000 k/uL, and C-reactive protein (CRP) was 8.5 mcg/dL. Urinalysis showed pyuria with 10 – 25 white blood cells, 3 – 5 red blood cells, specific gravity of 1.024, trace leukocytes, and 80 ketones. Echocardiogram was normal. He received antibiotics, antipyretics, acetylsalicylic acid, and intravenous immune globulin. The applicant reported the child had recovered completely 7 days after onset. His parents withdrew him from the study.

Latin America:

3. Subject 61/5003 (LA3) was a Hispanic female who was 61 days old at enrollment and developed pyrexia (39C) 97 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She was hospitalized 3 days later. White blood cell count was 16,700, and ESR was 50 mm/hour. She was treated with antibiotics and discharged and was reported as completely recovered. Insufficient information is provided with respect to the workup to determine the source of the fever, as well as the final diagnosis.
4. Subject 62/5033 (LA3b) was a Caucasian female who was 60 days old at enrollment and was hospitalized 74 days after vaccination with DTaP and Hib and almost one year after her 3rd vaccination with MenACWY, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She appears to have had 5 – 6 days of fever, accompanied by irritability and exanthemas on her hands, feet, and mouth. She received antipyretics and was reported as recovered completely the day after hospitalization. No further information was provided by the applicant. Intravenous immunoglobulin was not listed in the provided list of medication used for treatment. Given that she improved in its absence, Kawasaki disease is unlikely. However, the applicant should provide additional information on which to base that determination.

***Seizures or potential seizures*:**

Received MenACWY at any timepoint prior to the SAE:

US:

1. Subject 36/7008 (US3) was a Caucasian female who was 63 days old at enrollment and was hospitalized for complex partial seizures 31 days after the **2nd vaccination with MenACWY** and concomitant vaccines. The subject was afebrile, and the seizure lasted 30 minutes. Magnetic resonance imaging (MRI), electroencephalogram (EEG), and lumbar puncture were reported as normal, and she was discharged 2 days later. She was readmitted less than one month later for prolonged seizure associated with fever. During the hospitalization, she was diagnosed with an upper respiratory tract infection. The discharge data was unavailable. She was dropped from the study due to the events.
2. Subject 37/7053 (US3) was a Caucasian male who was 62 days old at enrollment and had a 1.5 minute seizure 8 days after vaccination with the **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. He had a 3 – 4 minute seizure 29 days after those vaccinations, and an EEG performed one week after that was reported as normal. He was reported as recovered.
3. Subject 06/7052 (US3) was a Hispanic female who was 63 days old at enrollment and was hospitalized for apnea 8 days after her **4th MenACWY dose**, which was concomitantly administered with MMRV, PCV7, and hepatitis A vaccines. No treatment details or other information was provided. She was

hospitalized overnight, developed fever (102.1F), and was discharged the next day. The investigator postulated that the apnea episode may have been part of a seizure. The child was reported as recovered.

4. Subject 53/7037 (US3) was a Caucasian male who was 61 days old at enrollment and was hospitalized for sleep apnea syndrome, gastroesophageal reflux, and complex partial seizures 63 days after his **1st dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. EEG and head CT were reported as normal, as were complete blood count, basic metabolic profile, electrocardiogram, and chest X-ray. The investigator withdrew the subject. The outcome for seizure was not reported, the outcome for the episode of sleep apnea syndrome was reported as "lasting damage", and the outcome for gastoesophageal reflux disease was reported as resolved.
5. Subject 58/7010 (US4a) was a Caucasian female who was 62 days old at enrollment and had a seizure 28 days after receiving **MenACWY**, Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She had been vaccinated with MenACWY at age 4 months inadvertently, and she received all but MenACWY at age 2 months. She was diagnosed with seizure disorder 27 days after the seizure and experienced three grand mal seizures over one month. EEG and MRI were normal. She was prescribed diazepam and oxcarbazepine. ----------(b)(6)-------- with epilepsy. The condition persisted but was reported as well-controlled with medications.

LA:

6. Subject 61/5037 (LA3a) was a Hispanic male who was 60 days old at enrollment and had his first and second seizures 55 and 62 days, respectively, after his **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He was hospitalized after the 2nd occurrence of seizures, as he had 4 seizures that day. He had his third episode of seizures 28 days after his 3rd dose of MenACWY, administered concomitantly with the same vaccines. The seizures were described as tonic clonic. He was evaluated by a neurologist. EEG, ECG, and echocardiogram were reportedly normal. MRI showed a finding in the white matter around the posterior ventricle. Another specialist evaluated this MRI finding as non-specific in children of his age and suggested repeating the MRI 6 months later. He was administered phenytoin for prophylaxics. He was reported as completely recovered. No further information was provided by the applicant.
7. Subject 62/5497 (LA3a) was a Caucasian male who was 65 days old at enrollment and had 2 episodes of seizures in the setting of fever 58 days after his **4th dose of MenACWY**, administered concomitantly with DTaP, Hib and 12 days after vaccination with hepatitis A and OPV vaccines. He was hospitalized and treated with diazepam and valproic acid. He was reported as recovered.
8. Subject 63/7182 (LA5) was a Hispanic male who was 65 days at enrollment and had 3 episodes of cyanosis 41 days after his **1st dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He was hospitalized for the cyanosis, diagnosed with a respiratory infection, and treated with beta-agonist. He was re-hospitalized 47 days after these vaccinations for a seizure, not associated with fever. He was treated with beta-agonist and phenytoin. He was reported as recovered.
9. Subject 71/7057 (LA5) was a Hispanic female who was 67 days old at enrollment and was diagnosed with pneumonia 7 days after her **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. The

next day, she was hospitalized for a seizure associated with fever. She received diazepam and was reported as recovered.

10. Subject 81/7085 (LA5) was a Hispanic male who was 81 days old at enrollment and had a seizure associated with fever 48 days after his **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. This was his second seizure, the first having occurred 6 months prior and in unknown temporal relationship to prior vaccinations, which included MenACWY. He was treated with antibiotics for acute otitis media and acute tonsillitis and was reported as recovered.
11. Subject 81/7153 (LA5) was a Hispanic female who was 72 days old at enrollment and was hospitalized for pneumonia 7 days after her **2nd MenACWY dose**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right-sided basilar pneumonia. She was treated with ducoid injection. She required mechanical ventilation for an unspecified number of days. She was reported as recovered. Subsequently, she was hospitalized for generalized tonic clonic seizure associated with fever 184 days after her 4th dose of MenACWY, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. She was reported as recovered. This summary is duplicated in the section on pneumonia.
12. Subject 81/7196 (LA5) was a Hispanic female who was 74 days old at enrollment and was hospitalized for a generalized tonic clonic seizure 4 days after her **4th dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. The seizure occurred in the setting of fever (39C). She had a red throat and was treated with antibiotics for acute pharyngitis. Additional details were not provided. She was reported as recovered.
13. Subject 82/7454 (LA5) was an African-American male who was 61 days old at enrollment and was hospitalized for seizure 30 days after his **1st dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. The seizure was tonic clonic, affected the right side of his body, and lasted for 20 minutes. Lumbar puncture was reported as negative. Serum sodium was low at 119 mmol/L. Head CT was normal. He received antibiotics, benzodiazepines, phenobarbital, and phenytoin and was discharged, and reported as recovered.
14. Subject 82/7616 (LA5) was a Hispanic female who was 55 days old at enrollment and had a seizure associated with fever 22 days after her **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. Her seizure was tonic clonic, with gaze deviation to the right, and of 15 minutes duration. She was hospitalized 6 hours later and had 2 additional seizures at the hospital. EEG and "head scanography" (presumably head CT) were normal. Lumbar puncture shoed no white blood cells, protein 8 mg/dL, and glucose 70 mg/dL; culture of cerebrospinal fluid was also normal. She received diazepam, Phenobarbital, and valproic acid. She was diagnosed with otitis media and pharyngo-tonsillitis but did not receive antibiotics. She was reported as recovered.
15. Subject 83/7173 (LA5) was a Hispanic female who was 63 days old at enrollment and was hospitalized for seizure associated with fever 58 days after her **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. The seizure was tonic clonic and lasted for 15 minutes. She received phenytoin and valproic acid. She was reported as recovered.
16. Subject 83/7199 (LA5) was a Hispanic male who was 55 days old at enrollment and was hospitalized for seizure 37 days after his **2nd dose of MenACWY**,

administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. The seizure was tonic clonic with gaze deviation and peribuccal cyanosis, lasted 5 minutes, and was not associated with fever. The event was preceded by yellow diarrhea (3 times per day), clear rhinorrhea, dry cough, and irritability. Gram stain, chemistry, and cell count performed on cerebrospinal fluid was normal, although glucose was 48 mg/dL, while blood glucose was 120 mg/dL. He received Phenobarbital and was told to take valproic acid. However, during follow-up, his mother said that he was not taking any medication and had had 2 new episodes of generalized tonic clonic seizure of 5 minutes duration each and not associated with fever. He started valproic acid but had another generalized tonic clonic seizure, not associated with fever, almost 6 months after the 1st seizure. He was reported as recovered. The case narrative states that the cerebrospinal fluid analysis was suspicious for bacterial or viral meningoencephalitis, but the clinical reviewer disagrees with that assessment.

17. Subject 71/7057 (LA5) was a Hispanic female who was 67 days old at enrollment and had a seizure 8 days after vaccination with her **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. She had had pyrexia and nasopharyngitis about 5 days prior to the seizure and was diagnosed with pneumonia the day before the seizure (7 days post-vaccination). She was hospitalized for the seizure and received diazepam and metamizole intravenously and was discharged the next day. She was reported as recovered.
18. Subject 81/7196 (LA5) was a Hispanic female who was 74 days old at enrollment and had generalized tonic-clonic seizure, pharygnitis, and a fever (39C) 4 days post-vaccination with the **4th MenACWY dose**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. She was hospitalized. She was reported as recovered.
19. Subject 82/7538 (LA6b) was a Hispanic male who was 56 days old at enrollment and was hospitalized for a tonic clonic seizure 6 days after his **2nd dose of MenACWY**. He had no associated fever. The seizure lasted for 5 minutes and occurred after physiotherapy. He presented with generalized seizure involving all 4 extremities and head, frequent eye blinking, bilateral nystamus, and altered facial expression. He had no loss of sphincter control. He then had a post-ictal period. Neurological examination revealed hypotonic limbs, symmetric pupils, positive Babinski and Hoffman bilaterally (indicating upper motor neuron dysfunction), increased tone. He was diagnosed with new onset seizure disorder. He received phenytoin, valproic acid. Approximately one year prior to the event, on the day of study visit 2, he was noted by a physician to have bilateral nystagmus and suspected psychomotor developmental delay. At 7 months of age, he had been evaluated by a pediatrician and noted to have a head circumference < 3% for age and was diagnosed with psychomotor developmental delay and microcephaly and was referred to a neurologist. By report, head CT revealed brain dysmorphism, schizencephaly, and hemiatrophy of the right hemisphere. The child had a history of sudden leg extension every 15 – 25 minutes since birth and developmental delay since 3 months of age. His seizure resolved, but psychomotor delay was persistent at the time of reporting.
20. Subject 82/7412 (LA6b) was a Hispanic female who was 55 days old at enrollment and had a tonic clonic convulsion with upward gaze deviation not associated with fever 17 days after her **1st dose of MenACWY**. EEG was normal. She received valproic acid and was reported as recovered. -------(b)(6)---------- with history of seizures.

Did not receive MenACWY at any timepoint prior to SAE:

LA:

21. Subject 61/5298 (LA4) was a Hispanic male who was 62 days old at enrollment and developed fever and seizures 41 – 44 days after his 2nd doses of **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. Renal ultrasound showed enlarged right kidney and alterations in the differentiation of renal cortical marrow. He was treated with antibiotics. He was reported as completely recovered. No etiology for the fever (40C) was provided by the applicant. Subject 71/7097 (LA6a) was a Hispanic female who was 62 days old at enrollment and was hospitalized for bronchiolitis 9 days after her 3rd vaccination with **routine infant immunizations** and then re-hospitalized 123 days after these vaccines for seizure. The seizure was tonic. EEG was normal, chest x-ray showed diffuse "shadowing" on the right lung, prompting a diagnosis of bronchiolitis. No fever was reported. She received diazepam and valproate for the seizure and beta-agonist for the bronchiolitis. It was noted that the child was receiving fluticasone and valproic acid already as prophylaxis medications. Additional details were not provided. The subject was withdrawn from the study by the investigator for safety reasons, as the seizure not associated with fever met exclusion criterion 13.
22. Subject 82/7111 (LA6a) was a Hispanic male who was 60 days old at enrollment and was hospitalized for seizure associated with fever 37 days after his 2nd vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. He had one episode of vomiting, hypotonia, and perioral cyanosis followed by a second episode in which he was atonic with gaze deviation upwards that lasted one minute and a post-ictal phase that lasted 20 minutes with peribuccal cyanosis, He received Phenobarbital, antibiotics, and steroids. He was reported as recovered.

Meningitis:

Latin America:

1. Subject 62/7064 (LA1a) was a Caucasian male who was 62 days old at enrollment and was diagnosed with brain neoplasm 123 days after his **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and HepA vaccines. Approximately 2 weeks later, the subject underwent surgical excision. Two days after the surgery, he developed fever which was reported in the case narrative as "central fever/chemical meningitis (NAO ENTENDI)". The subject was reported as recovered. *The applicant should provide additional details regarding this SAE.*

Pneumonia:

Received MenACWY at any timepoint prior to the SAE:

US:

1. Subject 59/7033 (US3) was a Caucasian female who was 62 days old at enrollment and had bacterial pneumonia 6 days after and was hospitalized 12 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed air trapping with bilateral infiltrates. She was treated with antibiotics and was reported as completely recovered.

Latin America:

2. Subject 61/5133 (LA3a) was a Hispanic male who was 62 days old at enrollment and was hospitalized for pneumonia 39 days after his **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus

vaccines. Chest x-ray showed right lung infiltrate. He was treated with beta-agonist, antibiotics, and steroids. He was reported as completely recovered.

3. Subject 61/5136 (LA3b) was a Hispanic female who was 61 days old at enrollment and was hospitalized with "primary atypical pneumonia" 54 days after her **4th dose of MenACWY**. Chest x-ray showed interstitial alveolar bilateral infiltrate. She received antibiotics, steroids, and beta-agonists. She was reported as completely recovered.
4. Subject 61/5216 (LA3b) was a Hispanic female who was 78 days old at enrollment and developed pyrexia 8 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He then developed irritability, cough, respiratory difficulty, vomiting, and change in eating habits and was diagnosed with and hospitalized for pneumonia 12 days after the vaccinations. Chest x-ray showed lobar pneumonia. She was treated with antibiotics and beta-agonist and was reported as completely recovered.
5. Subject 62/5383 (LA4) was a Caucasian female who was 78 days old at enrollment and was hospitalized for pneumonia 24 days after vaccination with her **2nd dose of MenACWY**, administered concomitantly with DTaP, Hib. Her first dose of MenACWY had been given 5 months prior, concomitantly with MMRV, PCV7, and hepatitis A vaccines. Chest x-ray showed a right-sided consolidation, and she was treated with antibiotics and inhaled steroids. She was reported as recovered.
6. Subject 61/7040 (LA5) was a Hispanic female who was 59 days old at enrollment and was hospitalized for pneumonia 57 days after her **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right lobar pneumonia. She received antibiotics, steroids, intravenous ranitidine, and beta-agonist. She was reported as completely recovered.
7. Subject 62/7056 (LA5) was a Caucasian female who was 57 days old at enrollment who was diagnosed with pneumonia 38 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed a right-sided infiltrate. She was treated with antibiotics, beta-agonists, and steroids.
8. Subject 71/7060 (LA5) was a Hispanic female who was 58 days old at enrollment and was hospitalized for pneumonia 41 days after her **4th dose of MenACWY**, concomitantly administered with MMRV, PCV7, and hepatitis A vaccines. Chest x-ray showed right-sided consolidation. She received antibiotics and beta-agonist and was reported as recovered.
9. Subject 71/7166 (LA5) was a Caucasian who was 79 days old at enrollment and was hospitalized for febrile neutropenia 39 days after her **1st dose of MenACWY**, concomitantly administered with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines and was hospitalized for pneumonia 18 days after her 3rd doses of these vaccines. Chest x-ray showed bilateral consolidation and air bronchogram on the left. The child was treated with antibiotics and beta-agonist and was reported as recovered.
10. Subject 81/7044 (LA5) was a Hispanic male who was 82 days old at enrollment and was diagnosed with pneumonia 27 days after his **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He presented with cough, fever, malaise, pharyngeal erythema, biltaral rhonchi, tachypnea, white blood cell count of 13200 (60% lymphocytes), platelets of 1174000 (units not specified), and a C reactive protein of 7. He was

treated with acetylsalicylic acid for 13 days and with antibiotics and beta-agonist. He was reported as recovered.

11. Subject 81/7109 (LA5) was a Hispanic female who was 80 days old at enrollment and was hospitalized for pneumonia 39 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed left-sided infiltrates. She received antibiotics and inhaled terbutaline. She was reported as recovered.
12. Subject 81/7145 (LA5) was a Hispanic female who was 73 days old at enrollment and was hospitalized for pneumonia 37 days after her 1st MenACWY dose, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She received antibiotics and was reported as recovered.
13. Subject 81/7153 (LA5) was a Hispanic female who was 72 days old at enrollment and was hospitalized for pneumonia 7 days after her **2nd MenACWY dose**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right-sided basilar pneumonia. She required mechanical ventilation for an unspecified number of days. She was reported as recovered. Subsequently, she was hospitalized for generalized tonic clonic seizure associated with fever 184 days after her 4th dose of MenACWY, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. She was reported as recovered. This summary is duplicated in the section on seizures.
14. Subject 81/7167 (LA5) was a Hispanic female who was 82 days old at enrollment and was hospitalized for pneumonia 7 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed apical right infiltrate. She was treated with antibiotics and beta-agonist and was reported as recovered.
15. Subject 81/7230 (LA5) was a Hispanic female who was 68 days old at enrollment and was hospitalized for pneumonia 54 days after her **2nd MenACWY dose**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right-sided infiltrates. She received antibiotics and steroids and was reported as recovered.
16. Subject 81/7314 (LA5) was a Hispanic male who was 63 days old at enrollment and was hospitalized for pneumonia 45 days after his **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed infiltrates. He received antibiotics and beta-agonist and was reported as recovered.
17. Subject 81/7369 (LA5) was a Hispanic female who was 58 days old at enrollment and was hospitalized for pneumonia 48 days after her **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She received antibiotics and inhaled terbutaline and was considered recovered.
18. Subject 81/7371 (LA5) was a Hispanic male who was 61 days old at enrollment and was hospitalized for pneumonia 31 days after her **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis vaccines. She was also diagnosed as having an asthma attack. She received beta-agonist, antibiotics, and steroids and was reported as recovered.
19. Subject 81/7537 (LA5) was a Hispanic male who was 56 days old at enrollment and was hospitalized for seizure associated with fever 92 days after his **4th dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He had abnormal tremor-like movements, eye deviation, and fever of 39C. He also had irritability and vomiting but no neurological deficit.

Chest x-ray showed bilateral reticular infiltrates, and the blood culture grew gram positive cocci in chains. As such, he was diagnosed with bacteremia and pneumonia. He was treated with antibiotics. No further details were provided, so the clinical reviewer cannot determine whether a lumbar puncture was performed. The gram positive cocci in chains were not identified in the case narrative, but *Streptococcus pneumoniae* is one of the organisms which would have this appearance. The applicant should confirm this, particularly as this may represent a vaccine failure since it occurred after the 4th dose of PCV7, concomitantly administered with MenACWY. This summary is duplicated in the sections on seizure, bacteremia, and other.

20. Subject 81/7584 (LA5) was a Hispanic female who was 54 days old at enrollment and was hospitalized for pneumonia and asthma 37 days after her **4th dose of MenACWY**, administered concomitantly with MMRV, PCV7, and hepatitis A vaccines. Chest x-ray showed right basilar infiltrates and air trapping. She received antibiotics, steroids, and beta-agonist and was reported as recovered.
21. Subject 82/7064 (LA5) was a Hispanic male who was 55 days old at enrollment and was hospitalized for pneumonia approximately 1 month after his **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed bilateral air trapping. White blood cell count was 19,710. He received antibiotics and beta-agonist and was reported as recovered.
22. Subject 82/7070 (LA5) was an African-American female who was 57 days old at enrollment and was hospitalized for pneumonia 57 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right-sided infiltrates. She received antibiotics, steroids, beta-agonist and was reported as recovered.
23. Subject 82/7104 (LA5) was an African-American female who was 61 days old at enrollment and was hospitalized for pneumonia 155 days after her **3rd MenACWY dose**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed bilateral infiltrates. She received antibiotics and was reported as recovered.
24. Subject 82/7358 (LA5) was a Hispanic female who was 55 days old at enrollment and was hospitalized for bronchopneumonia 29 days after her **1st dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. She was treated with antibiotics and was reported as recovered.
25. Subject 82/7360 (LA5) was a Hispanic male who was 55 days old at enrollment and was hospitalized 13 days after his **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Pneumonia was diagnosed 3 days later. He received antibiotics and was reported as recovered. He had been hospitalized recently for bronchiolitis.
26. Subject 82/7385 (LA5) was an African-American female who was 68 days old at enrollment and was hospitalized for pneumonia 40 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed right-sided infiltrates. She received antibiotics and beta-agonist and was reported as recovered.
27. Subject 82/7517 (LA5) was a Hispanic female who was 56 days old at enrollment and was hospitalized for pneumonia 11 days after her **3rd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. Chest x-ray showed edema in the bronchial walls and bilateral interstitial infiltrates. She received antibiotics and was reported as recovered.

28. Subject 82/7585 (LA5) was an African American male who was 55 days old at enrollment and was hospitalized for bronchiolitis 13 days after his **1st dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. The SAE is listed as "bronchiolitis", but according to the case narrative, the chest x-ray showed left-sided pulmonary infiltrate, in addition to bilateral interstitial infiltrates and air trapping. He received antibiotics, as well as steroids and beta-agonist. He was reported as recovered.
29. Subject 83/7017 (LA5) was a Hispanic male who was 62 days old at enrollment who died (b)(6) days after his **3rd vaccination with MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. During a phone contact to recover diary card information, it was learned that the subject had died, with lung infection reported as cause of death. ----------(b)(6)----------. Autopsy report and final diagnoses were pending at the time of report, but the subject's case reporting form (CRF) states that the site tried for more than one year to have access to the autopsy report or any source document related to the SAE without success.
30. Subject 83/7147 (LA5) was a Hispanic male who was 60 days old at enrollment and was hospitalized for pneumonia 47 days after his **2nd vaccination with MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He received antibiotics, steroids, and beta-agonist and was reported as recovered. He was subsequently hospitalized for asthma attack approximately 6 months later and reportedly recovered.
31. Subject 81/7124 (LA6a) was a Hispanic male who was 78 days old at enrollment and developed fever and pruritic maculopapular rash without mucosal lesions 39 days after his 2nd MenACWY dose, for which he was hospitalized 3 days later. He was diagnosed with urticaria, treated with epinephrine, hydrocortisone, hydroxyzine, and ketotifen, and recovered. He was hospitalized for pneumonia 152 days after his **2nd MenACWY dose**. Chest x-ray showed right paracardial infiltrates. He received antibiotics, epinephrine (inhaled), and beta-agonist and was reported as recovered.
32. Subject 81/7216 (LA6a) was a Hispanic female who was 73 days old at enrollment and was hospitalized for pneumonia 17 days after her **2nd dose of MenACWY**. Chest x-ray showed infiltrates in the lower right lung. She received antibiotics and was reported as recovered.
33. Subject 81/7506 (LA6b) was a Hispanic male who was 57 days old at enrollment and was hospitalized for pneumonia 61 days after his **2nd dose of MenACWY**. Chest x-ray showed right paracardial infiltrates. He received antibiotics, inhaled epinephrine, and beta-agonist and was reported as recovered. He was discharged and then re-hospitalized for asthma approximately 2 weeks later. He had been hospitalized previously for bronchiolitis (~ 4.5 months prior to the pneumonia episode).

Did not receive MenACWY at any timepoint prior to the SAE:

US:

34. Subject 34/7006 (US4b) was a Caucasian male who was 62 days old at enrollment and was hospitalized for pneumonia and bronchiolitis 40 days after his 2nd dose of **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. His RSV "test" was positive. He was treated with beta-agonist. He was reported as recovered.

Latin America:

35. Subject 62/5130 (LA4) was a Caucasian female who was 68 days old at enrollment and was hospitalized for pneumonia 9 days after her 3rd vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. She was treated with antibiotics and was reported as completely recovered.
36. Subject 81/7138 (LA6a) was a Hispanic male who was 76 days old at enrollment and was hospitalized for pneumonia 32 days after his 3rd vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. Chest x-ray showed right-sided infiltrates. He was treated with beta-agonist and antibiotics and was reported as recovered.
37. Subject 81/7351 (LA6a) was a Hispanic male who was 72 days old at enrollment and was hospitalized for pneumonia 25 days after his 2nd vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. He received antibiotics and was considered recovered.
38. Subject 83/7120 (LA6a) was a Hispanic female who was 64 days old at enrollment and was hospitalized for pneumonia and bronchiolitis 32 days after her 3rd vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. She received antibiotics and beta-agonist and was reported as recovered. She had a separate hospitalization for diarrhea and dehydration approximately 4 months later and recovered from those SAEs, as well.
39. Subject 81/7650 (LA6b) was a Hispanic male who was 57 days old at enrollment and was hospitalized for pneumonia 14 days after his 1st vaccination with **Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**. He received antibiotics, inhaled epinephrine, and beta-agonist and was reported as recovered.
40. Subject 71/7223 (LA6c) was a Hispanic male who was 61 days old at enrollment and was hospitalized for bronchiolitis 56 days after his **2nd doses of Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines**; chest x-ray performed 7 days later, during hospitalization, showed "bifocal" pneumonia. He received antibiotics, beta-agonist, and steroids. He was discharged but readmitted for pneumonia approximately 1.5 months after the 3rd vaccinations. He was treated with antibiotics and beta-agonist. He was reported as recovered.

***Bacteremia*:**
Received MenACWY at any timepoint prior to the SAE:
US: N/A
Latin America:

1. Subject 62/7085 (LA5) was a Caucasian male who was 68 days old at enrollment who was hospitalized 2 days after his **2nd dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He had a one day history of fever at the time of admission and was found to be bacteremic with *Streptococcus* based on a positive blood culture. He was reported as recovered following treatment with antibiotics. Further details, including the species and serotype of *Streptococcus* were not provided.
2. Subject 81/7537 (LA5) was a Hispanic male who was 56 days old at enrollment and was hospitalized for seizure associated with fever 92 days after his **4th dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He had abnormal tremor-like movements, eye deviation, and fever of 39C. He also had irritability and vomiting but no neurological deficit. Chest x-ray showed bilateral reticular infiltrates, and the blood culture grew gram positive cocci in chains. As such, he was diagnosed with bacteremia and pneumonia. He was treated with antibiotics. No further details were provided, so the clinical reviewer cannot determine whether a lumbar puncture was

performed. The gram positive cocci in chains was not identified in the case narrative, but *Streptococcus pneumoniae* is one of the organisms which would have this appearance. The applicant should confirm this, particularly as this may represent a vaccine failure since it occurred after the 4th dose of PCV7, concomitantly administered with MenACWY. This summary is duplicated in the sections on seizure, pneumonia, and other.

Did not receive MenACWY at any timepoint prior to the SAE:
US: N/A
Latin America: N/A

Other:

1. There were 2 SAEs of pertussis in MenACWY recipients, both occurring after subjects received only one dose of DTaP.

   Reviewer comment: These cases were more likely due to incomplete pertussis immunization, rather than vaccine failure when administered concomitantly with MenACWY. Two SAEs of pertussis occurred after the 1st or 2nd vaccinations in subjects receiving only routine infant immunizations.

2. Subject 81/7537 (LA5) was a Hispanic male who was 56 days old at enrollment and was hospitalized for seizure associated with fever 92 days after his **4th dose of MenACWY**, administered concomitantly with Hib, HBV, DTaP, IPV, PCV7, and rotavirus vaccines. He had abnormal tremor-like movements, eye deviation, and fever of 39C. He also had irritability and vomiting but no neurological deficit. Chest x-ray showed bilateral reticular infiltrates, and the blood culture grew gram positive cocci in chains. As such, he was diagnosed with bacteremia and pneumonia. He was treated with antibiotics. No further details were provided, so the clinical reviewer cannot determine whether a lumbar puncture was performed. The gram positive cocci in chains was not identified in the case narrative, but *Streptococcus pneumoniae* is one of the organisms which would have this appearance. The applicant should confirm this, particularly as this may represent a vaccine failure since it occurred after the 4th dose of PCV7, concomitantly administered with MenACWY. This summary is duplicated in the sections on seizure, pneumonia, and bacteremia.

Deaths:
No deaths were reported in US subjects. One Latin American subject (83/7017 in LA5) died due to lung infection during the period between the infant doses and the toddler dose, and 2 Latin American subjects died during the period of ages 12 – 18 months (71/7021 due to car accident trauma, and subject 83/7212 due to sepsis with history of tetralogy of Fallot).

Table 18. V59P14 Withdrawals due to an AE or death

	US1a	US1b	US2	US3	US4a	US4b	US4c	LA1a	LA1b	LA2	LA3a	LA3b	LA4	LA5	LA6a	LA6b	LA6c
n	2	0	2	4	2	1	1	0	0	0	0	0	0	3	1	1	2
N	154	166	159	680	76	70	203	151	150	148	5	150	709	1426	358	170	711
%	1.3	0	1.3	0.6	3	1	0	0	0	0	0	0	0	0.2	0.3	0.6	0.3

Source: CSR pages 142 and 146 of 31591 (adapted)
N = number enrolled
n = number withdrawn due to AE or death

7.1.1.3 Reviewer Summary & Conclusions

Study V59P14 is the pivotal immunogenicity trial to support a 4-dose primary series, administered at 2,4,6 and 12 months of age; one of two main trials that provide 4-dose detailed safety data (i.e. immediate AEs, solicited AEs, any AEs, MAEs and SAEs) to support MenACWY use in infants; and, the main trial for concomitant vaccine evaluation. This reviewer has significant concerns about the safety and immunogenicity data from this study.

General:

- The applicant reports that reconstruction of safety data without documentation occurred at site 34. The "COMMENTS" dataset indicates reconstruction of data occurred at other sites, as well. However, it is unclear whether the applicant will be able to determine the extent to which reconstruction occurred, given that at least one site did not document this.
- The IRB responsible for oversight at 19 US sites received a warning letter from the FDA citing serious concerns about its ability to protect human subjects. According to the applicant, enrollment had been completed already at these sites. Additionally, the applicant's August 2008 audit of the 2 ethics committees responsible for oversight of 3 Colombian sites revealed concerns which prompted transfer of IRB duties and responsibilities to another committee in October 2009. Due to resultant delays in approval of protocol amendment 5, there was disproportionate representation of Argentinian subjects in one treatment group.

Immunogenicity:

- 52-65% of subjects were excluded from the US per-protocol immunogenicity analysis. Main reasons for exclusion included: 1) no blood draw at Visit 1 (14% - 22%); 2) incomplete infant series (10% - 13%); incorrect vaccine/wrong dose given (3% - 7%); no blood draw at Visit 4 (8% - 11%). The primary analyses may not represent a randomized population of participants. The per-protocol populations included 323 subjects from the infant series and 267 subjects after the toddler vaccination. The MITT and PP populations for the infant series differed by $\leq$ 5%, and the MITT and PP populations differed by $\leq$ 10% for the toddler vaccination; i.e., a substantial proportion of subjects was missing from the MITT population.
- Retested sera for hSBA antibody responses are suboptimal due to potential introduction of bias introducted by correcting visit numbers, and, missing data. The original hSBA assay results were generated in an unblinded manner.

Safety:

- The control group used for 4th dose and 6 month follow-up safety comparisons was limited: MenACWY US1a + US3 (n= 834 enrolled vs control group US4c (n=203 enrolled, MenACWY LA5 (n=1426 enrolled) vs LA6c (n=183 enrolled). The control groups used for safety comparisons may not be representative of the overall population, since the percentage of subjects in US4c and LA6c comprised 58% and 26% of subjects, respectively, initially enrolled in US4 and LA4.
- The number of subjects who received a 4 dose series and have safety data that may be applicable to the US population is not greater than approximately 700.
- It is unclear that MAE and SAE data were collected systemically during days 8 – 28. No assessment of non-serious unexpected AEs occurred during this time peroid.

- For all safety parameters, the extent of reconstructed safety data, which may have been at least 1 – 6 months after vaccination, is unclear and may affect the accuracy of reported adverse events.
- The incidence rates for certain local and systemic reactions reported during the 7 day post-vaccination period is unexpectedly low. Possible reasons include underreporting due to recall bias introduced by reconstruction of safety data, choice of denominators, and inclusion of temperatures which are physiologically implausible.
- Receipt of routine childhood vaccines at variance with ACIP recommendations, such as DTwP and OPV, among Latin American subjects. This clinical reviewer was not able to determine the proportion of Latin American subjects affected.

Rates of solicited reactions and unsolicted AEs varied by geographic region. For example, post-vaccination 3, erythema ranged from 21% - 40% across Latin American groups and from 12% - 22% across US groups, while irritability ranged from 19% - 23% across Latin American groups and 42% - 50% across US groups. With respect to unsolicited AEs, upper respiratory tract infections were reported in ~ 34% - 36% of US subjects but in <1% - 1% of Latin American subjects, and otitis media was reported in 25% - 30% of US subjects and in 1% - 2% of Latin American subjects.

During previous communications which occurred under the IND, CBER advised the applicant that safety evaluation should be defined as solicited local and systemic reactogenicity data for 7 days post-immunization, unsolicited adverse event data collected for 30 days post-immunization, medically significant AEs from day 30 through 6 months post-vaccination, and SAEs through 6 months post-vaccination (e.g., February 12, 2007 telecon).

Pneumococcal IgG antibody responses to serotype 6B were statistically lower when the 3rd doses of PCV7 and MenACWY were given concomitantly. Both vaccines contain the same carrier protein, CRM_{197}. Non-inferiority criteria for pneumococcal 4th dose IgG GMCs were met for all serotypes. A confounding factor in the analyses of the 4th dose was the control group (US1b) used for immunogenicity comparisons. Routine vaccinations recommended by the ACIP at age 12 months were administered to US1b, but these subjects had received three doses MenACWY infancy (2, 4, and 6 months of age). Pneumococcal IgG GMCs in the control group might also have been reduced. In February 2010, a 13-valent pneumococcal CRM_{197} conjugate vaccine (PCV13) was licensed by the FDA and routinely given to US children at 2, 4, 6 and 12-15 months of age. PCV13 contains 34 mcg of CRM_{197}. Given that both PCV13 and MenACWY also contain the same carrier protein, assessment of potential immunological interference between antigens contained in both PCV13 and MenACWY, would be important to evaluate.

MenACWY vaccine used in this trial was prepared by reconstituting lyophilized MenA glycoconjugate (packaged in a single dose vial) with liquid MenCWY glycoconjugates contained a -------(b)(4)----------. During the review of this supplement, the agency became aware that translucent particles were observed in liquid CWY component packaged in -------(b)(4)--------. Information submitted to the IND indicated that the particles in part consisted of ----------(b)(4)----------. Assessments of particle size and distribution in expired and current vaccine lots, comparisons of total saccharide content for the C, W and Y components, stability of vaccine batches over time and comparisons

of immunogenicity data from young children/adolescent clinical trials for the two presentations were not provided in this sBLA, but are available in submitted IND amendments. No information about the impact on the safety of MenACWY doses ----------(b)(4)---------- was provided in the sBLA or IND. MenACWY safety and immunogenicity, when given as a 4-dose infant series with the vial/vial presentation, has not been previously assessed but is being evaluated in an ongoing trial.

7.1.2 Trial #2: V59P23 NCT # 00806195

7.1.2.1 Title

A Phase 3, Open-Label, Randomized, Parallel-Group, Multicenter Study to Evaluate the Safety of Novartis MenACWY Conjugate Vaccine when Administered with Routine Infant Vaccinations (RIV) to Healthy Infants.

7.1.2.1.1 Objective

Rationale

To evaluate the safety and tolerability of MenACWY conjugate vaccine when administered with routine vaccinations to healthy infants.

> *Reviewer Comment: This study was underway at the time of discussions between CBER and the applicant about data needed to support licensure of a four dose series of Menveo in children two months of age and older. The applicant subsequently revised this study to include more subjects that would provide detailed safety data for the entire series in the 2 month to 2 year age group.*

Primary Objectives:

1. To compare the percentage of subjects, during days 1-7 after any vaccination, with at least one severe systemic reaction after administration of MenACWY plus routine vaccine with the percentage of subjects presenting with at least one severe systemic reaction after routine vaccines alone at 2-,4-,6- and 12 mo. of age

Secondary Objective:

1. To compare the percentage of subjects with at least one serious adverse event (SAES) through 6 months post-final dose in subjects who receive MenACWY with routine vaccinations to the percentage in those subjects receiving routine vaccinations alone.
2. To assess the safety and tolerability of MenACWY through 6 months post-final dose when given concomitantly with routine infant vaccines.

> *Reviewer Comment: An interim clinical study report (CSR) was provided for this study and included results through at least one month after the last study dose. Therefore, the results for the two secondary objectives are not included in the CSR or in this review.*

7.1.2.1.2 Design Overview

This Phase 3 study was an open-label, randomized controlled safety trial in healthy children two months of age and older. Study vaccine was administered at 2, 4, 6, and

12 months. Subjects were randomized at a 3:1 ratio to receive either MenACWY + routine infant vaccines (RIV) concomitantly, or RIV alone. The study included four groups in two arms, which enrolled in parallel. More detailed safety data was collected for subjects enrolled in Groups 3 and 4 compared to in Groups 1 and 2.

Table 19. V59P23. Study Design

Study Group	Visit 1 (2 mo.)	Visit 2 (4 mo.)	Visit 3 (6 mo.)	Phone Call 1 (9 mo.)	Visit 4 (12 mo.)	Visit 5 (15 mo.)	Phone Call 2 (18 mo.)
1 (ND)	Men ACWY + RIV	Men ACWY + RIV	Men ACWY + RIV	Safety Follow-up	Men ACWY + RIV	RIV	Safety Follow-up
2 (ND)	RIV	RIV	RIV	Safety Follow-up	RIV	RIV	Safety Follow-up
3 (D)	*Men ACWY + RIV*	*Men ACWY + RIV*	*Men ACWY + RIV*	*Safety Follow-up*	*Men ACWY + RIV*	*RIV*	*Safety Follow-up*
4 (D)	*RIV*	*RIV*	*RIV*	*Safety Follow-up*	*RIV*	*RIV*	*Safety Follow-up*

Source: 15 Month CSR V59P23 Table 9.1-1. Men ACWY = Novartis MenACWY conjugate vaccine; RIV= Concomitant routine infant vaccinations; ND= Non-detailed safety data; D= Detailed safety data (as depicted by red italics throughout this review).

Subjects enrolled in the United States received concomitant routine infant vaccinations as recommended by the Advisory Committee on Immunization Practices (ACIP), including DTaP-IPV-Hib vaccine (Pentacel™), pneumococcal conjugate vaccine (Prevnar 7™), MMR vaccine (MMR-II™). Subjects enrolled in other countries were required to receive DTaP-IPV-Hib, pneumococcal conjugate, and MMR vaccines, and if required, country specific vaccinations

Reviewer Comment:

1. *The study was originally designed to only include the non-detailed safety groups (Groups 1 and 2) and was revised to include the detailed safety data groups (Groups 3 and 4) and to increase the number of subjects enrolled after discussion with CBER on the safety data available for MenACWY in the 2 month to 2 year age group.*
2. *Although the study enrolled subjects in multiple countries, study subjects from U.S. sites only were included in Groups 3 and 4. In addition, the interim study report includes only subjects from U.S. sites.*

Safety was evaluated by collection of medically attended adverse events (MAAEs), serious adverse events (SAEs), and AEs leading to premature study discontinuation in all four arms for the entire study period (from two to 18 months of age or 6 months after the last study vaccination). In two of the four arms (Groups 3 and 4, also referred to as Detailed Safety groups) information on solicited adverse reactions for seven days after each vaccination was also collected. Groups 1 and 2 were referred to as the Non-Detailed Safety groups (ND).

Table 20. V59P23. Safety Data Definition

Non-Detailed Safety Data (Groups 1 & 2)	Detailed Safety Data (Groups 3 & 4)
1. Serious Adverse Events (SAEs) 2. Medically Attended Adverse Events (MAAEs) 3. Concomitant prescription Medication to Treat SAEs or MAAEs	1. Solicited Local and Systemic Adverse Events for seven days post-vaccination* 2. Serious Adverse Events (SAEs) 3. Medically Attended Adverse Events (MAAEs) 4. Concomitant prescription Medication to Treat SAEs, MAAEs, or solicited adverse reactions and non-prescription meds for 7 days post-vaccination*

Source: 15 Month CSR V59P23, Section 9.1. *Vaccinations at Visits 1, 2, 3, 4 only. (Day 1= Vaccination Day).

In Group 3 MenACWY was administered in the right thigh while in Group 4, Prevnar was administered in the right thigh and served as the active control for local solicited adverse reactions. All other vaccines in these two groups were administered in the left thigh. Since the study was open-label study, both the study personnel and the subject's parents/legal guardian knew the identity of the study vaccine administered.

7.1.2.1.3 Population

Inclusion Criteria

1. Healthy 2 month old infants (aged 55-89 days), born after a full-term pregnancy with an estimated gestation age $\geq$37 weeks and a birth weight $\geq$ 2.5kg
2. Parent/legal representative has given written informed consent after the nature of the study had been explained
3. Available for all visits scheduled in the study

Exclusion Criteria

1. Previously had received any meningococcal vaccine or DTP, IPV, or OPV, *H. influenza* type b (Hib) or Pneumococcus (birth doses of BCG (one) and/or HBV (two) were permitted)
2. Previous confirmed or suspected disease caused by *N. meningitides, C. diphtheriae, C.tetani*, Poliovirus, Hepatitis B, Hib, Pneumococcus or *B. pertussis* (history of laboratory confirmed, or clinical condition of paroxysmal cough for a period of longer than or equal to 2 weeks associated with apnea or whooping)
3. Household contact with and/or intimate exposure to an individual with laboratory confirmed *N. meningitides* (serogroups A, C, W135, or Y), *B. pertussis*, Hib, *C. diphtheriae*, Polio, or pneumococcal infection at any time since birth
4. History of anaphylactic shock, asthma, urticaria, or other allergic reaction after previous vaccinations or known hypersensitivity to any vaccine component
5. Significant acute or chronic infection within the previous 7 days or have experienced fever (temperature >38.0C [100.4F]) within the previous 3 days
6. Any present or suspected acute (e.g., leukemia, lymphomas), or chronic disease (e.g., seizure disorder, cardiac disease, renal failure, severe malnutrition, or insulin dependent diabetes), progressive neurological disease, immunosuppression, or a genetic anomaly/known cytogenetic disorders
7. Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives

8. Prior receipt of blood, blood products, parenteral immunoglobulins, investigational agents
9. Relatives of site research staff working on this study

Removal of Subjects
The subject's parents/legal guardians were permitted to withdraw consent for participation in the study at any time during the study. An investigator could withdraw a subject from the study if it was in the interest of the subject, or if the subject could not comply with the protocol.

Study vaccination was delayed for a significant acute or chronic infection within the previous 7 days or fever (temperature >38.0C [100.4F]) within the previous 3 days.

Subjects did not receive further study vaccinations for any of the following:

- Development of exclusion criteria
- Any serious vaccine-related reaction to investigational or concomitant vaccines
- Febrile convulsions or neurologic disturbance after vaccination
- Hypersensitivity to the investigational vaccine
- Other suspected side effect that could compromise the subjects' well being.

7.1.2.1.4 Study Products

Study Vaccine
Menveo (MenACWY): The investigational vaccine was obtained by mixing the lyophilized Men A component (lot number 017011) with the MenCWY full liquid vaccine (lot number X79P45I1). The resulting composition was 0.5 mL injectable solution, which was administered intramuscularly.

7.1.2.1.5 Safety Endpoints and Monitoring

Safety endpoints included solicited adverse events collected for the day of vaccination and the subsequent six days and medically attended AEs, serious AEs, and AEs leading to premature study discontinuation collected for the entire study period.

Study personnel observed subjects for a minimum of 15 minutes following vaccination to assess for any immediate post-vaccination reactions. After each visit, the parents/guardians of subjects in all groups were given a worksheet to record AEs that required a medical office or emergency room visit, SAEs, AEs resulting in premature withdrawal of subjects from the study; and prescription medications to treat these AEs. The worksheet was to be completed from the 8th day after vaccination to the following visit at the 4-, 6-, 12-, or 15-month visit. The worksheet was to be returned at subsequent visits and information from the worksheet was to be entered onto an electronic CRF.

> *Reviewer Comment: Study personnel were provided with a script to collect information on the worksheet from the parents/guardians. However, this script does not address how information was collected if the parents/guardians lost, did not bring, or did not fill out the worksheet. The sponsor has allowed verbal recall of AEs in other studies. If AE information was collected by verbal recall without a diary card or worksheet in this study, the criteria for inclusion of such information, such as time since AE, was not provided and AEs collected by verbal recall were*

not identified in the CSR or datasets.

Safety information was collected for solicited local and systemic adverse reactions in subjects in Groups 3 and 4. Individual solicited events followed are described in the following table.

Table 21. V59P23. Individual Solicited Adverse Reactions

	Systemic Adverse Reactions
• Tenderness • Erythema • Induration	• Change in Eating Habits • Sleepiness • Persistent Crying • Vomiting • Diarrhea • Irritability • Rash • Axillary Temperature

Source: 15 Month CSR V59P23, Section 9.1

Information on solicited local and systemic adverse reactions was collected for the 7 day period after each study vaccination. Therefore, in addition to the worksheet, parents/guardians in Groups 3 and 4 were provided with diary cards to record solicited local and systemic reactions and temperature. In addition on these diary cards, all adverse events and medications were collected for the 7 days following each study vaccination. On the day of injection, parents/guardians were instructed not to begin collecting solicited adverse reactions until 6 hours after injection. Parents/guardians were instructed to complete each day's diary card at the same time of day, preferably in the evenings. The diary cards for Visits 1, 2, and 3 were collected at subsequent visits; at the time of collection, the diary card was reviewed with the parent/guardian and the information was subsequently recorded on the electronic CRF.

Local Reactogenicity Grading:

Tenderness: None; Mild- minor light reaction to touch; Moderate- cried or protested to touch; Severe- cried when injected limb was moved.

Erythema/Induration: None 0 mm; Mild 1-25 mm; Moderate: 26-50 mm; Severe: >50 mm

Systemic Reactogenicity Grading:

The severity of systemic solicited reactions was graded as none, mild, moderate, or severe except as described below.

Change in Eating Habits: None; Mild- eating <normal 1-2 feeds; Moderate- missed 1 or 2 feeds; Severe- missed > 2 feeds

Sleepiness: None; Mild- increased drowsiness; Moderate- sleeps through feeds; Severe-sleeps most of the time, hard to arouse

Persistent Crying: None; Mild- <1 hour; Moderate- several episodes, unable to keep food down; Severe- sleeps most of the time, hard to arouse.

Irritability: None; Mild- requires more cuddling, less playful than usual; Moderate- more difficult to settle; Severe- unable to console.

Vomiting: None; Mild- 1 or 2 episodes; Moderate- several episodes, unable to keep food down; Severe- little/no intake for more prolonged time.

Diarrhea: None; Mild- more loose stools than usual; Moderate- 3-5 loose stools/day, no solid consistency; Severe- ≥6 liquid stools, no solid consistency.

Rash: None; Urticarial; or Other and further description to be communicated by study personnel in Case Report Form (CRF).

Body Temperature: <38C; 38.0C to 38.4C; 38.5C to 38.9C; 39.0 to 39.4C; 39.5C to 39.9C; and >40C. The protocol specifies that temperature may be measured by axillary or rectal route.

Telephone calls were made two and seven days after each study vaccination to remind parents/guardians to complete the diary card and worksheet for each day. Parents/guardians were also contacted by telephone at 9 months and 18 months for safety follow-up (information on MAAEs and SAEs) of study subjects. Subjects who had withdrawn from the study prematurely were contacted 6 months after the last study vaccine dose for safety follow-up if consent had not been withdrawn. All SAES were followed to resolution or as deemed appropriate by the investigator or medical monitor.

Medication use prior to enrollment was recorded on the "Concomitant Medications" CRF. This included:

- all prescription medications/vaccinations since birth up to Visit 1, except routine prescription medications given as prophylaxis at birth, such as Vitamin K and erythromycin eye ointment
- all prescription medication to treat SAEs or MAAEs
- all prescription and non-prescription medications (except routine mineral and vitamin supplements) within 7 days post-vaccination for subjects in Groups 3 and 4 (Detailed Safety groups)
- any vaccines administered between study visits

All routine childhood vaccinations that were required per local guidelines, but not defined as a study product in the protocol were permitted to be given during the study and recorded in the "Vaccination" CRF.

7.1.2.1.6 Statistical considerations including plan for analysis

Subjects were randomized in a 3:1 ratio using a block randomization schema. The study was open-label due to ethical concerns about administered a placebo vaccine to young infants.

Endpoints

The primary endpoint was the percentage of subjects with severe systemic solicited adverse reactions in the seven days post-vaccination. MenACWY administered concomitantly with routine infant vaccines would be considered non-inferior to RIV alone, if the upper limit of the 2-sided 95% CI of the difference ([MenACWY vaccine + RIV] – [RIV alone]) in proportion of subjects experiencing at least one severe systemic reaction

after any vaccination was <6%. This endpoint was analyzed for subjects in Groups 3 and 4 only. Per the applicant, the 6% margin was chosen as the non-inferiority criteria based on their assessment of the rate of solicited systemic adverse reactions in previous studies of MenACWY and their judgment of a clinically meaningful increase over the anticipated range of severe systemic event rates. Therefore, if the true rates of severe systemic reactions in each group was 6%, (with an anticipated 1250 subjects in the MenACWY + RIV group and 417 in the RIV group, then the power of the study would be >99%, but if the true rate was 14% in each group, then the power would be 91%.

The secondary safety endpoints were the percentage of subjects with SAEs during the entire study period and the description of overall safety and tolerability of the study vaccines. These endpoints were based on results from the entire study period and were not included in the interim clinical study report. The analysis of safety and tolerability was descriptive.

> *Reviewer Comment: The study was designed to follow safety for six months after the last study vaccine. In pre-BLA discussions, CBER agreed that the applicant could submit an interim analysis of data up to the 15 month visit (Visit 5) only.*

Other safety endpoints were solicited local reactogenicity; solicited systemic (non-severe) reactogenicity; unsolicited adverse events for 7-days post vaccination in Groups 3 and 4 only; medically attended adverse events and adverse events lead to premature study discontinuation for all four study groups.

Study populations

The analyzed populations were as follows:

- *Enrolled population*: all subjects whose parents had signed an informed consent, undergone screening procedure and were randomized
- *Exposed population:* all enrolled subjects who actually received a study vaccination
- *Safety population*: all subjects enrolled who have received at least one study vaccination and provide post-baseline safety data

All subjects were analyzed as treated not as randomized.

> *Reviewer Comment: According to an applicant correspondence dated February 10, 2009 (BB-IND 11278, SN 119), the applicant agreed to provide safety information from this study for all four doses of study vaccine and one month follow-up after the last dose. These safety data were to provide the primary support of safety for the four dose Menveo series. However, the study was designed to include subjects who had received one or more doses of Menveo in the safety population and the applicant agreed to provide a post-hoc analysis of safety for the entire four dose series with one month follow-up.*

Handling of missing data

The sponsor did not replace missing data, so subjects with missing data were not included in the denominators of different safety analyses, including the analysis of the primary endpoint (percentage of subjects experiencing severe systemic reactions). Sensitivity analyses were performed to examine the effect of missing data on the endpoints based on several different scenarios. One such scenario included assuming a severe reaction for subjects with the missing data, thus inclusion of these subjects in the numerator and denominator of the primary analysis. Another scenario included

assuming no severe reactions for subjects with missing data, thus inclusion of these subjects in the denominator only.

7.1.2.2 Results

Study Period

The first subject was enrolled on December 05, 2008, and enrollment closed on July 31, 2010. The date of last visit is pending.

Study Sites and Recruitment

There were 153 study sites in six countries, including the US, Taiwan, Costa Rica, Guatemala, Peru, and Panama. Study sites by country included: 130 sites-US; 4 sites-Taiwan; 4 sites-Costa Rica; 7 sites-Guatemala; 3 sites-Panama; and 5 sites-Peru. A total of 7744 subjects were enrolled at all study sites (U.S. and non-U.S.). As noted previously in this review, only data from subjects enrolled in U.S. sites were included in the interim study report. This included 1898 subjects in the Detailed Safety (D) Arms and 1956 subjects in the Non-Detailed Safety (ND) Arms. Therefore, safety data from 3854 subjects were included in the interim study report and are discussed in this clinical review.

Table 22. V59P23. US and Non-US Site Enrollment

Groups by Safety Data Collection[Ω]	*US Sites Enrolled (# subjects)*	Non-US Sites Enrolled (# subjects)	Total
Groups 1 & 2: Non Detailed[§]	*1956**	3890	5846
Groups 3 & 4: Detailed[◊]	*1898***	-	1898
Total	*3854*	3890	7744

Source: 15 month CSR V59P23, Table 9.7.1.4-1. [Ω]Safety data collection was either Non-detailed or Detailed as outlined in Table B. [§]The Non-Detailed data provided in the interim analysis only represents US subjects, the Non-US subject data is pending. [◊] Detailed Safety data provided is only for US subjects. * US Data in the Non-Detailed Safety Groups included in the interim analysis were only AEs/SAEs till 15 months. **For the primary analysis of detailed safety, 1810 subjects were analyzed (80 subjects were without data and 8 subject were not vaccinated). For secondary analysis, 1890 were analyzed (8 not vaccinated).

7.1.2.2.1 Populations enrolled/analyzed

Of the 3854 subjects that were enrolled at U.S. sites and included in the interim study report, approximately 2855 subjects were enrolled in Groups 1 and 3 (MenACWY administered concomitantly with RIV) and 999 subjects were enrolled in Groups 2 and 4 (RIV only). Subject included in the applicant's detailed safety population included 1409 subjects in the MenACWY+ RIV arm (Group 3) and 489 in the control arm (Group 4). The numbers of subjects enrolled and exposed to study vaccines are shown in Table 23.

Table 23. V59P23. Study Populations included in Sponsor's Interim Analysis

Group	Treatment	Enrolled (N)	Exposed (N)	Safety (N)
1	**Men ACWY + RIV Non-detailed**	1446	1440	1440
2	**RIV only Non-detailed**	510	510	510
	Total Non Detailed	1956	1950	1950
3	***Men ACWY + RIV Detailed***	*1409*	*1403*	*1403*

4	***RIV only Detailed***	*489*	*487*	*487*
	Total Detailed	*1898*	*1890*	*1890*
	Total Men ACWY + RIV	2855	2843	2843
	Total RIV only	999	997	997

Source: 15 Month CSR Table 14.1.1.1.

The last column in this table is the safety population as defined by the sponsor to include subjects who had received at least one study dose and provided post-baseline safety data.

> *Reviewer Comment: Although the sponsor has provided the definition of its safety populations as any subject who received one dose of study vaccine and had any post-baseline safety assessment, CBER and Novartis agreed upon certain terms as outlined in applicant correspondence dated February 10, 2009 (BB-IND 11278, SN119). In this communication on page 7, the applicant states,*
>
> > *"More specifically, this interim analysis will be performed to assess the primary safety objective one month after all subjects in Groups 3 and 4 have completed their 12-month of age visit (Visit 4), in addition to all available safety data including that from subjects in Groups 1 and 2, will be included in this interim analysis. This interim analysis will be used to support a regulatory submission in an infant population, and will not alter the course of the trial."*

The number of subjects seen at each study visit, as described by the applicant in the CSR is shown below.

Table 24. V59P23. Sponsor's Summary of Subject Disposition at Each Visit* (% Ongoing Subject Participation)

Group	Treatment	Randomized	Visit 1 2mo. (as treated)	Visit 2 4mo.	Visit 3 6mo.	Visit 4 12mo.	Visit 5 15mo.
1	**Men ACWY + RIV Non-detailed**	1446	1440	1369	1326	1227	1172 (81.1%)
2	**RIV only Non-detailed**	510	510	493	474	432	403 (79.0%)
	Total Non Detailed	1956	1950 (99.7%)	1862 (95.2%)	1800 (92.0%)	1659 (84.8%)	1575 (80.5%)
3	***Men ACWY + RIV Detailed***	*1409*	*1403*	*1337*	*1303*	*1218*	*1156 (82.0%)*
4	***RIV only Detailed***	*489*	*487*	*464*	*443*	*401*	*387 (79.1%)*
	Total Detailed	*1898*	*1890 (99.5%)*	*1801 (94.9%)*	*1746 (91.9%)*	*1619 (85.3%)*	*1543 (81.3%)*

*7744 subjects initially randomized. Source: 15 Month CSR V59P23, Fig. 10.1-1

> *Reviewer Comment: The data in Table 24 could not be reproduced by this*

reviewer's analysis of the population and immunologic datasets (POP and IMMUN). The data in Table 25 describing Menveo exposure was obtained from analysis of these datasets by this clinical reviewer.

Table 25. V59P23. Reviewer Analysis: Number of Subjects *Exposed and Not Exposed to MenACWY by Injection Number[§]**

Group	Treatment based on Actual Exposure	Exposure	INJ #1	INJ #2	INJ#3	INJ#4	INJ #5
1	**Men ACWY + RIV Non-detailed**	1442	1442	1369	1329	1229	1173 (81.4%)
2	**RIV only Non-detailed**	508	508	492	473	433	402 (79.1 %)
	Total Non Detailed	1950	1950	1861 (95.4%)	1802 (92.4%)	1662 (85.2%)	1575 (80.8%)
3	***Men ACWY + RIV Detailed***	*1404*	*1404*	*1337*	*1304*	*1220*	*1156 (82.3%)*
4	***RIV only Detailed***	*484*	*484*	*462*	*443*	*400*	*387 (79.95%)*
	Total Detailed	*1888*	*1888*	*1799 (95.3%)*	*1747 (92.5%)*	*1620 (85.8%)*	*1543 (81.7%)*

Source: JMP file "P23 Master Total #Exp or Unexp at each Inj by Group." (merged POP + IMMUN)
[§]Table provides the percentage of subjects who received a specific injection compared to initial exposure

1. *Subjects were categorized as "exposed" to study vaccine in the datasets. Since the CSR states (page 73 of the CSR) that some subjects were vaccinated with MenACWY and with RIV at different times, it is unclear whether these subjects were exposed to MenACWY or to other vaccines when "exposed." In addition, subjects were included at study visits regardless of vaccine status; therefore this reviewer is unable to determine from the datasets whether subjects who were seen at a visit were the same as subjects vaccinated at the visit.*
2. *There are several small discrepancies in the number of subjects at each visit in each group when comparing the data provided by the applicant in the CSR and the data obtained on review of the datasets. However, these differences were observed for almost every visit and for every treatment arm, thus raising concerns about the consistency of the data and the ability to replicate data in the CSR using data in the datasets.*
3. *In addition, the subjects designated as "exposed" in the datasets were presented as "exposed" at Visit 5 in which MenACWY was not supposed to be administered; therefore, the definitions used in the datasets is unclear and the ability to identify subjects exposed to MenACWY by analysis of the datasets is **not** possible. In the opinion of this reviewer, these discrepancies are cause for concern about the reproducibility and accuracy of the data in the datasets and the Clinical Study Report.*

Protocol Deviations:
In the MenACWY + RIV groups, 64% of subjects (1840/2855) had a protocol deviation compared to 65% (650/999) of subjects in the control groups. In both groups, there were <1% major protocol deviations, however, the only protocol violation categorized as major was "no exposure to any vaccine," such as subjects enrolled but not vaccinated.

The most common protocol deviations (11-20% of subjects) for the MenACWY + RIV groups and 10-20% of the control groups were early termination and injection out of the window. Of note, the sponsor states on page 73 of the CSR, "The majority of vaccination noncompliance at several sites occurred due to poor labeling of the study subjects charts causing MenACWY vaccination to be missed altogether or to be given days after routine vaccines."

Reviewer Comment: Based on this reviewer's analysis of the PROTDEV dataset, there were 4,169 protocol deviations for 2,490 subjects (1438 in Group 1; 553 in Group 2; 1601 in Group 3; and 577 in Group 4). Of these protocol deviations, 14 were considered major (due to no exposure to any vaccine), while the remaining deviations were considered minor. The most common minor deviation was premature study discontinuation (661 deviations). Other common reasons included immunizations given one day prior to the beginning of the visit windows for Visit 2 and Visit 3.

1. *Although the number of major protocol deviations was low, the only protocol violation categorized as major was lack of exposure to study vaccine. Therefore, the category of major deviations is not very useful for analysis of the study.*
2. *In both study groups, there were high rates of "any" protocol deviation, which raises concerns about how the study was conducted. However, the percentages of subjects with protocol violations were similar between the groups.*
3. *The largest numbers of protocol violations were for early termination and injection outside of the visit window.*
    a. *It is unclear why premature study discontinuations occurring before receipt of all four vaccine doses are categorized as minor protocol violations and why the number of premature study discontinuations listed as protocol violations differs from the number of early terminations described in the study report.*
    b. *There were a large number of protocol deviations (8-21%) across groups and visits that were categorized as "out of window,' which is defined in the protocol as +14 days. While the effect that missing windows would have would be greater on immunogenicity than safety, it does raise additional questions about the quality of study conduct. In addition, the applicant states that there were visits in which the MenACWY vaccine was given "days after routine vaccines" but does not provide the number of visits or subjects with this protocol violation. Neither the number of times in which MenACWY and RIV were administered at different times or the exact visits in which MenACWY and RIV were administered at different times were identified in the study report or datasets, and a sensitivity analysis to determine the effect of this protocol violation cannot be performed. This violation could have results in decreased AEs in the MenACWY + RIV arm.*
4. *The number of subjects enrolled and who discontinued the study prematurely was not provided by study site in the CSR and was difficult to identify on analyses of datasets. Therefore, it is impossible to determine if problems in study conduct were consistent across all study sites or limited to a few sites.*
5. *As discussed previously, the number of subjects with missing Diary Cards*

and Worksheets cannot be identified on review of the datasets. When the COMMENTS dataset were searched for the words "missing" or "misplaced", 1732 line listings were identified. When the terms "incomplete, not returned, or lost" were included 8127 line listings were identified. These included multiple line listings for individual subjects, while most of the line listings referred to missing Diary Cards. However, this reviewer was unable to identify the timing of missing Diary Cards in relation to study visit or vaccination. In addition it was difficult to summarize the data due to a lack of consistent terminology to identify comment terms; lack of visit number or dose number in the comments; the variable amount of detail included in the comments; and the large number of line listings requiring review.

   a. *Line listings for subjects in the COMMENTS datasets were cross-referenced by this reviewer with protocol deviations for the same subjects in the PROT DEV datasets. Diary cards that were reported as missing in the COMMENTS datasets are frequently not included as protocol deviations in that dataset. In addition, line listings with missing diary cards were cross referenced with the ADVERSE EVENTS datasets, and there were several subjects who were listed to have missing diary cards but for whom AEs were reported for the same time period.*

6. *There are also multiple similar examples noted by this reviewer and by the BIMO inspector in which the worksheet is identified as missing but adverse events are included for the time frame covered by the missing worksheet.*
7. *Therefore, this reviewer is concerned with the apparently large number of the subjects with missing data; the inability to identify the exact number of subjects with missing data; and the lack of inclusion of missing diary cards as protocol violations. It is also concerning that adverse event data was included when diary cards and/or worksheets were missing. The safety data obtained by verbal recall was not flagged to allow for sensitivity analyses. In addition, the procedure for collecting data by verbal recall was not provided and the extent to which the AE data provided was obtained by verbal recall was not provided. This practice may have resulted in recall bias, may have affected one study arm more than another because of the open label study design, and/or may have resulted in an underestimate of the number of AEs that were reported.*
8. *In the opinion of this reviewer, conclusions about study conduct and the number of study subjects with adequate follow-up cannot be made without clarification of these issues.*

In the CSR, the applicant describes one subject who was placed in the MenACWY arm due to the parents' request that the child receive MenACWY. The investigator at that site (site #030) was able to bypass the randomization schema because the randomization lists were provided to the site. After the applicant was made aware of this subject, randomization lists were no longer provided to the study sites.

<u>Reviewer Comment</u>: It is unclear how many subjects were enrolled in the study prior to removal of randomization lists from the sites. The potential for errors in randomization exists, but it is unclear if or how often it occurred.

On page 73 of the Clinical Study Report, the applicant states that "A relatively significant number of diaries administered at visit 4 were not returned in the time frame needed for this interim database lock."

> *Reviewer Comment: The applicant did not provide the number of subjects with missing data from Visit 4 as described in this sentence from the CSR. The applicant references line listings of vaccine compliance data, but these listings include yes or no for compliance and do not contain the following: failure to return diary card at Visit 4 as a reason for non-compliance; a summary of reasons for non-compliance; consistent terms or documentation of non-compliance; or information on the number of subjects with complete data. Therefore, it is impossible for this reviewer to determine the exact number of subjects with or without one-month follow-up after the 4th dose, which is the population that the applicant agreed to provide safety data based on pre-BLA communications, in addition to correspondence dated February 10, 2009 (BB-IND 11278, SN 119).*

Early Termination:

Table 26 below provides the sponsor's summary of subjects who were terminated from the study prematurely. As depicted in this table, 661 subjects were terminated early from the study. Of the subjects enrolled in the MenACWY arm, 17% (473/2855) were terminated, as compared to 19% (188/999) of subjects enrolled in the control arm.

Table 26. V59P23. Sponsor's Summary Number of Subjects Terminated/Withdrawn from Study (%)

	Group 1 MenACWY + RIV	Group 2 RIV Alone	*Group 3 MenACWY + RIV*	*Group 4 RIV Alone*	MenACWY + RIV Total	RIV Alone Total
Enrolled	1446	510	*1409*	*489*	**2855**	**999**
Ongoing	1200 (83%)	414 (81%)	*1182 (84%)*	*397 (81%)*	**2382 (83%)**	**811 (81%)**
Terminated/Early D/C	246 (17%)	96 (9%)	*227 (16%)*	*92 (19%)*	**473 (17%)**	**188 (19%)**
Reasons terminated:[§]						
• Death	1 (<1%)	0	*1 (<1%)*	*0*	**2 (<1%)**	**0**
• AE	13 (<1%)	1 (<1%)	*10 (<1%)*	*1 (<1%)*	**23 (<1%)**	**2 (<1%)**
• Withdrew consent	67 (5%)	25 (5%)	*71 (5%)*	*31 (6%)*	**138 (5%)**	**56 (6%)**
• Lost to F/Up	81 (6%)	35 (7%)	*66 (5%)*	*28 (6%)*	**147 (5%)**	**63 (6%)**
• Inappropriate Enrollment	0	1 (<1%)	*0*	*0*	**0**	**1 (<1%)**
• Administrative Reason[*]	68 (5%)	23 (5%)	*57 (4%)*	*23 (5%)*	**125 (4%)**	**46 (5%)**
• Protocol Dev./Violation	16 (1%)	11 (2%)	*22 (2%)*	*9 (2%)*	**38 (1%)**	**20 (2%)**

Source: 15 Month CSR V59P23, Table 10.1-2. [§]Primary Reason. [*] Loss of insurance, premature site (20) closure, moving from area.

The most frequent reasons for early termination/withdrawal were loss to follow-up and withdrawn consent. Based on the data from CSR Figure 10.1-1, the most common reason for early termination/withdrawal from the study after Visit 1 was withdrawal of

consent, which was reported in 68 subjects who received MenACWY compared to 15 subjects in the control arm. Early termination/withdrawal due to loss to follow-up and administrative reasons[1] was seen more frequently later in the study.

Reviewer Comment:

1. *The most common reasons for early termination were withdrawn consent and loss to follow-up. Withdrawn consent was approximately six fold higher in the MenAWCY arms than in the control arms between the first and second visits, which may reflect the tolerability of the MenAWCY vaccine.*
2. *A substantial number of subjects were discontinued prematurely due to administrative reasons. It is unclear what this category included. However, the large number of subjects discontinued prematurely due to administrative reasons or due to loss to follow-up raises additional questions about the quality of the study conduct.*

Demography:

The mean age of subjects at the time of enrollment was 65.3 days and 51% of all subjects were male. The majority of subjects were Caucasian (63%); 15% were Hispanic, 12% were Black, 2% were Asian, and 8% were other. The mean weight at enrollment was 5.4 kg, and the mean height was 58.5 cm.

Reviewer Comment: Demographic characteristics were similar between the four groups.

7.1.2.2.2 Efficacy outcomes

The study collected information on safety outcomes only.

7.1.2.2.3 Safety outcomes

Primary Safety Endpoint

The primary safety objective was to compare the percentage of subjects with at least one severe systemic solicited adverse reaction in the seven days after administration of MenACWY plus routine vaccine with the percentage of subjects with at least one severe systemic reaction after routine vaccines alone. This was to be calculated from severe solicited adverse reactions after all scheduled vaccinations (2-, 4-, 6- and 12 mo. of age); and these data were collected only in Groups 3 and Group 4. The criteria for demonstration of non-inferiority would be met if the upper bound of the 95% confidence interval for the difference in percentage of systemic solicited adverse reactions was less than 6%. The results for the primary endpoint are shown in the following table.

Table 27. V59P23. Results for Primary Endpoint: Percentage of Subjects with at Least One Severe Systemic Reaction Days 1 to 7 after any Vaccination in the Detailed Safety Group in US subjects*

Systemic Reaction	Number (%) of Subjects with Solicited Reactions (95% CI)		[MenACWY + RIV] minus [RIV alone]
	Group 3 MenACWY+ RIV N= 1349	Group 4 RIV Alone N= 461	
Severe	213 (16%)	59 (13%)	3.0% (-0.8, ***6.4***)

Source: 15 Mo CSR V59P23, Table 12.2.1 and Table 14.1.1.2.4. *Subjects with no postvaccination systemic

[1] Administrative Reasons for early withdrawal/termination from study include loss of insurance, premature site closure (site 20), moving of the area.

reactogenicity data were not included in the denominators when calculating the percentage of subjects experiencing severe systemic reactions

As shown in Table 27, the primary endpoint was not met. The applicant attributes this result to the wide variation in the percentage of systemic solicited adverse reactions by site. The applicant performed a post-hoc analysis of the primary endpoint using a categorical linear model to adjust for the site-by-site variation. In this analysis, the risk difference was -0.1% with an upper bound 95% CI of 4.7%, this lower bound 95% CI did meet the criteria for non-inferiority.

Reviewer Comment:

1. *The results for the primary endpoint did not meet the protocol-defined criterion for demonstration of safety; however, the results were very close (6.4%) to the criterion for demonstration of safety (<6.0%).*
2. *The clinical significance of individual severe solicited adverse reactions may vary, for example, high fever in a two month old might result in invasive diagnostic tests while severe malaise might not have result in as much concern. Therefore, the type of differences between the study arms would influence the clinical significance of the results for the primary endpoint. Please see the discussion of the types of severe systemic adverse reactions presented later in this review.*
3. *The applicant attributed the failure to meet the primary endpoint to site-to-site variation in results. However, the applicant did not address reasons for the difference between sites. The applicant will be asked to address the potential reasons for variation by site. Use of a post-hoc analysis to correct for site-to-site variation does result in a significant lower bound confidence interval, but a significant result obtained only in a post-hoc analysis is unacceptable due to the potential for bias.*
4. *As indicated in Table K, the data provided represents post vaccination systemic reactogenicity data for only those subjects with available data post vaccination, e.g. had one or more study vaccinations. Results were not provided for the group of subjects who received all four study vaccinations; therefore it is unclear how to interpret on the results for children for whom the vaccine would be indicated (e.g., those receiving a four dose series of MenACWY).*

Subgroup Analysis of Primary Endpoint:

The difference between the percentages of subjects with severe systemic solicited adverse reaction by vaccine dose was analyzed by the applicant. The differences between arms were small after each dose. The applicant states that the upper bound 95% CI for the analysis of the primary endpoint after each vaccines dose was less than 6%.

Reviewer Comment: The study was designed to evaluate the percentage of subjects with severe solicited adverse reactions after all study vaccinations. Clearly, analysis of this endpoint after individual study vaccinations would results in smaller point estimates and upper bound 95% CIs. Therefore, use of an upper bound 95% CI of less than 6% for this analysis is inappropriate.

Systemic Solicited Adverse Reactions:

As shown in Table 28 below, rates of any individual systemic solicited adverse reaction

by injection number were similar across groups, except for diarrhea which was seen in 31% of MenACWY + RIV subjects compared to 23% for the RIV alone group. In addition, the rates of those subjects who experienced severe reactogenicity after any individual solicited systemic reaction were also similar across groups and for subsequent injections.

The most frequently reported systemic solicited adverse events were irritability, sleepiness, and persistent crying. At injection #1, these 3 adverse reactions were the most frequent and seen in 40-59% of subjects at equal rates across groups. However, the rate of these symptoms, while still the most commonly reported, did decrease after the fourth dose (24-49%) and were similar across groups. Diarrhea was seen at higher rates in the MenACWY group at each injection compared to the control by 2-5%. Rash was seen at equal rates at each injection across groups (3-5%).

The rates of fever ($T \geq 38.0C$) increased slightly over time but were similar between the two arms; the rates of fever for the MenACWY arm and the control arm were 3% and 2% respectively after Injection #1; 4% and 6% after Injection #2; 7% and 6% after Injection #3; and 9% and 8% after Injection #4.

The rates of individual severe systemic adverse reactions after all doses of study vaccine were similar between the two study arms (3-6%). There was no single individual severe systemic adverse reaction that was reported with a difference of more than 1% between the arms. The rates by individual vaccine dose and across groups were low (1-2%). Of note, severe fever (≥40.0° C) was reported in 1% or less of subjects in either arm at any time in the study.

Table 28. V59P23. Number of Subjects (%) with *Any and Severe* Systemic Reactogenicity in Group 3 (MenACWY+RIV) vs Group 4 (RIV alone) by Injection

Systemic Reactions	Inj# ALL		Inj#1		Inj#2		Inj#3		Inj#4	
	Grp 3 N=1348	Grp 4 N= 461	Grp 3 N=1302	Grp 4 N= 448	Grp 3 N=1254	Grp 4 N= 417	Grp 3 N=1106	Grp 4 N= 370	Grp 3 N=1096	Grp 4 N= 354
Irritability-										
Any	1032(77%)	358(78%)	764 (59%)	263 (59%)	633 (50%)	199 (48%)	503 (46%)	51(41%)	544 (50%)	172 (49%)
Severe	79 (6%)	27 (6%)	26 (2%)	8 (2%)	21 (2%)	11 (3%)	16 (1%)	5 (1%)	24 (2%)	5 (1%)
	N=1346	N=460	N=1300	N=446	N=1254	N=416	N=1104	N=369	N=1094	N=354
Sleepiness-										
Any	927 (69%)	306 (67%)	671 (52%)	231 (52%)	479 (38%)	152 (37%)	348 (32%)	107 (29%)	334 (30%)	103 (29%)
Severe	55 (4%)	12 (3%)	30 (2%)	7 (2%)	16 (1%)	5 (1%)	6 (1%)	1 (<1%)	7 (1%)	0 (0)
	N=1348	N=460	N=1297	N=447	N=1253	N=416	N=1104	N=367	=1096	N=353
Persistent Crying-										
Any	851 (63%)	273 (59%)	543(42%)	177(40%)	395(31%)	116 (28%)	284 (26%)	73 (20%)	306 (28%)	85 (24%)
Severe	61 (5%)	20 (4%)	22 (2%)	8 (2%)	21 (2%)	8 (2%)	11 (1%)	3 (1%)	16 (1 %)	6 (2%)
	N=1346	N=460	N=1299	N=446	N=1254	N=417	N=1103	N=368	N=1094	N=353
Change in Eating-										
Any	593 (44%)	187 (41%)	301 (23%)	105 (24%)	229 (18%)	71 (17%)	188 (17%)	50 (14%)	201 (18%)	56 (16%)
Severe	46 (3%)	12 (3%)	12 (1%)	6 (1%)	15 (1%)	4 (1%)	8 (1%)	1 (<1%)	13 (1%)	1 (<1%)
	N=1343	N=461	N=1289	N=446	N=1245	N=414	N=1094	N=367	N=1089	N=348
Diarrhea-										
Any	414 (31%)	104 (23%)	214 (16%)	47(11%)	140 (11%)	34 (8%)	90 (8%)	21 (6%)	135(12%)	33 (9%)
Severe	28 (2%)	7 (2%)	7 (1%)	1 (<1%)	6 (<1%)	1 (<1%)	7(1%)	1 (<1%)	10 (1%)	4 (1%)
	N=1346	N=460	N=1299	N=446	N=1254	N=416	N=1102	N=369	N=1094	N=353
Vomiting-										
Any	283 (21%)	78 (17%)	136 (10%)	42(9%)	95 (8%)	25 (6%)	70 (6%)	15 (4%)	51 (5%)	13 (4%)
Severe	10 (1%)	0	4(<1%)	0	1(<1%)	0	3 (<1%)	0	2 (<1%)	0
	N=1346	N=460	N=1298	N=446	N=1254	N=416	N=1106	N=369	N=1094	N=353
Rash-										
Any	121 (9%)	44 (10%)	38 (3%)	12 (3%)	36 (3%)	15 (4%)	31 (3%)	10 (3%)	44 (4%)	16 (5%)
Severe	40 (3%)	14 (3%)	7 (1%)	2 (<1%)	8 (1%)	4 (1%)	10 (1%)	5 (1%)	19 (2%)	6 (2%)
	N=1346	N=460	N=1296	N=446	N=1253	N=416	N=1101	N=367	N=1093	N=353
Fever										
Any ≥38.0C	232 (17%)	69 (15%)	35 (3%)	8 (2%)	56 (4%)	25 (6%)	82 (7%)	21 (6%)	100 (9%)	28 (8%)
Severe ≥40.0C	4 (<1%)	3 (1%)	0	1 (<1%)	0	1 (<1%)	0	0	4 (<1%)	1 (<1%)
	N=1345	N=460	N=1297	N=446	N=1251	N=416	N=1101	N=368	N=1092	N=353
Analgesic/ Antipyretic Medication Given (Yes)	1110 (82%) N=1347	368 (80%) N=460	865 (66%) N=1297	269 (60%) N=446	730 (58%) N=1251	229 (55%) N=416	584 (53%) N=1103	181 (49%) N=368	542 (49%) N=1095	176 (50%) N=353

Source: 15 Month CSR V59P23 Table 12.2.1-3.

Reviewer Comment:

1. *The increase in severe systemic solicited adverse reactions that was reported in the two arms was similar. The difference in overall rate noted in the analysis of the primary endpoint was not due to an increase in any single individual systemic solicited adverse event.*
2. *The rates for any fever (temperature ≥ 38.0°C) after individual doses were unexpectedly low (range 2 to 8%) compared to the agency's general experience with vaccines given to infants/toddlers. Collection of safety information by verbal recall is one possibility for underreported AEs, due to introduction of reporting bias. Also, all temperatures were measured by the axillary route.*
3. *Based on the information provided in the CSR, the number of subjects in Group 3(MenACWY + RIV) with systemic reactogenicity data available for Injections #1 to #4 ranged from 1302 to 1096, as compared to the number of subjects who were exposed to Injection #1 to # 4 which was 1404 to 1220, respectively. The percent missing data by injection number is provided below in Table 29 for both groups in the detailed safety population.*

Table 29. **V59P23. Reviewer Analysis of Percent Missing Systemic Reactogenicity Data by Injection**

	Group 3 (MenACWY + RIV)	*Group 4 (RIV alone)*
Inj #1	*7.2%*	*7.4%*
Inj# 2	*6.2%*	*9.7%*
Inj#3	*15.2%*	*16.5%*
Inj#4	*10.2%*	*11.5%*

The relatively high percentage of data missing at each time point is of concern, and raises additional questions about the conduct of the study. It also raises questions about the way that clinical study results were provided in the clinical study report and in the datasets and may represent either a discrepancy between the term vaccine "exposure" and actual receipt of study vaccine, or it might represent the number of missing diary cards.

4. *The use of analgesic medication in the 7 days after each vaccination dose was high (80-82%), but similar in both groups.*

Other Safety Endpoints:

The percentage of subjects in the MenACWY + RIV group (Group 3) with any (local or systemic) reactogenicity during the 7 day period after all injections was 96%, compared to 97% in the RIV alone (Group 4). (See Table L). Note that, as per protocol, local solicited adverse reactions were compared between Prevnar and MenACWY.

Table 30. V59P23. Overview of Number of Subjects (%) with Any, Local, or Systemic Reactogenicity 7 days Post-Vaccination

	Inj Any		**Inj#1**		**Inj#2**		**Inj#3**		**Inj#4**	
	Group 3 N=1350	**Group 4 N=462**	**Group 3 N=1312**	**Group 4 N=451**	**Group3 N=1261**	**Group 4 N=421**	**Group3 N=1110**	**Group 4 N=376**	**Group 3 N=1102**	**Group 4 N=355**
Any	1301 (96%)	446 (97%)	1168 (89%)	395 (88%)	1009 (80%)	343 (81%)	846 (76%)	285 (76%)	874 (79%)	286 (81%)
Local	1009 (75%)	375 (81%)	693 (53%)	252 (56%)	575 (46%)	227 (54%)	463 (41%)	186 (49%)	520 (47%)	202 (57%)
Systemic	1218 (90%)	411 (89%)	1017 (78%)	329 (73%)	826 (66%)	265 (63%)	656 (59%)	202 (54%)	693 (63%)	220 (62%)

Source: 15 Mo CSR V59P23, Table 12.2.1-1

As shown in Table 30, the rates of any, local, and systemic solicited adverse reactions were similar across groups for each individual injection. In addition the rates of any, local, and systemic solicited adverse reactions remained fairly consistent with subsequent vaccinations.

> *Reviewer Comment: Although there were a higher percentage of subjects in the MenAWCY arm with severe solicited systemic adverse reactions, the percentages with any adverse reactions and with solicited local or systemic adverse reactions overall were similar between the comparison groups.*

Local Solicited Adverse Reactions:

Individual local solicited adverse reactions were collected for the 7 day post vaccination. As specified in the study protocol, the MenACWY vaccination site for subjects in Group 3 was the right thigh while concomitant vaccinations were given in the left thigh. For Group 4 subjects, pneumococcal conjugate vaccine (comparator for local reactogenicity) was given alone in the right thigh, while all other concomitant vaccines were given in the left thigh. The results for the solicited local reactions of tenderness, erythema, and induration are presented in Table 31 below.

Table 31. V59P23. Percentage of Subjects with Any/Severe Individual Local Solicited Adverse Reactions

Local Reactions	Inj Any		Inj#1		Inj#2		Inj#3		Inj#4	
	Group 3 N=1350	Group 4 N=462	Group 3 N=1301	Group 4 N=446	Group 3 N=1257	Group 4 N=418	Group 3 N=1107	Group 4 N=372	Group 3 N=1098	Group 4 N=353
Tenderness-Any	913 (68%)	336 (73%)	602(46%)	218 (49%)	464 (37%)	177 (42%)	329 (30%)	136 (37%)	433 (39%)	175 (50%)
Severe-cried	90 (7%) N=1348	44 (10%) N=461	40 (3%) N=1301	23 (5%) N=446	24 (2%) N=1255	11 (3%) N=418	15 (1%) N=1106	9 (2%) N=372	19 (2 %) N=1098	9 (3%) N=353
Erythema-Any	509 (38%)	236 (51%)	216 (17%)	93 (21%)	236 (19%)	122 (29%)	240 (22%)	106 (29%)	232 (21%)	106 (30%)
Severe >50mm	3(<1%) N=1346	2(<1%) N=460	2(<1%) N=1297	2(<1%) N=445	1(<1%) N=1257	0 N=417	0 N=1104	0 N=370	0 N=1095	0 N=349
Induration-Any	281 (21%)	178 (39%)	108 (8%)	73(16%)	116 (9%)	72 (17%)	98 (9%)	70 (19%)	114 (10%)	80 (23%)
Severe >50mm	0 N=1346	1(<1%) N=460	0 N=1297	1(<1%) N=446	0 N=1257	0 N=418	0 N=1107	0 N=370	0 N=1095	0 N=351

Source: 15 Month CSR V59P23 Table 12.2.1-2

The most frequently reported local solicited adverse reaction in both arms was tenderness, which ranged from 30-46% after study vaccine in the MenACWY arm and 37-50% in the Prevnar 7 arm. In the MenACWY arm, the rate of subjects with any erythema ranged from 17-22%; and with any induration ranged from 8-10%. In the control arm, the rate of subjects with any erythema ranged from 21-30%; and with any induration ranged from 16-23%. Severe erythema and severe induration were similarly low across groups and by injection, while severe tenderness was seen in 1-3% of subjects in the MenACWY arm and in the 2-5% of subjects in the control arm. Based on these results, the pneumococcal conjugate vaccine appears to be more locally reactogenic compared to MenACWY.

Reviewer Comment:

1. *The percentage of subjects with individual solicited local adverse reactions was higher in the active control arm compared to the MenACWY arm. The percentage of subjects with severe individual adverse reactions was low in both arms.*
2. *The percentages of study group 3 and 4 subjects with tenderness at the injection site were unexpectedly low, compared to the agency's general experience with vaccines given to infants/toddlers. The reason for lower rates is unclear, but in the opinion of this reviewer, these inconsistencies raise concerns about how the study was conducted and how adverse event data were collected.*

Unsolicited Medically Attended Adverse Events:

A listing of unsolicited adverse events that were seen >5% in each arm is presented in Table 32 below for those exposed to MenACWY compared to those who received routine vaccinations only.

Table 32. V59P23. Reviewer's Analysis of the Number and Percentage of Subjects with Medically Attended Adverse Events Observed in >5% of Subjects (Subjects Exposed to MenACWY+RIV vs Subjects Exposed to RIV alone)

Preferred Term	MenACWY + RIV (Groups 1 & 3) N= 2846*	RIV alone (Group 2 & 4) N= 994*
Upper Respiratory Tract Infection	1553 (54.5%)	538 (54.1%)
Otitis Media	1366 (47.9%)	487 (48.9%)
Conjunctivitis	530 (18.6%)	148 (14.8%)
Pyrexia	526 (18.4%)	175 (17.6%)
Bronchiolitis	479 (16.8%)	169 (17.0%)
Viral Infection	472 (16.5%)	138 (13.8%)
Dermatitis Diaper	377 (13.2%)	124 (12.4%)
Cough	326 (11.4%)	116 (11.6%)
Diarrhea	313 (10.9%)	97 (9.7%)
Otitis Media-Acute	298 (10.3%)	110 (11.0%)
Eczema	295 (10.3%)	107 (10.7%)
Gastroenteritis	286 (10.0%)	94 (9.4%)
Pharyngitis	284 (9.9%)	89 (8.9%)
Teething	268 (9.4%)	98 (9.8%)
Sinusitis	226 (7.9%)	75 (7.5%)
Croup	225 (7.9%)	76 (7.6%)
Candidiasis	190 (6.6%)	62 (6.2%)
Constipation	188 (6.6%)	66 (6.6%)
Vomiting	161 (5.6%)	53 (5.3%)
GERD	152 (5.3%)	44 (4.4%)
Irritability	152 (5.3%)	48 (4.8%)
Rash	146 (5.1%)	52 (5.2%)
Viral Rash	146 (5.1%)	53 (5.3%)
Ear Pain	129 (4.5%)	51 (5.1%)

Source: Reviewer analysis of POP + IMM +ADVERSE datasets. *N (denominator) for Group 3 was determined by the number of subjects actually exposed to MenACWY. *For Group 4, N was determined by the actual number of subjects unexposed to MenACWY.

Reviewer Comment:

1. *The rates of individual medically attended adverse events are similar between those subjects exposed to MenACWY and those who received routine vaccines only. Approximately 50% of all subjects in each group had an upper respiratory tract infection or otitis media. Other common AEs seen were conjunctivitis, pyrexia, bronchiolitis, viral infection, diaper dermatitis, cough, diarrhea, acute otitis media, eczema, and gastroenteritis.*
2. *The sponsor generated CSR Table 12.2.1-6 provides similar data as that in Table 32 above, but with different percentages and denominators. This reviewer was unable to replicate the sponsor's data.*
3. *The temporal relation between an AE and the corresponding most recent study vaccine cannot be determined from review of the datasets. The study day that individual AEs occurred; the calendar date for each individual study vaccination; and the identity of that vaccination were not provided.*

Serious Adverse Events:

There were 298 SAEs reported in the ADVERSE datasets with 229 in the MenACWY arm and 69 in the control arm. The number of SAEs observed in each system organ class (SOC) is listed below. Of note, randomization ratio MenACWY to Control was 3:1.

Number of Subjects in Each SOC by Arm:	*MenACWY*	*Control*
Infections/Infestations:	111	35
Respiratory/Thoracic/Mediastinal:	32	16
Metabolism/Nutrition:	19	6
Nervous System:	13	4
Gastrointestinal:	12	4
Injury/Poisoning/Procedural Complications:	10	0
Congenital, Familial, and Genetic:	8	0
General Disorders and Administration Site Conditions:	6	1
Psychiatric:	3	0
Cardiac:	2	1
Vascular:	2	0
Skin/Subcutaneous Tissue:	1	0
Reproductive System and Breast:	1	0
Hepatobiliary:	1	0
Eye:	1	0
Blood/Lymphatic:	0	1

Reviewer Comment:

1. *With a randomization ratio of 3:1 (MenACWY+ RIV Arm: RIV Alone Arm), the incidence of SAE by SOC appears to be comparable across arms, with approximately 50% classified as an Infection/Infestation for both groups. Respiratory related-SAEs were seen frequently in both arms. There were more Injury, Congenital, and General Disorders related-SAEs in the MenACWY arm, however, in the opinion of this reviewer; these were unlikely to be related to study vaccine.*

The applicant provided an analysis of the rates of subjects with SAEs for the 14 days after each study injection as shown in the following table.

Table 33. V59P23. SAE Incidence Rates After Each Injection

Group	Day 1 to Day 14 *Inj #1*	Day 1 to Day 14 *Inj #2*	Day 1 to Day 14 *Inj #3*	Day 1 to Day 14 *Inj #4*
Group 1-ND MenACWY+RIV	8 N=1440	3 N=1369	4 N=1327	2 N=1230
Group 2- ND RIV only	2 N=510	1 N=494	1 N=474	1 N=432
Group 3- D MenACWY+RIV	*3 N=1403*	*4 N=1338*	*2 N=1304*	*0 N=1219*
Group 4- D RIV only	*0 N= 487*	*0 N= 464*	*2 N=443*	*4 N=401*
Total MenACWY+RIV	11 N=2843	7 N=2707	6 N=2631	2 N=2449
Total RIV only	2 N= 997	1 N= 958	3 N=917	2 N=833

Source: 15 Month CSR V59P23 CSR Table 14.3.1.1.7.3.1

The applicant also provided the rate of SAEs for selected time points during the study.

Table 34. V59P23. SAE Onset by Sponsor Selected Time Points

Group	Day 1 to <Month 7	Day 1 to <Month 12	Month 7 to <Month 12	Month 12 To <Month 13	Month 13 To <Month 15
Group 1 MenACWY+RIV	45 N=1440	n/a	32 N=1314	8 N=1228	13 N=1197
Group 2 RIV only	5 N=510	n/a	8 N=469	1 N=432	6 N=414
Group 3 MenACWY+RIV	*32 N=1403*	*n/a*	*26 N=1299*	*1 N=1219*	*4 N=1185*
Group 4 RIV only	*7 N= 487*	*n/a*	*15 N=441*	*1 N=401*	*2 N=396*
Total MenACWY+RIV	77 N=2843	127 N=2843	58 N=2613	9 N=2447	17 N=2382
Total RIV only	12 N= 997	35 N=997	23 N=910	2 N=833	8 N=810

Source: 15 Month CSR V59P23 Tables 14.3.1.1.7.2, 14.3.1.1.7.3, 14.3.1.1.7.4, 14.3.1.1.7.5, 14.3.1.1.7.6

Reviewer Comment:

1. *As discussed in the section of this review described medically attended adverse events, this reviewer was unable to determine the temporal relationship between the administration of study vaccine and the onset of adverse events, including SAEs reported in this study.*
2. *While the absolute number of subjects experiencing a SAE was provided by*

the applicant and the percentages for different time points were provided, the percentage of subjects with SAEs from enrollment to time of dataset lock was not. This information could not be reproduced since the number of subjects with available data for the entire study period was not provided in the Clinical Study Report.

a. *In the opinion of this reviewer, no conclusions about safety can be made without these important data.*

AEs Leading to Premature Study Discontinuation/Withdrawal:

There were a total of 39 adverse events that lead to the premature study discontinuation of 31 subjects, of which 27 were in the MenACWY+RIV arm and 4 were in the RIV alone arm. The following list is reviewer generated and provides the number of AEs by System Organ Classification (SOC) and by the # in MenACWY Arm/RIV Alone Arm: Of note, randomization ratio MenACWY to Control was 3:1.

Number of Subjects in Each SOC by Arm:	MenACWY	Control
Nervous System:	13	3
Infections/Infestations:	4	0
Respiratory/Thoracic/Mediastinal:	1	3
Injury, Poisoning, and Procedural Complications:	3	0
Blood/Lymphatic System:	1	1
Congenital/Familial/Genetic	2	0
General Disorders/Administration Site Conditions:	2	0
Metabolism/Nutrition Disorders:	2	0
Cardiac:	1	0
Immune System:	1	0
Psychiatric:	1	0
Vascular:	1	0

In the MenACWY + RIV arm, the majority of premature discontinuations (13) were due to a Nervous System disorder. These included five subjects with febrile seizures; three with seizures; one with epilepsy; and one with Acute Disseminated Encephalomyelitis. One of the febrile seizures was listed by the investigator to be related to vaccination. It occurred three months after the third dose of MenACWY and the subject was also diagnosed with otitis media and diarrhea at the time of the febrile seizure, therefore in the opinion of the reviewer it does not appear to be related to vaccination.

Other adverse events that led to study withdrawal in the MenACWY + RIV arm included hydrocephalus that occurred 1 day after receiving dose #2; pneumonia 3 months after vaccination with dose #2; gastroenteritis 3 days after vaccination with dose #1; and bronchiolitis on the same day of vaccination with dose #1. Additionally, a subject was withdrawn after having injection site pain on the same day of vaccination with dose #1 of MenACWY + RIV. One subject was withdrawn due to an angiopathy adverse event 1 month after receiving dose #2 of MenACWY + RIV.

In the RIV alone arm, four subjects were withdrawn prematurely from the study for 7 adverse events. The adverse events leading to study termination in this arm included head titubation and nystagmus 6 months after receiving study vaccine; febrile seizure approximately six months post-vaccination; respiratory distress, bronchial hyper-reactivity, and pneumonitis one week after receiving dose #3 of RIV alone; and idiopathic thrombocytopenic purpura (ITP) three months after vaccination with dose #3.

Reviewer Comment:

1. *In the submitted CSR, the sponsor had provided narratives on seven of the 39 AEs found in the ADVERSE datasets that led to study discontinuation. Additional narratives, but not all of the narratives, were included in the narratives of subjects with SAEs. Case narratives for all subjects that were withdrawn are need for this reviewer to complete an assessment of safety.*
2. *As with other adverse events, the temporal relationship of AEs leading to study discontinuation and administration of study vaccine could not be determined unless described in the case narrative.*

Reviewer Analysis of Other Adverse Events:

On review of the safety data, adverse events of interest were identified due to the possible relationship between AE and meningococcal disease or between AE and meningococcal vaccines. These AEs are listed below.

Reviewer Comment: As noted previously in this review, temporal relationship of vaccination dose to adverse events was not provided in the datasets. However, study day with temporal relationship were provided for a few subjects in case narratives. Yet, for the majority of adverse events, the temporal relationships could only be determined by an examination of line listings and calendar dates. Therefore, the submission did not allow for reviewer determination of temporal relationship for more than just a few subjects as described in the list below.

1. Bacteremia: five cases (four in the MenACWY +RIV arm & one in the RIV alone). Of the four cases in the MenACWY arm, three occurred after dose #3 and one after Dose #2. The 1 case in the RIV alone arm was after dose #3. All five cases had start dates that were 4 weeks (study arm) to 4 months after vaccination.
2. Sepsis: one case in the MenACWY + RIV arm, 6 months after dose #3.
3. Meningitis: 1 case in the MenACWY + RIV arm with positive cerebrospinal fluid PCR for enterovirus
4. Pneumonia: 182 cases (148 MenACWY + RIV and 34 in RIV alone) including 22 classified as SAEs (15 in MenACWY arm an done in the RIV arm) and one death The death was in the study arm Subject No. 067/0004 who was hospitalized and received intravenous antibiotics for pneumonia 36 days after receiving MenACWY + RIV dose#1. The subject developed fever and respiratory distress while traveling to Mexico and died despite medical treatment. No autopsy report or medical records from Mexico were available.
5. Febrile Convulsions: 24 cases (17 in MenACWY + RIV arm & 7 in the RIV alone arm). Eight febrile convulsions were reported as SAEs and five resulted in premature study discontinuation. Additional information was provided in case narratives for three of the 24 subjects: one subject had a febrile seizure nine days after the fourth dose of MenACWY + RIV; the second reported narrative was a febrile seizure 96 days after dose #3 MenACWY + RIV, and the third had a febrile convulsion 38 days after receiving dose #3 MenACWY +RIV.
6. Convulsions: 7 cases (6 in MenACWY + RIV & 1 in RIV alone). 3 of the cases led to withdrawal from the study, while 2 convulsions were not reported as recovered. Of the 6 convulsions seen in the MenACWY + RIV study arm, the time after vaccination ranged from 6 weeks to 6 months, half of which were after dose#4.

7. Urticaria: 82 cases (61 in MenACWY + RIV & 21 in RIV alone). In the MenACWY + RIV arm, there was one event that was reported as serious in Subject #068/0003 for a 2 day hospitalization for a maculo-papular rash associated with a possible streptococcal infection. This subject had received dose #3 MenACWY + RIV 129 days earlier, thus the PI did not report this as related. In addition, Subject #123/0002 developed urticaria after receiving dose #3 MenACWY + RIV 10 ½ weeks earlier which the PI reported as possibly related, though there is no case narrative to provide further details.
8. Vasculitis: 1 case in MenACWY + RIV arm. Subject #43/5031 received dose #3 MenACWY + RIV. Two months later the infant developed otitis media treated with amoxicillin which subsequently was believed to have caused an allergic reaction rash. By 78 days after the 3rd dose, the subject was hospitalized for worsening symptoms. While inpatient, the rash became purpuric and petechial and the infant's blood culture grew *Haemophilus influenza* Group 1, beta lactamase negative. This infant's final diagnosis *H. Influenza* bacteremia/vasculitis which was treated with IV antibiotics to complete a 9 day hospitalization.
9. Hypersensitivity: 15 cases (12 in MenACWY + RIV & 3 in RIV alone). Of the 12 in the study arm, 4 recovered and 8 did not, though all were not considered serious and were reported as unrelated to vaccination. No case narratives were provided.
10. Anaphylaxis: 1 case in the RIV alone arm approximately 3 months after dose #3 which the PI reported as not serious and not related to vaccination.

Deaths:

There were two deaths, both in the MenACWY Arm. The first death was described in the section of this review on AEs leading to premature study discontinuation. This was a 3 month old Hispanic female who died (b)(6) days after her first study vaccination (MenACWY, Prevnar, Pentacel, Engerix, and Rotateq) on ---(b)(6)------. The infant was hospitalized 36 days after these vaccinations for consolidated bilateral lung infiltrates/pneumonia. The infant received intravenous antibiotics and was discharged home on oral antibiotics and oral decongestants. Three weeks later the infant traveled with her family to Mexico, and subsequently developed severe respiratory distress with a fever to 103° F. Attempts to resuscitate the child in a local hospital failed, and the child died. There were no tests done at the hospital, but the Medical Examiner's Report stated the cause of death as cardiorespiratory failure that was attributed to an unspecified congenital cardiomyopathy. No autopsy results were provided.

The second death was a 6 month old Hispanic female who died (b)(6) days after her second study vaccination (MenACWY, Prevnar, Pentacel, Recombivax HB, and Rotateq) on ---------(b)(6)-------. The infant had a one week history of upper respiratory infections symptoms and was noted not to be sleeping on the evening prior to her death. The infant's mother had noted a purple tongue 2-3 times in the past. The infant was put down for a nap with the father and was found to be dead in bed after the father awoke. The autopsy report showed no evidence of injury, SIDS, congenital cardiac defects, coronary artery abnormalities, or myocardial inflammation including at the sinoatrial node. The cause of death was attributed to acute bronchopneumonia.

Reviewer Comment:

1. In the opinion of this reviewer, neither death appears to be vaccine related.

Conclusion:
This reviewer cannot reach any conclusions about the safety of MenACWY based on the results of Study V59P23. Issues with this review include both missing data and concerns about study conduct. The safety results for the population of interest (those receiving four doses of MenACWY with follow-up for one month after the fourth dose) were not provided. The temporal relationship of adverse events to vaccination could not be determined. The percentage of subjects receiving four doses of study vaccine and reporting SAEs was not provided. Multiple case narratives for subjects discontinuing the study prematurely due to an adverse event were not provided.

Indication 2: A two-dose "catch-up" vaccination schedule in infants aged 6 to 23 months

7.1.3 Trial 3: V59P21
NCT# 00626327

7.1.3.1 Title
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

7.1.3.1.1 Objective/Rationale:
The study's purpose was to evaluate the safety and immunogenicity of MMRV when given with MenACWY and vice versa, and to show that two doses of MenACWY at 7 to 9 and 12 months of age induced adequate antibody responses to each serogroup.

Immunogenicity Objectives:
Primary objectives:

- To compare the immune responses of MMRV vaccine concomitantly administered with MenACWY to that of MMRV vaccine given alone as measured by seroconversion rates to measles, mumps, and rubella; and seroprotection rates for varicella.
- To compare immune responses of two doses of MenACWY given to healthy young children at 7 – 9 and 12 months of age when MenACWY is administered either concomitantly with MMRV at 12 months of age or alone, as measured by the proportion of subjects with serum bactericidal activity using human complement (hSBA) > 1:8 directed against N. meningitidis serogroups A, C, W-135, and Y.
- To assess the immunogenicity of two doses of MenACWY given to healthy young children at 7 – 9 and 12 months of age as measured by the proportion of subjects with hSBA > 1:8 against N. meningitidis serogroups A, C, W-135, and Y.

All primary endpoints were measured 6 weeks after the 12 month vaccination visit

Secondary objectives:

- To compare the immune responses of two doses of MenACWY given to healthy children at 7 – 9 months and 12 months of age when MenACWY is administered either concomitantly with MMRV or alone at 12 months of age, as measured by the proportion of subjects with hSBA $\geq$ 1:4 and hSBA geometric mean titers (GMTs) directed against all 4 serogroups
- To assess the immune responses of MMRV vaccine when administered

concomitantly with MenACWY or alone to healthy 12 month old children, as measured by GMTs for measles, mumps, rubella, and varicella.
- To assess the anti-varicella antibody response when MMRV vaccine is administered with MenACWY or alone to healthy 12 month-old children, as measured by the proportion of subjects who seroconverted.
- To assess the immunogenicity of MenACWY after a single dose given at 7 – 9 months of age, as measured by the proportion of subjects with hSBA $\geq$ 1:8, hSBA $\geq$ 1:4, and hSBA GMTs directed against all 4 serogroups.

Safety Objectives:
- To describe the safety profile of subjects in each vaccine group in terms of immediate hypersensitivity, local and systemic reactions days 1 – 7 after each vaccination, adverse events (AEs) requiring medical visits days 8 – 28 after each vaccination, medically significant AEs and SAEs throughout the study, and protocol-specified reactions of interest days 1 – 28 after the vaccination at 12 months of age.

7.1.3.1.2 Design Overview
This trial is an open-label study, due to differences in enrollment age, study procedures, number of injections, and routes of administration. Children 7 – 9 months of age were randomized (1:1 ratio) to receive two doses of MenACWY at 7 – 9 months and at 12 months, with either MMR-V concomitantly at 12 months (Group 1) or alone at 13.5 months (Group 2). Another group of children were enrolled at age 12 months old, and received MMR-V alone at 12 months (Group 3). Blood samples were collected at Visit 2 for group 2 (age 8 – 10 months), at Visit 3 for groups 1 and 3 (age 12 months), and at Visit 4 for all groups (age 13.5 months). The study was conducted at 90 US sites. Study dates: February 27, 2008 – October 26, 2010.

7.1.3.1.3 Population
Inclusion criteria:
- Completed infant vaccinations as recommend by the ACIP (rotavirus vaccination optional)
- Available for all scheduled visits and telephone calls
- Healthy, as determined by medical history, physical assessment, and investigator's clinical judgment
- Age 7 – 9 months(Groups 1, 2) or 12 months (Group 3)

Exclusion criteria:
- Parent or legal guardian unable to give written informed consent or comply with study procedures
- Previous or suspected *N. meningitidis* disease or infection with measles, mumps, rubella, varicella, and/or herpes zoster
- Household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis,* measles, mumps, rubella, or varicella infection within 60 days prior to enrollment
- Previously immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s), except for OMP-containing Hib vaccines
- Previously vaccinated with any measles, mumps, rubella, or varicella vaccine either alone or in any combination
- Received any investigational agents or vaccines within 90 days prior to enrollment

or expected to receive an investigational agent or vaccine prior to study completion
- Received any licensed vaccines within 30 days prior to enrollment or for whom receipt of a licensed vaccine was anticipated within 30 days after vaccination (except for influenza vaccine, which could have been administered within a 15 day window)
- Significant acute or chronic infection within 7 days prior to enrollment or fever (axillary T≥38.0°C) within 3 days prior to enrollment
- Any serious acute, chronic, or progressive disease, such as history of cancer, diabetes mellitus, blood dyscrasia, thrombocytopenia, congestive heart failure, renal failure, or severe malnutrition
- Epilepsy, any progressive neurological disease, or history of Guillain Barre Syndrome
- History of anaphylaxis, serious vaccine reactions, or allergy to any part of the vaccine, gelatin, latex, and neomycin
- Any other condition that was a contraindication to vaccination
- Known or suspected impairment/alteration of immune function
- Known bleeding diathesis or any condition associated with a prolonged bleeding time
- Down syndrome or other known cytogenic disorder
- History of seizure disorder (history of one febrile seizure was not cause for exclusion)
- Whose families were planning to leave the study site area prior to the end of the study
- Any condition that, in the opinion of the investigator, interfered with evaluating the study objectives
- Receipt of any vaccines routinely administered at 12 months of age (Group 3 only)

Reasons for delaying immunizations:
- Significant acute or chronic infections with systemic antibiotic treatment or antiviral therapy taken within 7 days of vaccination
- Axillary T≥ 38.0°C or presence of an acute systemic illness within 3 days of vaccination
- Receipt of systemic antibiotics delayed vaccination until at least 7 days after the last dose

7.1.3.1.4 Products mandated by the protocol

Please see section 7.1.1.1.4 for a description of product information for MenACWY, MMRV, MMR and Varicella vaccines.

MenACWY: Lot no. Z79P42I1 (comprised of MenA Lot Z009011 and MenCWY Lot Z79P42I1) and MenACWY Lot no. X79P45I1 (comprised of MenA Lot 017011 and MenCWY Lot X79P45I1). The lyophilized MenA component (vial) was reconstituted with the liquid MenCWY component (----(b)(4)-------).

Due to a shortage of MMRV (ProQuad) vaccine, an option to administer separate injections of measles, mumps, rubella (MMR) and varicella (V) vaccines instead of MMRV was added to the protocol procedures.

7.1.3.1.5 Endpoints

Primary Immunogenicity Endpoints:

- % with hSBA titer ≥1: 8 for each meningococcal serogroup
- Measles seroconversion rate: % of pts who are initially seronegative and achieve anti-measles antibody ≥255 mIU/mL (ELISA)
- Mumps seroconversion rate: % of pts who are initially seronegative, and achieve anti-mumps antibody ≥10 ELISA Ab units
- Rubella seroconversion [i.e., seroresponse] rate: % of pts who are initially seronegative, and achieve anti-rubella antibody ≥10 IU/mL (ELISA)
- Varicella seroprotection i.e, seroconversion] rate: % with anti-varicella antibody ≥5 gp ELISA units/mL

Primary Success Criteria:

- hSBA antibody responses in the study group receiving concomitant MenACWY + MMRV were considered non-inferior to hSBA responses in the study group receiving MenACWY alone if the lower 95% confidence limit for the difference in two proportions [*p*MMRV + MenACWY- *p*MenACWY] was > -10% for each serogroup (study group 1 vs group 2 at Visit 4).
- Lower 95% confidence limit for % of subjects with an hSBA titer ≥ 1:8 is ≥ 85% for serogroups C, W-135, and Y and ≥ 65% for serogroup A (study group 2)
- MMRV immune responses in the study group receiving concomitant MenACWY + MMRV were considered non-inferior to corresponding responses in the study group receiving MMRV if the lower limit (LL) of the 95% CI for the difference in two proportions [*p*MMRV +MenACWY – *p*MMRV] was > -5% for MMR antigens and > -10% for varicella (study group 1 vs group 3).

Secondary Immunogenicity Endpoints:

- % of initially seronegative subjects who demonstrate seroconversion for varicella (by gpELISA) at 6 weeks post-vaccination
- GMTs for antibodies to measles, mumps, rubella, and varicella
- Proportion of subjects with hSBA ≥ 1:4 for each meningococcal serogroup
- hSBA GMTs for each meningococcal serogroup

Safety Endpoints:
Proportions of subjects in each group with local reactions, systemic reactions, AEs with onset during the first 7 days after each vaccination, SAEs and AEs within 28 days after each vaccination that required medical attention and/or resulted in premature withdrawal.

7.1.3.1.6 Surveillance/Monitoring

Safety:
Subjects were monitored in the clinic for 15 minutes after each injection to evaluate for signs or symptoms of anaphylaxis, local injection site reactions, and systemic reactions, and recorded by the parent on a diary card. Thereafter, parents recorded daily local and systemic reactions, axillary temperatures, any AEs for 7 days after each study vaccination on a diary card. Solicited local reactions included tenderness, erythema, and induration; solicited systemic reactions included changes in eating habits, sleepiness, persistent crying, irritability, vomiting, diarrhea, and rash. When MMR and V vaccines were administered separately, the MMR injection site was chosen for monitoring local reactions. Study personnel contacted the parent by telephone 2 days after each vaccination as a reminder to complete the diary card, to query for SAEs, and to answer questions about study procedures. Diary cards were collected at the next visit,

except for the diary provided to study group 2 at age 13.5 months (after the 28 day safety assessment, the card was mailed back to the site). At the visit, diary cards were reviewed with the parent/guardian for completeness to obtain daily temperature measurements and descriptions of any local or systemic reactions, AEs, or concomitant medications. The telephone information was reviewed and reconciled with medical records/ diary card information at the subject's next visit.

Depending on the number of study visits, the total number of diary cards provided to parents differed: Study group 1 participants received a diary card at the 7-9 month and 12 month old vaccination visits. Study group 2 participants received a diary card at visits occurring at age 7-9 months, 8-10 months, 12 months and 13.5 months. Study group 3 participants received a single diary card (12 month old vaccination visit).

For Days 8-28, AEs which required medical attention or resulted in premature withdrawal were collected, except for medical visits for common acute conditions, such as otitis media and gastroenteritis, which were not recorded. The method for collecting this information during this time period was unclear.

In addition, when MMR/V vaccination(s) were administered, daily axillary temperature measurements, use of analgesics or antipyretics, and rashes resembling measles, rubella, or varicella and of mumps-like symptoms were assessed by the parent for 28 days and recorded on a diary card.

Information about SAEs was collected throughout the study period. Depending on the study group, the interim time period between visits varied from 1-2 months (study groups 2 and 3) to 3-5 months (study group 1). For all study groups, the parent was contacted by telephone 6 months after vaccination at Visit 3 (i.e. after the second MenACWY dose for study groups 1 and 2, after the MMR/V vaccination for study group 3). A worksheet was provided to parents to record SAEs and AEs necessitating a medical office/emergency room visit which had occurred during this time period; however, the worksheet was not provided until Visit 4 (6 week post-vaccination blood sampling visit).

> *<u>Reviewer comment</u>: It is unclear if information about unsolicited AEs, SAEs, and medically attended AEs was collected systematically, since the timing of safety assessments and methods for collecting safety information varied between study groups. Additionally, due to 100% diary compliance rates at site 34 in study V59P14, the applicant conducted a study site audit. Reasons for high compliance rates at this site included reconstruction of safety information The investigator at site 34 in study V59P14 is the same investigator as at site 39 in study V59P21. Reference to this method of safety data collection was also noted by this reviewer in the Investigator Comments section for other sites. Reconstruction of safety data may introduce reporting biases, which can result in underestimated frequencies of adverse events.*

Immunogenicity:
Blood samples were collected at Visit 2 (one month after the first MenACWY dose) for study group 2, for study groups 1 and 3 who received MMRV (or MMR+V) at 12 months of age, and at Visit 4 (6 weeks after the 12 month visit) for all groups.

7.1.3.1.7 Changes in the Conduct of the Study:
Enrollment was paused for approximately 6 months, due to shortage of MMRV vaccine.

Thus, enrollment of the planned number of subjects was not attained.

During the trial, enrollment at 2 sites was terminated prematurely by the applicant due to non-compliance with Good Clinical Practices and management changes at another site, respectively.

7.1.3.1.7.2 Protocol Amendments

Main changes:
September 19, 2007 (amendment 1): To provide an adequate control group for MMRV safety comparisons, the study design for group 3 modified so that subjects did not receive MenACWY at the 7-9 month and 12 month visits. Accordingly, children in study group 3 were enrolled at 12 months of age as a separate open-label group; a co-primary immunogenicity objective was added to assess immunogenicity (inferred effectiveness) of 2 doses of MenACWY.

October 2, 2008 (amendment 2): Inclusion criteria were clarifed (rotavirus vaccinations were a requirement for study entry).

February 17, 2009 (amendment 3): Subjects enrolled in Groups 1 and 2 could receive MMR+V in place of MMRV if the available refrigerator-stable MMRV vaccine expired prior to the scheduled vaccination visit. Separate analyses for MMRV and MMR+V provided.

May 28, 2009 (amendment 4): subjects could receive MMR+V, or a new vaccine lot of MMRV (if available).

March 4, 2010 (amendment 5): Immunogenicity and safety analyses through Visit 4 initiated prior to study completion. Safety data collected after Visit 4 (13.5 months of age) would be provided as an addendum to the study report. MMRV (frozen) vaccine was provided.

7.1.3.1.7.3 Changes in the analysis plan

Major protocol deviations were defined in statistical analysis plan, dated October 18, 2010 (version 2), which included wider blood draw intervals for subjects included in the per-protocol population (from 28-42 days to 23-55 days after MenACWY vaccination 1, and from 42-56 days to 27-84 days after the 12-month old vaccination visit).

7.1.3.1.8 Statistical considerations including plan for analysis

With 518 evaluable subjects per group, the combined power to demonstrate non-inferiority of MMRV coadministered with MenACWY to MMRV alone, for all four antigens, was 96%. With 550 evaluable subjects for serogroup A, and 208 evaluable subjects for each of the serogroups C, W-135, and Y, the power to demonstrate non-inferiority for all 4 serogroups was 94%. The overall power for the three co-primary objectives was 88%.

7.1.3.2 Results

7.1.3.2.1 Populations enrolled/analyzed

A total of 1630 subjects were enrolled and randomized: 504 MenACWY + MMRV subjects, 510 MenACWY subjects, and 616 MMRV subjects. A total of 1603 subjects were vaccinated (500 MenACWY + MMRV subjects, 503 MenACWY subjects, and 600

MMRV subjects). Of the 225 subjects who withdrew prematurely, 78 were in the MenACWY + MMRV group, 88 were in the MenACWY group, and 59 were in the MMRV group. Therefore, 1405 subjects completed the study per protocol.

The 27 subjects not vaccinated were excluded from the safety analysis. Four MenACWY subjects and 3 MMRV subjects received incorrect vaccines and were excluded from the safety summaries. Safety analyses were performed on the safety population, which included subjects who received at least one study vaccination and provided post-baseline safety data.

All enrolled population: all subjects enrolled.

Modified Intention-to-treat (MITT) population, Immunogenicity – MMRV analysis: all subjects who received a study vaccination, provided at least one evaluable serum sample before and after vaccination, and were seronegative at baseline for any of the four MMRV antigens.

MITT population, Immunogenicity – MenACWY analysis: all subjects who received a study vaccination and provided at least one evaluable serum sample after vaccination.

Per protocol (PP) population, Immunogenicity: all subjects in the MITT population who received all the relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, were seronegative at baseline for any of the 4 MMRV antigens (MMRV analyses only), were included in the analysis of that antigen, and had no major protocol deviations defined prior to unblinding. The PP population, Immunogenicity was the basis for analyses of all primary and secondary immunogenicity endpoints.

Exposed population: all enrolled subjects who actually received a study vaccination.

Safety population: all subjects in the Exposed Population who provided post-baseline safety data.

7.1.3.2.1.1 Demographics:

In the randomized population, the majority of the subjects were Caucasian (59 – 62% in each group); the proportions of subjects who were African American and Hispanic were 10 – 13% and 11 – 15%, respectively. The mean age was 8.5 months in the MenACWY + MMRV and MenACWY groups and 12.1 months in the MMRV group, due to the different ages at enrollment. Gender proportions were similar across all groups (49 – 50% female). The demographics of safety and per protocol immunogenicity populations were similar, except that a higher proportion of the 29 subjects from the MMRV group in the MenACWY per protocol population were African American (24%), and a higher proportion were female (66%). Baseline height and weight were greater in the MMRV group, as these children were 12 months old at enrollment, rather than 7 – 9 months old, as in the ACWY + MMRV and ACWY groups.

Table 35. V59P21. Study Populations

	Group 1: MenACWY + MMRV	Group 2: MenACWY	Group 3: MMRV
Enrolled	504	510	616
Randomized	504	510	616
Vaccinated	500 (99%)	503 (99%)	600 (97%)
Withdrawn	78 (15%)	88 (17%)	59 (10%)
Due to AE	1 (<1%)	--	--
Withdrew consent	21 (4%)	30 (6%)	29 (5%)
Vaccinated	21	27	18
Not vaccinated	--	3	11
Lost to follow-up	24 (5%)	23 (5%)	21 (3%)
Protocol deviation	26 (5%)	26 (5%)	4 (<1%)
Vaccinated	26	25	4
Not vaccinated	--	1	--
Administrative	2 (< 1%)	6 (1%)	--
Inappropriate Enrollment (not vaccinated)	4 (< 1%)	3 (< 1%)	5 (< 1%)
Safety	500 (99%)	500 (98%)	597 (97%)
Safety Follow Up	460 (91%)	453 (89%)	556 (90%)
MITT MenACWY	455 (90%)	483 (95%)	--
MITT MMRV	397 (79%)	--	536 (87%)
PP MenACWY	389 (77%)	386 (76%)	--
PP MMRV	388 (77%)	--	528 (86%)
Completed study	426 (85%)	422 (83%)	557 (90%)

Source: V59P21 CSR pages 99/9389 Table 10.1-1 and pages 101/9389 Table 11.1-1

7.1.3.2.1.2 Protocol deviations:

A total of 867 subjects had protocol deviations during the study: 286 (57%) in the MenACWY + MMRV group, 354 (69%) in the MenACWY group, and 227 (37%) in the MMRV group. Of these, 365 subjects' protocol deviations were major: 139 (28%) in the MenACWY + MMRV group, 133 (26%) in the MenACWY group, and 93 (15%) in the MMRV group.

Table 36. V59P21 Common Protocol Violations

Major Protocol Deviations	**Total**	**MenACWY + MMRV**	**MenACWY**	**MMRV**
No blood draws	95	49 (10%)	27 (5%)	19 (3%)
No blood draws at Visit 4	138	34 (7%)	59 (12%)	45 (7%)
No MMRV immunization	61	45 (9%)	N/A	16 (3%)
No MenACWY immunization Visit 3	87	41 (8%)	46 (9%)	N/A
Sample available but no ACWY serology results	50	26 (5%)	24 (5%)	N/A
Subjects received excluded concomitant treatment or vaccine	37	17 (3%)	18 (4%)	2 (< 1%)
Seropositive for all MMRV antigens	8	4 (< 1%)	0	4 (< 1%)

Source: V59P21 CSR Table 10.2-2

7.1.3.2.2 Efficacy endpoints/outcomes

The PP population, Immunogenicity was the basis for analyses of all primary and secondary immunogenicity endpoints. The hSBA GMTs to each meningococcal serogroup were calculated for the following timepoints: Visit 2 (group 2 only), Visit 3 (group 1 only), and Visit 4 (groups 1 and 2 only). To show assay control, a random selection of 30 subjects from group 3 were selected for inclusion in the hSBA assays for Visits 3 and 4 serum samples. The ELISA GMTs to measles, mumps, rubella, and varicella were calculated for the following timepoints: Visit 3 (baseline, for groups 1 and 3 only) and Visit 4 (post-vaccination, for Groups 1 and 3 only).

Table 37. V59P21. Primary Analyses of MMRV Immunogenicity (Per-Protocol Population)

		Number (%) of subjects [95% CI]		
		MenACWY + MMRV	**MMRV**	**Difference (MenACWY + MMRV – MMRV)**
Measles seroconversion ≥ 255 mIU/mL	Post-dose	**N = 350**	**N = 467**	
		342 (98%) [96 – 99]	462 (99%) [98 – 100]	-1% [-3.4 – 0.5]
Mumps seroconversion ≥ 10 ELISA Ab units	Post-dose	**N = 365**	**N = 499**	
		357 (98%) [96 – 99]	481 (96%) [94 – 98]	1% [-1.0 – 3.7]
Rubella seroconversion ≥ 10 IU/mL	Post-dose	**N = 370**	**N = 515**	
		353 (95%) [93 – 97]	500 (97%) [95 – 98]	-2% [-4.5 – 0.8]
Varicella seroprotection ≥ 5 gpELISA units/mL	Post-dose	**N = 337**	**N = 459**	
		325 (96%) [94 – 98]	448 (98%) [96 – 99]	-1% [-3.9 – 1.2]
Varicella seroconversion ≥ 1.25 gP ELISA units/mL	Post-dose	**N = 337**	**N = 459**	
		333 (99%) [97 – 100]	456 (99%) [98 – 100]	-1% [-2.4 – 0.8]

Source: V59P21 CSR, Table 11.4.1.1-1, page 105/9389

Non-inferiority critieria for co-administration of MenACWY with MMRV were met. The lower limit of the 95% CI for the difference between the proportion of subjects with seroconversion for measles, mumps, and rubella was > -5%, and the difference in the seroprotection rate for varicella was > - 10%. The secondary endpoint of non-inferiority of MenACWY + MMRV concomitant administration compared with MMRV administration alone with respect to varicella seroconversion rates was met. Except for antibody response to the mumps antigen, post-vaccination GMTs were similar in groups that received MenACWY + MMRV vs MenACWY + MMR+V. Anti-mumps GMT was higher in participants receiving MenACWY + MMR+V. However, the analyses were performed on groups 1-3 as a pooled population rather than within group comparisons of MMRV vs. MMR+V responses.

Table 38. V59P21. GMTs (95% CI) for MMRV antigens (Per-protocol population)

		ACWY + MMRV	MMRV	GMT ratio ACWY + MMRV/MMRV
Measles	Pre-dose	N = 357	N = 470	1 (0.94 – 1.06)
		74 (71 – 77)	74 (71 – 77)	
	Post-dose	N = 350	N = 467	1.11 (0.99 – 1.25)
		4049 (3701 – 4430)	3632 (3350 – 3938)	
Mumps	Pre-dose	N = 372	N = 502	1 (1 – 1)
		5 (5 – 5)	5 (5 – 5)	
	Post-dose	N = 365	N = 499	1.2 (1.06 – 1.35)
		97 (89 – 107)	81 (75 – 88)	
Rubella	Pre-dose	N = 377	N = 518	1 (1 – 1)
		5 (5 – 5)	5 (5 – 5)	
	Post-dose	N = 370	N = 515	1.01 (0.89 – 1.14)
		57 (52 – 62)	56 (52 – 61)	
Varicella	Pre-dose	N = 344	N = 461	1 (1 – 1)
		0.63 (0.63 – 0.63)	0.63 (0.63 – 0.63)	
	Post-dose	N = 337	N = 459	1.05 (0.94 – 1.16)
		19 (17 – 20)	18 (17 – 19)	

Source: V59P21 CSR, Table 11.4.1.1-2, page 106/9389

1.1.1.2.2.2 Analyses of MenACWY Immunogenicity:
MenACWY Primary Endpoints:

Table 39 V59P21. Number (Proportion) of Subjects with hSBA Titers ≥ 1:8 Against N. meningitidis Serogroups A, C, W-135, and Y, MenACWY-PP Population

		ACWY + MMRV	ACWY	ACWY + MMRV – ACWY
MenA		N = 384	N = 379	
	Pre			
	Post-1st dose		175 (50% of N = 349) [45 – 56]	
	Pre-2nd dose	105 (31% of N = 340) [26 – 36]		
	Post-2nd dose	338 (88%) [84 – 91]	334 (88%) [84 – 91]	0% (-4.7 – 4.5)
Men C		N = 204	N = 199	
	Pre			
	Post-1st dose		175 (88%) [83 – 92]	
	Pre-2nd dose	191 (94% of N= 203) [90 – 97]		
	Post-2nd dose	204 (100%) [98 – 100]	195 (100% of N = 195) [98 – 100]	0% (-1.8 – 1.9)
Men W		N = 205	N = 199	
	Pre			

	Post-1st dose		73 (37%) [30 – 44]	
	Pre-2nd dose	163 (80%) [73 – 85]		
	Post-2nd dose	203 (100% of N = 204) [97 – 100]	193 (98% of N = 196) [96 – 100]	1% (-1.3 – 3.9)
MenY		N = 201	N = 198	
	Pre			
	Post-1st dose		60 (31% of N = 196) [24 – 38]	
	Pre-2nd dose	129 (64%) [57 – 71]		
	Post-2nd dose	196 (98% of N = 200) [95 – 99]	191 (96%) [93 – 99]	2% (-1.9 – 5.3)

Source: V59P21 CSR, page 111/9389 Table 11.4.1.2-1

This primary endpoints for meningococcal hSBA antibody responses were met. The lower limit of the 95% CI for the proportions of subjects achieving hSBA $\geq$ 1:8 were $\geq$65% for serogroup A and $\geq$ 85% for serogroups C, W-135, and Y.

MenACWY Secondary Endpoints:

GMTs for each serogroup in the PP population are presented in the table below.

Table 40. V59P21. GMTs [95% CI] Against N. meningitidis Serogroups A, C, W-135, and Y, MenACWY-PP Population

		ACWY + MMRV	ACWY	ACWY + MMRV: ACWY
MenA		N = 384	N = 379	
	Post-1st dose		8.16 (N=349) [6.96 – 9.58]	
	Pre-2nd dose	4.76 (N=340) [4.1 – 5.53]		
	Post-2nd dose	39 [34 – 45]	37 [32 – 42]	1.07 [0.89 – 1.28]
Men C		N = 204	N = 199	
	Post-1st dose		26 [22 – 31]	
	Pre-2nd dose	44 (N=203) [37 – 53]		
	Post-2nd dose	194 [170 – 220]	180 (N=195) [158 – 205]	1.08 [0.91 – 1.27]
Men W		N = 205	N = 199	
	Post-1st dose		5.11 [4.15 – 6.29]	
	Pre-2nd dose	17 [14 – 21]		
	Post-2nd dose	132 (N=204) [113 – 155]	119 (N=196) [101 – 139]	1.11 [0.91 – 1.37]
MenY		N = 201	N = 198	
	Post-1st dose		4.09 (N=196) [3.36 – 4.98]	

	Pre-2nd dose	11 [8.75 – 13]		
	Post-2nd dose	97 (N=200) [81 – 116]	88 [73 – 105]	1.11 [0.88 – 1.39]

Source: V59P21 CSR page 112/9389 Table 11.4.1.2-2

Safety outcomes

Due to 100% diary card compliance in another study (V59P14), Novartis performed anaudit of site 39 (site 34 in study V59P14). The applicant reported to CBER in a letter submitted to IND 11278 on March 17, 2010 that the site had not documented verbally collected safety data as such in source documents. In this communication, the applicant informed CBER's OCBQ of the related issues and stated that:

> *The study documentation [for study V59P14] allowed sites, in the event that parents lost a diary card, to ask the parent to reconstruct as much of the information as they could from memory regarding adverse events and concomitant medications given during the period between study visits. Sites were to clearly document [sic] on the source documentation that this was verbal data, the identity of the person who provided that data, who collected the data, and the date/time the data was verbally collected [sic]….We found out that, for study cards that were not originally completed at the subjects' homes, these steps were not routinely followed in reconstructing data from memory concerning subjects' temperatures, adverse events, concomitant medications, and solicited local/systemic reactions.*

Table 41. V59P21. Overview of Solicited Adverse Events (Safety Population)

Visit	1 (study vaccination 1)		3 (study vaccination 2)			4 (study vaccination 3)
Group	MenACWY + MMRV	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MenACWY
Received at Visit	MenACWY	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MMRV
	N = 500	N = 500	N = 459	N = 456	N = 597	N = 429
Any	335 (67%)	351 (70%)	337 (73%)	275 (60%)	478 (80%)	281 (66%)
Local	159 (32%)	170 (34%)	227 (49%)	141 (31%)	316 (53%)	188 (44%)
Systemic	270 (54%)	271 (54%)	263 (57%)	195 (43%)	381 (64%)	195 (45%)
Other	118 (24%)	165 (33%)	143 (31%)	105 (23%)	203 (34%)	108 (25%)

Source: Table 12.2.1.1.-1a, page 123/9389, P21 CSR

Results were similar for subjects who received MMRV or MMR+V.

Reviewer Comment: The summary tables of local and systemic reactions include diary card information reconstructed at subsequent visits and safety data collected during the 15 minute observation period post-vaccination. For some subjects, data collected during the 15 minute observation period was the only reactogenicity

data recorded during 7 days post-vaccination period, which might lead to an underestimation of local and systemic reactogenicity rates. For example, the rate of irritability post-vaccination with MMRV among subjects in study group 3 is reported below as 298/595 (50%); if the denominator used is all subjects in Group 3 who reported any information regarding irritability after the 15 minute observation, the rate is 298/553 (54%). Also, the reported fever rates in all study groups is unexpectedly low, given that MMRV was administsered to the majority of subjects.

Table 42. V59P21. Local Reactions* Within 7 Days After Each Vaccination, by Study Group and Vaccination Visit (Safety population)

Visit		1 (study vaccination 1)		3 (study vaccination 2)			4 (study vaccination 3)
Group		MenACWY + MMRV	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MenACWY
Received at Visit		MenACWY	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MMRV
Number of subjects		N = 499	N = 500	N = 458	N = 456	N = 593	N = 425
Tenderness MenACWY site	Any	73/498 (15%)	80/499 (16%)	94 (21%)	72 (16%)	NA	NA
	Cried Inj. Limb moved	4/498 (1%)	2/499 (<1%)	5 (1%)	1 (< 1%)	NA	NA
Tenderness MMR site	Any	NA	NA	105/455 (23%)	NA	179/592 (30%)	102/424 (24%)
	Cried Inj. Limb moved	NA	NA	7/455 (2%)	NA	5/592 (1%)	2/424 (<1%)
Erythema MenACWY site	Any	103 (21%)	115 (23%)	98/457 (21%)	96 (21%)	NA	NA
	> 50 mm	1 (<1%)	1 (< 1%)	7/457 (2%)	3 (1%)	NA	NA
Erythema MMR site	Any	NA	NA	156/456 (34%)	NA	224 (38%)	145 (34%)
	> 50 mm	NA	NA	18/456 (4%)	NA	22 (4%)	8 (2%)
Induration MenACWY site	Any	43 (9%)	53 (11%)	46/457 (10%)	40 (9%)	NA	NA
	> 50 mm	0	1 (< 1%)	2/457 (< 1%)	1 (< 1%)	NA	NA
Induration MMR site	Any	NA	NA	90/456 (20%)	NA	102 (17%)	60/424 (14%)
	> 50 mm	NA	NA	2/456 (< 1%)	NA	0	0

*Includes adverse events occurring within 15 minutes after vaccination
Source: V59P21 CSR, Table 12.2.1.1-2a, page 125/9389

Table 43. V59P21. Systemic Adverse Events* Within 7 Days After Each Vaccination, by Study Group and Vaccination Visit (Safety population)

Visit		1 (study vaccination 1)		3 (study vaccination 2)			4 (study vaccination 3)
Group		MenACWY + MMRV	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MenACWY
Received at Visit		MenACWY	MenACWY	MenACWY + MMRV	MenACWY	MMRV	MMRV
Number of subjects		N = 499	N = 500	N = 458	N = 456	N = 593	N = 425
Change in eating habits	Any	75/467 (16%)	81/481 (17%)	78/419 (19%)	47/409 (11%)	105/550 (19%)	51/355 (14%)
	severe	3/467 (1%)	2/481 (< 1%)	7/419 (2%)	3/409 (1%)	5/550 (1%)	4/355 (1%)
Sleepiness	Any	142 (28%)	138/499 (28%)	132/458 (29%)	77 (17%)	197/595 (33%)	74/424 (17%)
	severe	6 (1%)	16/499 (3%)	7/458 (2%)	5 (1%)	15/595 (3%)	4/424 (1%)
Persistent crying	Any	89/466 (19%)	97/481 (20%)	76/419 (18%)	49/408 (12%)	109/550 (20%)	43/355 (12%)
	severe	4/466 (1%)	8/481 (2%)	3/419 (1%)	4/408 (1%)	8/550 (1%)	6/355 (2%)
Irritability	Any	184 (37%)	194 (39%)	185/458 (40%)	132 (29%)	298/595 (50%)	152/424 (36%)
	severe	7 (1%)	12 (2%)	13/458 (3%)	7 (2%)	21/595 (4%)	9/424 (2%)
Vomiting	Any	43 (9%)	43/499 (9%)	25/458 (5%)	23 (5%)	36/595 (6%)	20/424 (5%)
	severe	2 (< 1%)	2/499 (< 1%)	1/458 (< 1%)	1 (<1%)	2/595 (< 1%)	0
Diarrhea	Any	71 (14%)	73/499 (15%)	60/458 (13%)	40 (9%)	107/595 (18%)	41/421 (10%)
	severe	2 (< 1%)	8/499 (2%)	2/458 (< 1%)	4 (1%)	8/595 (1%)	4/421 (1%)
Rash	Any	30 (6%)	17/499 (3%)	29/458 (6%)	21 (5%)	46/595 (8%)	15 (4%)
	Urticarial	11 (2%)	6/499 (1%)	11/458 (2%)	5 (1%)	17/595 (3%)	4 (1%)
Fever (T≥ 38C)	Any	25/498 (5%)	26/499 (5%)	35/458 (8%)	22/455 (5%)	42 (7%)	33/421 (8%)
Other							
Temp (C)	< 38.0C	473/498 (95%)	473/499 (95%)	423/458 (92%)	433/455 (95%)	554 (93%)	388/421 (92%)
	≥ 40.0C	1/498 (< 1%)	2/499 (< 1%)	1/458 (< 1%)	2/455 (< 1%)	0	1/421 (< 1%)

Analgesic or Antipyretic medications	Yes	118/494 (24%)	165/499 (33%)	143 (31%)	105/454 (23%)	203/594 (34%)	108 (25%)

*Includes adverse events occurring within 15 minutes after vaccination
Source: V50P21 CSR.Table 12.2.1.1-2b, page 126/9389

The proportion of subjects reporting systemic adverse events during the 7 days post-dose 1 of MenACWY was similar between the two relevant treatment groups vaccinated at 7- 9 months. The proportion of subjects reporting systemic adverse events during the 7 days post-dose 2 of MenACWY given concomitantly with MMRV was similar to the proportion reporting these events in the group receiving MMRV alone. Irritability was the only systemic AE which was reported with > 5% rate difference between these 2 groups and was higher among subjects receiving MMRV alone. With the exception of fever, which tended to peak days 9 – 10 post-MMRV vaccination, most solicited adverse events occurred within the first 1 - 2 days post-vaccination and resolved within 2 – 3 days.

The proportions of subjects reporting fever during the 7-day post-vaccination period were similar across groups. However, since fever post-MMRV vaccination tends to occur approximately one week post-vaccination, body temperature and analgesic/antipyretic medication use were collected for 28 days after Visit 3. A limitation of this data is that 10 – 13% of subjects were missing from the diary card data days 5 – 28 post-vaccination; proportions were calculated on the total number of subjects in the safety population, so the true proportions may have been higher. Among subjects with reported temperature data during days 5 – 12 after Visit 3, similar proportions of subjects reported fever $\geq$ 38C in the MenACWY + MMRV and MMRV groups (21% and 20%, respectively); a lower proportion of subjects in the MenACWY group reported fever $\geq$ 38C (8%). Similar proportions of subjects reported fever $\geq$ 39C in MenACWY + MMRV, MenACWY, and MMRV groups (5%, 3%, and 5%, respectively). On days 13 – 28 after Visit 3, proportions reporting fever in either range were similar across groups.

From day 4 to 28 post-vaccination at 12 months of age, 10%, 4%, and 14% of subjects reported rash in MenACWY + MMRV, MenACWY, and MMRV groups, respectively. Most rashes were mild, few were moderate, and < 1% were severe. Rashes specific to the MMRV components were rare in all groups and generally not observed after MenACWY alone. Morbilliform (measles-like) rash was reported in 8/462 MenACWY + MMRV recipients and in 23/597 MMRV recipients. Varicella- and rubella-like rashes were observed in 1 – 3 subjects in those groups. Rash at the injection site after MMRV administration was reported in 5/462 MenACWY + MMRV recipients and 8/597 MenACWY + MMRV recipients.

Use of analgesic/antipyretic medication did not reveal major differences across groups.

Unsolicited adverse events:
Interpretation of these data is complicated by the difference in time on study for subjects in the groups receiving MenACWY compared with the subjects receiving MMRV only. The proportion of MenACWY + MMRV recipients reporting any AEs was 67% (335/500), while these proportions were 71% (353/500) and 52% (311/597) for MenACWY and MMRV recipients, respectively. The most frequently reported AEs reported among

MenACWY + MMRV, MenACWY, and MMRV recipients, respectively were: otits media, reported by 92 (18%), 120 (24%), and 40 (7%) subjects; upper respiratory tract infection, reported by 71 (14%), 92 (18%), and 20 (3%) subjects; teething, reported by 41 (8%), 60 (12%), and 41 (7%) subjects; rash, reported by 39 (8%), 24 (5%), and 66 (11%) subjects; and pyrexia, reported by 47 (9%), 48 (10%), and 36 (6%) subjects.

Serious Adverse Events:
Serious adverse events (SAEs) were reported in 18/500 (4%) of MenACWY + MMRV subjects, 19/500 (4%) MenACWY subjects, and 9/597 (2%) of MMRV subjects.
Pertinent case narratives:

- A 7 month-old Caucasian male developed fever and pneumonia 139 days after MenACWY vaccination. He received intravenous antibiotics during hospitalization and was discharged, completely recovered. The event occurred while he was traveling in --(b)(6)-, and no hospital records were available.
- A 7 month-old Caucasian female with history of otitis media was hospitalized for febrile seizures 100 days after her second MenACWY vaccination. She had a one day history of runny nose, nasal congestion, cough, and fever, then awoke the next day with fever of 104.6F and an episode of vomiting. Shortly thereafter, she had two generalized seizures lasting seconds and about 5 minutes apart. In the ER< she had one short generalized seizure and a second seizure lasting several minutes. She was treated with diazepam per rectum with no further seizures. Head computed tomography (CT) showed non-specific fluid in the mastoids and middle ears. White blood cell count was elevated. Her tympanic membranes were noted to have erythema and fluid bilaterally. Intravenous fluids and ceftriaxone were given. Due to wheezing and retractions, she received steroids and albuterol. She was discharged, and her pediatrician noted on follow-up that her asthma, upper respiratory tract infection, and serous otitis media were improving. A few days later, her mother reported intermittent, unusual twitching/jerking while she was sleeping. An electroencephalogram (EEG) and magnetic resonance imaging (MRI) were normal or non-specific. A neurology consultant concluded the event was simple febrile seizures, and the twitching episodes were sleep myoclonus. The twitching episodes persisted for 3 months.
- A 9 month-old Caucasian female with history of recurrent otitis media and right lower lobe pneumonia presented to the ER 3 days after vaccination with MMRV and her second dose of MenACWY with cough and fever. Chest X-ray showed viral pneumonia. She was discharged the next day and recovered completely.
- A 9 month-old Caucasian male was hospitalized with fever of 103.8F and cough 99 days after MMRV and his second dose of MenACWY. He had had a runny nose and cough for 2 weeks. He was diagnosed with a left lower lobe pneumonia, leukocytosis, hyponatremia, and bilateral acute otitis media. RSV and rapid influenza tests were negative. White blood cell count was 43,600 with 66.0% neutrophils. Serum sodium was 133, and chest X-ray showed mild to moderate peribronchial cuffing with focal consolidation in the left lower lobe. He received intravenous ceftriaxone, acetaminophen, and benzocaine hyroxyquinoline sulfate. Blood cultures had no growth. He was discharged “in good condition” 2 – 3 days later on oral cefdinir.

- A 9 month-old Caucasian male with history of recurrent otitis media presented with fever of 104F and purulent nasal discharge 12 days after his second MenACWY vaccination. His white blood cell count was elevated at 33,000, blood cultures were obtained, and he received ceftriaxone intramuscularly. The next day, he was hospitalized for sepsis and treated with intravenous ceftriaxone and fluids and antipyretics. Blood cultures were positive for gram positive cocci in chains, and ceftriaxone was changed to piperacillin-tazobactam for suspected pneumococcus or enterococcus. The organism was identified as pneumococcus. His fever, oral intake, and laboratory data (CRP and white blood cell count) improved, and he was discharged to home, with the event resolved.

  Reviewer comment: the participant had received 3 doses of pneumococcal conjugate vaccine at the time of the event, and it appears form the case narrative that he received routine infant vaccinations and no meningococcal vaccine, concomitantly.
- A 9 month-old Caucasian female presented 39 days after her second MenACWY vaccination with cough, runny nose, wheezing, and difficulty sleeping. She received levosalbutamol and oxygen and was hospitalized with a diagnosis of respiratory failure; oxygen saturation was 85%. She was treated for respiratory failure and bronchiolitis and considered completely recovered the next day, when she was discharged.
- A 9 month-old Caucasian male with history of asthma was hospitalized 35 days after vaccination with MMRV and approximately 2.5 months after his second MenACWY vaccination following a one day history of fever, poor oral intake, and decreased energy. He was treated with intravenous fluids and ceftriaxone. Blood cultures grew Streptococcus pneumoniae, and electrophoresis testing was negative for evidence of sickle cell disease or trait. He developed a pruritic erythematous macular type rash on his chest, back, legs, and behind his ear and was treated with diphenhydramine hydrochloride. He was discharged on cefdinir, and the event resolved.
- A 9 month-old Caucasian male with history of bronchiolitis developed wheezing and fever 55 days after MenACWY vaccination. He then developed diarrhea and was hospitalized for viral pneumonitis. Chest X-ray supported this diagnosis. Respiratory panel was negative for adenovirus, RSV, parainfluenza 1, 2, and 3, and influenza. He received albuterol, oseltamivir, and acetaminophen. The event resolved.
- A 10 month-old Caucasian male was hospitalized for respiratory distress associated with otitis media and bronchiolitis 51 days after vaccination with MenACWY. Chest X-ray showed mild peribronchial thickening, and RSV test was negative. He received intravenous steroids, nebulized treatments, and azithromycin. He recovered completely.
- A 9 month-old Caucasian male experienced a grand mal seizure 40 days after vaccination with MMRV and 5 months after MenACWY vaccination. He was found unresponsive with rhythmic jerking of arms and legs lasting 2 – 3 minutes and some drooling. The mother reported a minor head injury in the morning, prior to the seizure, but without loss of consciousness or vomiting. He was evaluated in the ER, where he had a normal neurological assessment and was diagnosed with grand mal seizure. He was discharged from the ER with complete recovery. EEG 2 weeks later was normal.
- A 10 month-old Caucasian male developed cough, congestion, and vomiting 149 days after MMRV and his second MenACWY vaccination. He was hospitalized

for pneumonia the next day. Chest X-ray showed pneumonia with perihilar infiltrate; influenza screen was negative. He received oxygen therapy, nebulized albuterol, intramuscular steroids, and antibiotics with good response. He was discharged and recovered completely a few days later.

Withdrawals due to AEs:
Three subjects (one in each vaccine group) withdrew due to an AE. These AEs were as follows: varicella and diarrhea for subject 17/0003 (MenACWY + MMRV), varicella, wheezing, and otitis for subject 02/0024 (MenACWY), and diarrhea and vomiting for subject 48/5003 (MMRV).

Deaths:
No deaths were reported during this trial.

7.1.3.3 Reviewer Summary and Conclusions

Study V59P21 was a trial with objectives to evaluate the safety and immunogenicity of MMRV and MenACWY given concomitantly, and to show that two doses of MenACWY at 7 to 9 and 12 months of age induced adequate antibody responses to each meningococcal serogroup.

Safety: Solicited local and systemic adverse events were generally similar across relevant groups. Similarly, the proportions of subjects reporting fever during the 7-day post-vaccination period were similar across groups. However, since the duration of fever post-MMRV vaccination tends to be longer than 7 days, body temperature and analgesic/antipyretic medication use were collected for 28 days after Visit 3. A limitation of this data is that 10 – 13% of subjects were missing from the diary card data days 5 – 28 post-vaccination; proportions were calculated on the total number of subjects in the safety population, so the true proportions may have been higher. Additional reasons for lower than expected fever rates, given fever data in the ProQuad Package Insert, include recall bias related to reconstruction of safety data, use of axillary temperatures, and non-systematic collection of safety data, with diary cards distributed with varying frequencies across study groups. The applicant should clarify the proportion of safety data which was reconstructed, as well as the method for doing so (e.g., the timepoint at which the reconstruction occurred). While a protocol-specified phonecall was scheduled for 7 days after each vaccination, the applicant does not describe whether safety data may have been reconstructed at that timepoint or whether this reconstruction occurred at the next study visit.

MMRV (MMR+V) concomitant vaccine evaluation: Non-inferiority critieria for co-administration of MenACWY with MMRV were met. The lower limit of the 95% CI for the difference between the proportion of subjects with seroconversion for measles, mumps, and rubella was > -5%, and the difference in the seroprotection rate for varicella was > -10%. The secondary endpoint of non-inferiority of MenACWY + MMRV concomitant administration compared with MMRV administration alone with respect to varicella seroconversion rates was met. Except for antibody response to mumps antigen, post-vaccination GMTs were similar among subjects who received MenACWY + MMRV vs MenACWY + MMR+V. However, the analyses were performed on groups 1-3 as a pooled population rather than within group comparisons of MMRV vs. MMR+V responses. The results from the per protocol and modified-intention-to-treat populations for assessment of MMRV seroconversions rates and proportions of subjects with hSBA

titers ≥ 1:8 post-vaccination with MenACWY were similar. However, due to the allowable blood sampling window defined for the per-protocol population differed from the protocol-specified blood sampling window (Visit 2: 23-55 days vs. 28-42 days; Visit 4: 27-84 days vs. 42-56 days). In this regard, very few participants (range: <1 to 3%) were excluded from the per-protocol population for blood samples obtained outside a pre-specified window.

MenACWY immunogenicity: The per-protocol populations for subjects receiving concomitant MMRV+MenACWY (study group 1) or MenACWY alone at age 12 months was 77% and 76% of the enrolled population, respectively. The large proportion of subjects excluded from the per-protocol population raises a concern regarding how generalizable the results are to the entire study population. Additionally, immunogenicity (inferred effectiveness) of a 2-dose MenACWY series was not assessed with concomitantly administered PCV7. V59P14 results indicated reduced pneumococcal serotype 6B IgG antibody responses following the 3rd dose of PCV7 concomitantly administered with a 3rd MenACWY dose. Thus, MenACWY immunogenicity (inferred effectiveness) would be important to demonstrate in the context of participants who receive concomitant CRM_{197}-based PCV. Since meningococcal hSBA antibody responses in study groups 1 and 2 were measured 6 weeks (range: 27-84 days) post-vaccination, comparisons of immunogenicity (inferred effectiveness) might not be reflective of effectiveness at a different timepoint (e.g. 4 weeks post-vaccination hSBA antibody responses). Please see section 7.1.1.3 for discussion of MenACWY dose preparation.

The reviewer has overall concerns with the ability of study V59P21 safety data to support use of MenACWY in young children. The extent to which safety data were reconstructed and the validity of the data are unknown. Until these issues are resolved satisfactorily, this reviewer cannot make definite conclusions regarding the safety of MenACWY when given as a 2-dose series.

7.1.4 Trial #4: V59P9

7.1.4.1 Title

A Phase 2, Partially Randomized, Open Label, Multicenter Study to Evaluate the Safety and Immunogenicity after One or Two Doses of Chiron Meningococcal ACWY Conjugate Vaccine Administered to Healthy Infants and Young Children.

7.1.4.1.1 Objectives

Primary Objectives:

Immunogenicity

- To assess the immunogenicity of Novartis MenACWY conjugate vaccine (MenACWY) when administered as a two-dose schedule at 6 and 12 months of age, where immunogenicity was defined as serum bactericidal assay using human complement (hSBA) of 1:4 or greater (i.e., the percent response), against serogroups A, C, W, and Y.

Safety

- To evaluate the safety and tolerability of the study vaccine and the concomitant vaccines in all study subjects.

7.1.4.1.2 Design Overview

This Phase 2 study was an open-label, controlled, multicenter, partially randomized study in healthy infants 6 months or 12 months of age conducted in Canada. Approximately 200 subjects (125 exposed) ≥ 6 months of age were randomized 1:1 to Groups 1 and 2, while 50 subjects 12 months old were enrolled/exposed in Group 3. The three study groups are shown in Table 44 below and were:

- Group 1 received two doses of MenACWY at 6 months and 12 months with concomitant routine vaccines including PCV-7 and DTaP-Hib-IPV at 6 months and PCV-7 at 12 months.

- Group 2 received one dose of MenACWY at 12 months with concomitant routine vaccines including PCV-7 and DTaP-Hib-IPV at 6 months and PCV-7 at 12 months.

- Group 3 received one dose of Menjugate C® (Novartis Vaccines and Diagnostics S.R.L.) at 12 months concomitantly with PCV-7 and MenACWY at 18 months concomitantly with recommended Canadian routine immunizations including DTaP-Hib-IPV.

Table 44. V59P9. Study Design

Visit	Group 1: MenACWY 6 mo & 12 mo	Group 2: MenACWY 12 mo		Group 3: MenC 12 mo & MenACWY 18 mo
Visit 1 (6 mo) -	*Serology* **MenACWY** PCV-7 DTaP-Hib-IPV	*Serology* PCV-7 DTaP-Hib-IPV	**Visit 1 (12 mo)**	*Serology* **MenC** PCV-7
Visit 2 (7 mo) -	*Serology*	*Serology*	**Visit 2 (13 mo)**	*Serology* MMR+Varicella
Visit 3 (12 mo) -	*Serology* **MenACWY** PCV-7	*Serology* **MenACWY** PCV-7	**Visit 3 (18 mo)**	*Serology* **MenACWY** DTap-Hib-IPV
Visit 4 (13 mo) -	*Serology* MMR+ Varicella	*Serology* MMR+Varicella	**Visit 4 (19 mo)**	*Serology*

Source: Clinical Study Report V59P9, Table 9.1-1. MenACWY= Menveo®, MenC= Menjugate®

> *Reviewer Comment: Only safety and immunogenicity data from study groups 1 and 2 are included in this review. Menjugate is not currently approved for use in the United States. Therefore, safety and immunogenicity data from study group 3 are not relevant to support Menveo use in children 6-23 months of age.*

Each group had four visits, with the collection of serology at each visit and study vaccination on Visits #1 and #3 only. Diary cards were given to parents/legal guardians to monitor for 7 day post vaccination solicited reactions. For local reactions this included tenderness, erythema, and induration. The severity of erythema and induration were graded as none (0); 1mm-25mm; 26mm to 50mm; and >50mm. For systemic it included

eating habits, sleepiness, vomiting, diarrhea, and irritability. In addition, axillary temperatures were recorded on a daily basis. Axillary temperatures were graded in severity as <38C; 38C to 38.9C; 39C to 39.9C; and >40C. Follow-up telephone calls were made on Day 3 and 8 to assess subject's status.

Unsolicited adverse events were collected for 7 days following each vaccination. Information on serious adverse events (SAEs) and medically attended adverse events (MAAEs), and AEs resulting in early withdrawal of subjects from the study were collected for the entire study period.

> *Reviewer Comment: The applicant did not collect information on "common acute conditions" which included illnesses such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis and traumatic injuries. The decision on what illnesses were common acute conditions was up to individual investigators, and therefore, the type of adverse events collected as MAAEs were likely to have varied between investigators and may have resulted in underreporting of AEs.*

Telephone contact for collection of information on SAEs and MAAEs was made monthly after Visit #2 and six months after the last study vaccination.

Blood for antibody response was collected at each study visit.

7.1.4.1.3 Population

The study enrolled healthy children who were ≥6 months to 12 months old. Individuals were excluded from participation if they had prior receipt of a meningococcal vaccine, or previously ascertained or suspected disease caused by *N. meningitidis*.

7.1.4.1.4 Products mandated by the protocol

Study Vaccine

Menveo (MenACWY): The investigational vaccine was obtained by mixing the lyophilized Men A component (lot number 002011) with the MenCWY full liquid vaccine (lot U79P33D1). The vaccine dosage was 0.5 mL and administration was intramuscular in the anterolateral area of the right thigh (Groups 1 and 2) or in the anterolateral area of the right arm (Group 3).

Comparator Vaccine:

Menjugate (MenC): Manufactured by Novartis Vaccines and Diagnostics S.R.L., this vaccine contained lyophilized Men C component (lot for MenC: UA9477AF) and a saline solvent with aluminum hydroxide. The dosage was 0.5mL administered intramuscular in the arm region.

7.1.4.1.5 Endpoints

Immunogenicity

- Anti-*N-meningitidis* serogroups A, C, W-135, and Y human-SBA GMT
- Percentage of subjects with human SBA of 1:4 or greater and 1:8 or greater.

7.1.4.1.6 Statistical considerations including plan for analysis

Immunogenicity Analysis:

Primary Immunogenicity Measure

- Percentage of subjects with hSBA titers of 1:4 or greater at 1 month after the

second vaccination. The percentage of subjects with hSBA titers of 1:4 or greater and the associated two-sided 95% confidence interval (CI) was computed for each vaccine group within each serogroup.

Safety Analysis:
The statistical analysis of safety was descriptive.

Results

7.1.4.2 Populations enrolled/analyzed

A total of 175 subjects were randomized with 64 subjects in Group 1 (MenACWY at 6 and 12 months); 61 subjects in Group 2 (MenACWY at 12 months); and 50 subjects in Group 3 (Men C at 12 months and MenACWY at 18 months). Approximately 92% of subjects in Groups 1 and 2 (59, and 56, respectively) completed the study, while 84% (42 subjects) in Group 3 completed the study. The reasons for withdrawal for the 18 subjects who did not complete the study included: loss to follow-up (9 subjects), withdrawn consent (6 subjects), inappropriately enrolled (2 subjects), and unable to classify (1 subject).

Demography:
The mean age of subjects was 6.0 months for group 1 and 2 and 12.1 months for Group 3.The ratio of males to female subjects varied by arm: 61% males and 39% females in Group 1, 49% male and 51% females in Group 2, and 58% males and 42% females in Group 3. The majority of subjects in all three groups were Caucasian (78-83%).

7.1.4.2.1 Immunogenicity outcomes

Overall, 19 subjects were excluded from the immunogenicity analysis due to withdrawals as also described above. Another 58 subjects were excluded because of incomplete hSBA test results. Results for the primary endpoint for study groups 1 and 2 are shown in Table 45.

Table 45._V59P9. Primary Immunogenicity Endpoint Results: Number of Subjects (%) with hSBA Titers of ≥1:4 and ≥1:8; and GMT Results for Serogroups A, C, W-135, and Y One Month after last dose, Study groups 1 and 2 (Per-protocol Pop.)

Serogroups (Parameter)	**Group 1: MenACWY 6mo & 12 mo**			**Group 2: MenACWY 12 mo**		
	≥1:4 (%)	**≥1:8 (%)**	**GMT**	**≥1:4 (%)**	**≥1:8 (%)**	**GMT**
A						
% or GMT	88%	84%	44	74%	60%	11
(95%CI)	(76-95)	71-93	(29-65)	(60-85)	(46-74)	(7.55-16)
N	N= 50	50	50	N=53	53	53
C						
% or GMT	100%	100%	302	96%	93%	40
95%CI	(94-100)	(94-100)	(224-405)	(87-100)	(82-98	(30-54)
N	N=55	55	55	N=54	54	54

W **% or GMT** ***95%CI*** ***N***	100% (91-100) N=40	100% (91-100) 40	220 (155-313) 40	95% (83-99) N=41	93% (80-98) N=41	30 (21-43) 41
Y **% or GMT** ***95%CI*** ***N***	100% (93-100) N=53	100% (93-100) 53	136 (100-185) 53	78% (64-88) N=54	67% (53-79) 54	10 (7.68-14) 54

Source: CSR V59P9, Table 11.4.1.1-1, Table 11.4.1.2.1-2, Table 11.4.1.2.1-1

The post-vaccination GMTs for Serogroups A, W, and Y were higher after two doses of MenACWY at 6 and 12 months, compared to either a single dose at 12 months.

7.1.4.2.2 Safety outcomes

The safety populations contained all 175 enrolled subjects (100% of those randomized) who received study vaccination and who had some safety data after vaccination: 64 subjects in Group 1; 61 in Group 2.

Solicited Adverse Events:

Table 46. V59P9. Incidence (%) of Any, Local, and Systemic Reaction after Any Vaccination, Study groups 1 and 2

	Group 1: MenACWY 6 mo & 12mo (N= 64)	Group 2: MenACWY 12 mo (N=61)
Any	62 (97%)	58 (95%)
Local	53 (83%)	49 (80%)
Systemic	59 (92%)	55 (90%)

Source:CSR V59P9, Table 14.3.1.1.2

The incidence of any solicited adverse reaction in study groups 1 and 2 was 95-97% after any injection, local reactions were seen 80-83% of subjects; and systemic were seen 90-92% of subjects. Severe local adverse reactions for tenderness were seen in two subjects in Groups 2; there were no severe adverse reactions for erythema or induration.

For Group 1 subjects exposed to 2 doses of MenACWY, the rates of local reactogenicity were as follows: 39% tenderness, 52% erythema, and 45% induration. These rates in Group 1 were similar to that seen after DTaP-Hib-IPV injections. Yet, the local reactogenicity seen after Prevnar-7 injections in this group were higher, with 50% tenderness, 61% erythema, and 48% induration.

The rates of systemic reactions after any vaccination are described in Table 47.

Table 47. V59P9. Incidence (%) of Systemic Reactogenicity after Any Vaccination, Study Groups 1 and 2

	Group 1: MenACWY 6mo & 12mo (N= 64)	Group 2: MenACWY 12mo(N=61)
Change Eating Habits	28 (45%) N=62	21 (35%) N=60

Sleepiness	35 (55%) N=64	32 (52%) N=61
Irritability	57 (89%) N=64	45 (74%) N=61
Vomiting	9 (14%) N=64	11 (18%) N=61
Diarrhea	12 (19%) N=64	18 (30%) N=61
Fever Any ≥38.0C	6 (9%) N=64	12 (20%) N=61
Fever Severe>40.0C	0 N=64	1 (2%) N=61

Source: V59P9 CSR Table 14.3.1.1.3.2

Irritability was seen in 89% of subjects in Group 1 compared to 74 of subjects in Group 2. Diarrhea was more commonly reported in Group 2 (30%) compared to 19 of subjects in Group 1. Fever (≥38.0C) was less common in Group 1 (9%) compared to Group 2 (20%); severe fever was uncommonly reported in the two study groups.

Unsolicited Adverse Events:
At least one AE was experienced by 48% of subjects in Groups 1 and 2. The most frequently reported AE was nasopharyngitis (8-9% of subjects across groups). Other frequently experienced adverse events include pyrexia (2-8%); irritability and vomiting (2-6%); constipation (2-5%); upper respiratory tract infection (2-5%); eating disorder (2-5%); and cough (0-5%).

Serious Adverse Events:
Seven subjects who experienced 9 SAEs (three subjects in Group 1; two subjects in Group 2; and two subjects in Group 3). The majority these SAEs (5 SAEs) were classified under the System Organ Class preferred term of Infections/Infestations, while two were reported as Respiratory/ Thoracic/Mediastinal Disorders, and one was reported as Nervous System Disorders. The only serious adverse events reported within 14 days of vaccine administration was an exacerbation of asthma 10 days after receipt MenC and Prevnar 7 in a subject in Group 3. None of these events were deemed related to study vaccination by the investigator.

No subjects were withdrawn from the study due to an adverse event. There were no deaths reported during the course of the study.

> *Reviewer Comment: There were no serious adverse events that were judged as vaccine related by the study investigators. This reviewer agrees that it is unlikely that any of these SAEs were related to study vaccine.*

7.1.4.3 Comments & Conclusions

This is a phase 2 safety and immunogenicity study to support a 2-dose MenACWY series given at 6 and 23 months of age. The percentage of subjects who achieved a hSBA titer >1:8 was 84% for serogroup A and 100% for serogroups C,Y and W-135. No new safety signals were noted in this study. Tenderness at the injection site was reported in more than 90% of subjects and irritability was reported in 74% or more of subjects. Unsolicited adverse events were consistent with commonly observed childhood illnesses. No serious adverse events were considered by this reviewer to be

related to vaccination.

7.1.5 Trial #5: V59P5

7.1.5.1 Title

A Phase II, Randomized, Open label, Controlled, Multicenter Study to Evaluate the Safety, Immunogenicity, and Induction of Immunological Memory after Two or Three Doses of Meningococcal ACWY Conjugate Vaccine (MenACWY) to Healthy Infants at 2, 3, 4, and 6 months of age.

7.1.5.1.1 Objectives

Primary Objectives:

Immunogenicity

- To assess the immunogenicity of three doses of Novartis MenACWY with --(b)(4)-- Conjugate Vaccine (MenACWY(b)(4)) given at 2, 3, and 4 months of age or at 2, 4, and 6 months of age, as measured by the percentage of subjects with hSBA ≥1:4, against *N meningitides* serogroups A,C,W, and Y.

Safety

- To evaluate the safety and tolerability of MenACWY(b)(4) when given concomitantly with other licensed pediatric vaccines at 2, 3, and 4 months of age or at 2, 4, and 6 months of age;
- To evaluate the safety and tolerability of MenACWY ---------(b)(4)------- (MenACWY) when given concomitantly with other licensed pediatric vaccines at 2 and 4 months of age;
- To evaluate the safety and tolerability of MenACWY(b)(4) and MenACWY when given concomitantly

Secondary immunogenicity objectives included assessment of the immunogenicity of 2 doses of MenACWY (the currently licensed formulation) as measured by hSBA≥1:4, hSBA ≥1:8, and hSBA GMT directed against the four *N.meningitidis* serogroups when compared to MenACWY(b)(4). In addition, persistence of antibodies was assessed at 12 months of age in subjects who received 2 doses of MenACWY as measured by hSBA≥1:4 and hSBA ≥1:8, and hSBA GMT against these four serotypes. Finally, the immunogenicity of routine vaccines was assessed when given concomitantly with study vaccines.

7.1.5.1.2 Design Overview

This is a Phase II, open-label study to evaluate the immunogenicity and safety of MenACWY --------(b)(4)----------. The study was conducted in the UK and Canada. Routine childhood vaccinations were given as recommended in each country.

Table 48. V59P5. Study Design

	Group:Vaccine (Schedule)	Booster Vaccine at 12 months
UK	1:MenACWY(b)(4) (2,3,4 mo) N=90	MenACWY(b)(4) N= 90
	2: MenACWY(b)(4) (2,4 mo) N=90	MenACWY(b)(4) N=90
	3: Menjugate (2,4 mo) N=45	MenACWY(b)(4) N=45
	6: MenACWY (2,4 mo) N=90	MenACWY N=90
Canada	4: MenACWY (b)(4) (2,4,6 mo) N=90	PS N=45
	5: MenACWY(b)(4) (2,4 mo) N= 90	MenACWY(b)(4) N=45

		PS	N=45
	7: MenACWY (2,4 mo) N= 90	MenACWY	N=45
		PS	N=45

Source: V59P5 CSR, Table 9.1.1-1. 'MenACWY'= Menveo®, 'MenACWY(b)(4) = MenACWY ----(b)(4)----------, 'MenC'= Menjugate®, 'PS'= Menomune® US-licensed meningococcal polysaccharide vaccine.

In the UK subjects were randomized to receive either MenACWY (b)(4), MenACWY, or Menjugate® conjugate C vaccine (MenC) on a 2, 3, 4 month schedule or 2, 4 month schedule with re-randomization at 12 months of age to receive either a booster dose of MenACWY(b)(4) or MenACWY. In Canada subjects were randomized to receive MenACWY ----------(b)(4)-------- at 2 and 4 months with subsequent re-randomization to receive a booster dose of MenACWY(b)(4), a reduced (1/5th) dose of Menomune® [a US-licensed meningococcal polysaccharide vaccine (PS)], or MenACWY.

> *Reviewer Comment: The CSR included only the results for the ---(b)(4)----- Menveo formulation from the second phase of the study. Since this formulation is the formulation currently marketed in the U.S., this is the only information relevant to evaluation of the safety and immunogenicity of Menveo in children 6 months of age and older.*

Diary cards were given to parents/legal guardians to monitor for solicited adverse reactions during the seven days post-vaccination. Local solicited adverse reactions to the study vaccines were followed and included tenderness, erythema, and induration. The size of erythema and induration reactions were graded as none (0), 1 mm-25 mm, 26 mm to 50 mm, and >50 mm. Systemic solicited adverse reactions followed included sleepiness, vomiting, diarrhea, irritability, change in eating habits and persistent crying. In addition, axillary temperatures were recorded on a daily basis. Temperature was graded as <38C, 38C to 38.9C, 39C to 39.9C, and >40C. Follow-up telephone calls were made on Day 3 and 8 to assess subject's status.

Unsolicited adverse events were collected for 7 days following each vaccination. Information on serious adverse events (SAEs), medically attended adverse events (MAAEs), and AEs resulting in early withdrawal of subjects from the study was collected for the entire study period.

> *Reviewer Comment: MAAEs that were considered 'common acute conditions' did not have to be reported. However, the determination of whether a sign or symptom was an adverse event or a "common acute condition" was subjective and may have varied by investigator.*

Serology was obtained one month after the completion of the primary 3 dose series for MenACWY(b)(4) (Group 1 in the UK, and Group 4 in Canada), one month after the 2 dose series and the booster doses, at12 months of age serum in all groups, and 28 days after the booster dose on Visit 5.

7.1.5.1.3 Population

The study enrolled healthy 2 month old infants who met the inclusion and exclusion criteria. Subjects were not enrolled if they had prior vaccination with any meningococcal vaccine, DTP, IPV/OPV, HBV, Hib, or pneumococcal vaccine, or if they had prior infections with any of pathogens associated with these vaccines.

7.1.5.1.4 Products mandated by the protocol

Study Vaccine

Menveo® (MenACWY): The investigational vaccine was obtained by mixing the lyophilized Men A component (lot 563001011 for UK and Canada) with the MenACWY full liquid vaccine (lot U79P27D1 for UK and lot U79P27D1A for Canada). The vaccine dosage was 0.5 mL of injectable solution.

Menveo ---(b)(4)------ (MenACWY(b)(4)): The investigational vaccine was obtained by mixing the lyophilized Men A component (lot number 563001011 for UK and Canada) with the MenACWY full liquid vaccine (lot U79P27D1A for UK and lot U79P27D1 for Canada). ----------(b)(4)----------. The vaccine dosage was 0.5 mL of injectable solution.

Menomune ® MenACWY polysaccharide (PS): This US-licensed meningococcal capsular polysaccharide serogroups A, C, Y, W-135 vaccine is manufactured by Aventis Pasteur. After reconstitution the dosage was 0.5 mL of injectable solution.

Comparator Vaccine:

Menjugate® (MenC): Vaccine composition is described in section 7.1.4.1.4.

7.1.5.1.5 Endpoints

Immunogenicity

- The primary endpoint was the percentage of subjects in the -----(b)(4)----- group with hSBA titer ≥1:4 to the four vaccine antigens.

Safety

Safety endpoints were solicited adverse reactions, unsolicited reactions, medically attended AEs, SAEs, and AEs leading to premature study discontinuation.

7.1.5.1.6 Statistical considerations including plan for analysis

This study was open label; therefore both the study personnel and the parents/legal guardians knew which vaccines were administered.

Study Populations

The primary population for evaluation of immunogenicity was the Per Protocol population, which included all subjects who received all relevant doses of vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violations.

The primary population for evaluation of safety included all subjects who had at least one vaccination and any post-baseline safety data.

Immunogenicity Analysis:

Primary Immunogenicity Null Hypotheses:

For at least one serogroup the lower limit of the two-sided 95% confidence interval (CI) of the underlying percentages of subjects with hSBA titer >1:4 at 1 month after the 3rd dose was less than 70%.

Safety Analysis:

The statistical analysis of safety was descriptive.

7.1.5.2 Results

Study Period

The first subject was enrolled on September 1, 2004 and the last subject completed the study on October 2, 2006.

7.1.5.2.1 Populations enrolled/analyzed

A total of 601 subjects were randomized into seven groups: 315 subjects randomized in the UK and 286 in Canada. Of the 601 subjects, 559 (93%) completed the study. The percentage of subjects completing the study varied, ranging from 88% in Group 1 to 100% in Group 3.

The most commonly reported reasons for premature study withdrawal of the 42 subjects were protocol deviations (17 subjects); consent withdrawal (13 subjects); lost to follow-up (5 subjects); and premature withdrawal due to an AE in the study (4 subjects).

Demography:

The mean age of subjects was 64.6 days and was similar across all groups. There was an almost equal number of males and females in the study. The majority of subjects were Caucasian (94% in the UK and 74% in Canada), with more Asian and 'other' ethnicities in Canada (12% each) compared to the UK (2% and 3%, respectively).

7.1.5.2.2 Immunogenicity outcomes

The primary objective evaluated 3 doses of MenACWY(b)(4) vaccine at 2, 3, and 4 months or at 2, 4, and 6 months as measured by the percentage of subjects with hSBA titers ≥1:4 against each of these 4 serogroups. In this study, antibody response (hSBA titers ≥1:4 and ≥1:8, and the GMTs) after vaccination with -----(b)(4)------ MenACWY was compared to that after ------(b)(4)------ with vaccine given as a two dose series at 2 and 4 months, and with a 12 month booster dose. The results are shown in Table 49.

Please note that the results provided in Table 49 are for the time point, one month post completion of vaccination primary series or booster dose.

Table 49. V59P5. Secondary Immunogenicity Objective Results: Percentage of Subjects with hSBA titers ≥1:4 and ≥1:8, and GMTs of *MenACWY* ----------*(b)(4)*---------- One Month after 2-dose Primary Series and *with 12 mo Booster*

Sero-group		Group 2 (UK) *MenACWY* (b)(4) Primary Series: 2mo & 4mo and *with 12mo Booster (MenACWY* (b)(4)*)*			Group 5 (Canada) *MenACWY*(b)(4) Primary Series: 2mo & 4mo and *with 12mo Booster (MenACWY* (b)(4)*)*			Group 6 (UK) *MenACWY* Primary Series: 2mo & 4mo and *with 12mo Booster (MenACWY)*			Group 7 (Canada) *MenACWY* Primary Series: 2mo & 4mo and *with 12mo Booster (MenACWY)*		
	Immune Parameters	≥1:4 (%)	≥1:8 (%)	GMT	≥1:4 (%)	≥1:8 (%)	GMT	≥1:4 (%)	≥1:8 (%)	GMT	≥1:4 (%)	≥1:8 (%)	GMT
A	Primary Series % or GMT 95%CI N	60% 48-72 68	54% 42-67 68	12 8.36-16 68	66% 54-76 79	58% 47-69 79	11 7.71-14 79	50% 38-62 78	44% 32-55 78	7.3 5.31-10 78	57% 45-67 83	49% 38-61 83	7.2 5.26-9.79 83
	with Booster % or GMT 95%CI N	*86% 75-93 64*	*83% 71-91 39*	*47 31-72 64*	*92% 79-98 39*	*90% 76-97 39*	*67 43-106 39*	*79% 66-88 61*	*77% 65-87 61*	*30 19-47 61*	*95% 82-99 38*	*92% 79-98 38*	*59 38-93 38*
C	Primary Series % or GMT 95%CI N	84% 74-92 77	83% 73-91 77	52 36-75 77	91% 81-96 74	85% 75-92 74	53 37-75 74	86% 76-93 79	82% 72-90 79	40 28-57 79	93% 85-97 85	89% 81-95 85	69 50-95 85
	with Booster % or GMT 95%CI N	*96% 87-99 57*	*96% 87-99 67*	*236 159-349 67*	*98% 87-100 40*	*95% 83-99 40*	*216 130-356 40*	*94% 85-98 40*	*94% 85-98 63*	*129 86-194 63*	*100% 91-100 40*	*100% 91-100 40*	*258 156-426 40*
W	Primary Series % or GMT 95%CI N	92% 83-97 73	84% 73-91 73	48 34-68 73	91% 81-96 74	85% 75-92 74	42 31-58 74	82% 71-90 72	75% 63-84 72	29 20-41 72	95% 87-99 75	92% 83-97 75	70 51-96 75
	with Booster % or GMT 95%CI N	*100% 94-100 57*	*100 94-100 57*	*503 347-732 57*	*100% 90-100 35*	*100% 90-100 35*	*381 224-650 35*	*100% 91-100 41*	*100% 91-100 41*	*311 200-485 41*	*100% 90-100 35*	*100% 90-100 35*	*402 236-684 35*
Y	Primary Series % or GMT 95%CI N	84% 74-92 76	76% 65-85 76	26 19-37 76	86% 77-93 74	80% 69-88 74	26 19-36 74	74% 63-83 77	70% 59-80 77	21 15-29 77	91% 82-96 85	86% 77-92 85	41 30-55 85
	with Booster % or GMT 95%CI N	*100% 95-100 66*	*100% 95-100 66*	*508 358-723 66*	*100% 91-100 40*	*100% 91-100 40*	*308 191-499 40*	*100% 94-100 63*	*100% 94-100 63*	*438 305-628 63*	*100% 91-100 38*	*100% 91-100 38*	*527 322-862 38*

Source: V59P5 CSR, Table 11.4.1.2.2-1; Table 11.4.1.2.3-1; Table 11.4.1.2.3-2

After completing the 3-dose series, 81-93% of subjects met this endpoint for Serogroup A; 96-98% for Serogroup C; 97-99% of subjects for Serogroup W; and 94-98% of subjects for Serogroup Y. Of note, hSBA titers ≥1:4 and ≥1:8, and the GMT values are generally low for Serogroup A compared to Serogroups C, W, and Y.

Reviewer Comment:

1. *Based on the immune parameters used to assess the study vaccines as a 2-dose primary series or as a 2-dose primary series with a booster dose; the --(b)(4)--- formulation does not appear to have a clear advantage over the final formulation. The GMT values for Serogroup A though low for both formulations, appear to be slightly higher for the --(b)(4)--- groups.*
2. *When the results for the two dose series are compared, the antibody response varied by country. For the --(b)(4)--- formulation, there appears to be a better GMT immune response in the UK. But for the final formulation -----(b)(4)-------, there appears to be a better GMT immune response in Canada.*
3. *Overall, the --(b)(4)--- did not appear to provide added immunologic value compared to -----(b)(4)---- MenACWY formulation, which is the currently marketed formulation.*

7.1.5.2.3 Safety outcomes

The safety dataset included all 601 subjects who were enrolled.

Solicited Adverse Events:

After the primary series vaccination, 97-98% of subjects across all 7 groups experienced at least one local, systemic or other sign of reactogenicity. The most common local solicited adverse reaction in the primary series was erythema with 71-83% of subjects experiencing this compared to 76% in the MenC arm. This was followed by tenderness (MenACWY=33-47% vs 40% in the MenC arm), and then induration (MenACWY 18-44% vs 13% in the MenC arm). The most common systemic solicited adverse reaction across all 7 groups was irritability, seen in 68-85% of MenACWY subjects compared to 69% in the MenC arm.

The percentage of subjects reporting individual solicited adverse reactions is shown in Table 50 after receiving a 2-dose primary series with MenACWY ----(b)(4)-------- as compared to subjects who received MenACWY ----(b)(4)-------.

Table 50. V59P5. Number and Percentage of Subjects with Individual Local and Systemic Adverse Reaction after Any Vaccination in Subjects who Received a Two Dose Series

	Group 2 (UK) ***MenACWY (b)(4)*** **2mo & 4mo N=90**	**Group 5 (Canada)** ***MenACWY(b)(4)*** **2mo & 4mo N=98**	**Group 6 (UK)** ***MenACWY*** **2mo & 4mo N=90**	**Group 7 (Canada)** ***MenACWY*** **2mo & 4mo N=90**
Local:				
-Tenderness	31 (34%)	32 (33%)	41 (46%)	35 (39%)
-Erythema	64 (71%)	67 (68%)	78 (87%)	66 (73%)

-Induration	24 (27%)	18 (18%)	40 (44%)	24 (27%)
Systemic:				
-Eating Habit	25 (28%)	27 (28%)	21 (23%)	20 (22%)
-Sleepiness	49 (54%)	62 (63%)	45 (50%)	52 (58%)
-Persistent Crying	7 (8%)	4(4%)	5 (6%)	4 (4%)
-Irritability	71 (79%)	70(71%)	61 (68%)	73 (81%)
-Vomiting	26 (29%)	15(15%)	14 (15%)	11 (12%)
-Diarrhea	27 (30%)	22 (22%)	18 (20%)	16 (18%)
-Fever (≥38C)	4 (4)	7 (7%)	5 (6%)	5 (6%)
-Fever (≥40C)	0	0	0	0
-Anal/Antipyr	35 (39%)	46 (47%)	36 (40%)	45 (50%)

Source: V59P9 CSR Table 12.2.3.1.2-1

Reviewer Comment: There does not appear to be a clear difference in local and systemic solicited reactogenicity between those subjects exposed to MenACWY (b)(4) compared to those exposed to MenACWY final formulation

Unsolicited Adverse Events:

At least 79-90% of subjects in all groups reported an adverse event in the seven days post-vaccination. In the two dose series groups for MenACWY ------(b)(4)----- (Groups 2 & 5), 87-90% of subjects experienced at least one adverse event, compared to 79-82% of subjects in the MenACWY ---------(b)(4)----- groups (Groups 6 & 7). The most frequently reported adverse event was rhinitis, seen in 20% of subjects, followed by upper respiratory tract infection (16%), diarrhea (12%), irritability (11%), and eczema (11%). In the 2-dose series, there were 17 AEs rated as severe in the -------(b)(4)-------- formulation groups, while there were 12 AEs in the final formulation groups.

Serious Adverse Events:

Across all groups there were 73 subjects who experienced a serious adverse event (SAE). In the 2-dose series there were 17 SAEs in those subjects exposed to MenACWY and 21 SAEs in those subjects exposed to MenACWY(b)(4). The most frequently reported SAEs were bronchiolitis (15 cases) and viral infection (8 cases); other SAEs included 3 cases of lower respiratory tract infections, 2 cases of pneumonia, 3 cases of febrile convulsions, and one SAE each of convulsion, petechiae, of erythema multiforme, idiopathic thrombocytopenic purpura (ITP), and supraventricular tachycardia (SVT). Of the SAEs, only ITP and SVT were judged as related to the study vaccine. A summary of each SAE is provided below:

The ITP case (Subject# 01062) occurred in a one year male in the UK seven days after receiving the booster dose (12 month dose) of the 3-dose series of MenACWY(b)(4). He was symptomatic with a platelet count of 6 x 10^9/L and required hospitalization. His past medical history was significant for a viral illness 20 days prior to diagnosis. Upon follow-up the child had recovered completely. The investigator assessed the ITP event as possibly related to vaccination based on temporal association and the subject was withdrawn from the study.

The SVT case occurred (Subject# 01149) in a male subject in the UK 2-dose MenACWY(b)(4) group who had previously been diagnosed with SVT at 19 days

of life. This subject experienced two episodes of SVT during the study: the first episode was 36 days after the first dose of MenACWY***(b)(4)***; and the second episode was 6 hours after the 2nd dose of MenACWY***(b)(4)***. The first episode was associated with diarrhea/vomiting inability to tolerate his oral anti-arrhythmic medication. Since this episode was not judged as related to study vaccine, the subject remained in the study. Six hours after receiving the second dose of MenACWY***(b)(4)***, SVT episode again occurred and required hospitalization and vagal manuever treatment. The subject was withdrawn from the study after the second episode SVT episode as it was considered serious and related to vaccination.

Study Withdrawals/Deaths:
The adverse events associated with these withdrawals included convulsion; idiopathic thrombocytopenic purpura; supraventricular tachycardia; large local reaction on right leg after MenACWY vaccination; and developmental delay.

There were five subjects removed from the study due to adverse events. This included the two subjects with SAEs of ITP and SVT events and three additional subjects. All three subjects were in the MenACWY***(b)(4)*** group. One was diagnosed with developmental delay (delayed walking) 2 weeks after receiving booster dose of MenACWY***(b)(4)*** at 12 months, one had a large local reaction (tenderness/ erythema) observed 15 minutes after the third vaccination with MenACWY***(b)(4)*** vaccination, and one with a febrile convulsion. The episode of SVT and the local reaction were judged as vaccine related. There were no deaths reported during the study period across all 7 groups.

Reviewer Comment:

1. *While the subject with SVT had the condition prior to study vaccination, there was a strong temporal relationship between the second study vaccination and an episode of SVT in this subject. It is difficult to rule out any causal relationship between vaccination and the recurrence of SVT.*
2. *The ITP serious adverse was judged as possibly related to study vaccination, and in the opinion of the reviewer, vaccine causality cannot be ruled out because of the biological plausibility of an autoimmune event after an ---(b)(4)---- vaccine and the temporal association.*
3. *In addition, the local reaction was clearly related to study vaccine.*
4. *No narrative was provided for the study withdrawal of Subject #01050 for the convulsion AE that persisted; therefore no conclusion about causality can be made.*

Overall, three serious adverse events or AEs resulting in premature study discontinuation were possibly related to study vaccination. However, the types of AEs were all associated with the ---(b)(4)---- formulation, which is no longer being clinically developed.

7.1.5.3 Comments & Conclusions

Safety and immunogenicity results from this study support the selected -------(b)(4)-------- vaccine formulation for phase 3 studies.

7.1.6 Trial #6: V59P7

7.1.6.1 Title

A Phase 2 Randomized, Observer Blind, Multi-Center, Active Controlled Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Children Aged 12 to 59 Months

7.1.6.1.1 Objective/Rationale

Primary Objectives:

Immunogenicity:

- To compare the immune response 28 days after administration of one dose of MenACWY with that of Mencevax® (MenACWY PS) *in subjects 36 to <60 months old*, as measured by the percentage of subjects with human complement (hSBA) of ≥1:4 against serogroups *N meningitides* serogroups A, C, W, and Y.

Safety

- To evaluate the safety and tolerability of MenACWY (b)(4) or MenACWY or MenACWY PS when administered to healthy children *12 to < 60 months old*.

  Reviewer Comment: The primary immunogenicity objective was evaluated only in children 36-60 months old, while the secondary immunogenicity objectives evaluated immune responses in the 12-35 month age groups

7.1.6.1.2 Design Overview

This Phase 2 study was designed to evaluate the safety and immunogenicity of MenACWY versus MenACWY-PS when given to older children (36 to < 60 months of age, N=200) and of MenACWY alone compared to MenACWY ---(b)(4)----- when given to younger children (12-<36 months of age, N=400). It was controlled, randomized, observer blind study conducted at 2 centers in Poland and 1 center in Finland that enrolled 600 healthy children from 12 months to <60 months of age. Treatment arms are shown in the table below.

Table 51. V59P7. Study Design

V59P7 Study Design		GROUP #1			GROUP #2			GROUP #3		GROUP #4	
		Toddler			Toddler			Children		Children	
Visits		12 Months - 35 Months			12 Months - 35 Months			36 - 59 Months		36 - 59 Months	
Visit 1	Day 1	Serology			Serology			Serology		Serology	
		MenACWY (b)(4) N=207			MenACWY N=206			MenACWY N=128		MenACWY PS N=82	
Visit 2	Day 29	Serology			Serology			Serology		Serology	
		Men ACWY(b)(4) N=68			Men ACWY N=68						
Visit 3	Day 50	Serology			Serology						
	Day 169		Serology Men ACWY(b)4 N=69			Serology Men ACWY N=68		Serology Men ACWY N=63		Serology Men ACWY N=40	
	Day 337			Serology Men ACWY(b)4 N=70			Serology Men ACWY N=70		Serology Men ACWY N=40		Serology Men ACWY N=42
Visit 4	Day 190		Serology			Serology		Serology		Serology	
	Day 358	Serology		Serology	Serology		Serology		Serology		Serology

Source: CSR V59P7; Table 9.1-1. 'MenACWY'= Menveo®, 'MenACWY(b)(4)' = MenACWY ----(b)(4)------, 'MenACWY-PS' = Mencevax® polysaccharide vaccine

As shown in Table 51, each toddler group was further divided into 3 subsets of 68-70 subjects each as follows:

- 1st subset received a 2nd dose of the same vaccine at Visit 2 (Day 29)
- 2nd subset received a 2nd dose of the same vaccine 6 months later at Visit 3 (Day 169)
- 3rd subset received a 2nd dose of the same vaccine 12 months later at Visit 3 (Day 337)

Study subjects 36-60 months of age were randomized to receive a single dose of MenACWY or of Mencevax polysaccharide vaccine (MenACWY-PS) on Visit 1 (Day 1). Although MenACWY-PS is licensed for subcutaneous administration; all vaccines were administered intramuscularly to maintain the blind in the study.

> *Reviewer Comment: The results for the age group 36-60 months of age were reviewed in* STN 125300.*95 (s*BLA for Menveo use in children 2-10 year of age). *Therefore, only the results for children <36 months are presented in this review.*

After each vaccination, subjects were observed for 30 minutes post-vaccination. Diary cards were given to parents/legal guardians to monitor for 7 day post vaccination solicited reactions. Local solicited adverse reactions followed included tenderness, erythema, and induration. Erythema and induration were graded in severity as none (0); 1mm-25mm; 26mm to 50mm; and >50mm. Systemic solicited adverse reactions followed included eating habits, sleepiness, vomiting, diarrhea, and irritability. In addition, axillary or rectal temperatures were recorded on a daily basis for these 7 days.

The severity of temperature was categorized as <38C; 38C to 38.9C; 39C to 39.9C; and >40C.

Unsolicited adverse events were collected for 7 days following each vaccination. Serious Adverse Events (SAEs), medically attended adverse events (MAAEs), and AEs resulting in premature study discontinuation were collected for the entire study (6 months after the last study vaccination).

Follow-up telephone calls to collect safety information were made on Days 3 and 8 and 6 months after the last study vaccination.

Blood for antibody titers was obtained pre- and post-vaccination for each subject as shown in Table A.

7.1.6.1.3 Population

Subjects who met the inclusion and exclusion criteria were eligible for enrollment. The study enrolled healthy subjects 12 months to <60 months old. Subjects were not enrolled if they had prior receipt of a meningococcal vaccine, or previously ascertained or suspected disease caused by *N. meningitidis*.

7.1.6.1.4 Products mandated by the protocol

Study Vaccine

Menveo® (MenACWY): The investigational vaccine was obtained by mixing the lyophilized MenA component (lot number 002011) with the MenCWY full liquid vaccine (lot U79P33D1). The vaccine dosage was 0.5 mL of injectable solution.

Menveo® ---(b)(4)------- (MenACWY(b)(4)): ----------(b)(4)---------- to the MenCWY full liquid vaccine (lot U79B32D1). The vaccine dosage was also 0.5 mL of injectable solution.

Mencevax ® MenACWY polysaccharide (MenACWY-PS): This meningococcal capsular polysaccharide with serogroups A, C, Y, W-135 vaccine is manufactured by GSK. After reconstitution the dosage is 0.5 mL of injectable solution.

Reviewer Comment: MenACWY-PS is not approved for use in the United States.

7.1.6.1.5 Endpoints

Immunogenicity

- Percentage of subjects with hSBA titer ≥1:4 and ≥1:8 or greater, for each serogroup

Safety

Safety endpoints included solicited adverse reactions and unsolicited adverse events collected for the seven days post-vaccination and medically attended adverse events, serious adverse events, and AEs leading to premature study withdrawal for the entire study period.

7.1.6.1.6 Statistical considerations including plan for analysis

Study Populations:

The primary population for analysis of immunogenicity was the Per Protocol population which included all subjects who received at least one dose of study vaccine, had at least one evaluable serum sample pre- and post-vaccination, and who had no major protocol violations.

The primary population for analysis of safety was the Safety Population, which included all subjects who had at least 1 vaccination and any post-baseline safety data.

Immunogenicity Analysis:

- The primary immunogenicity endpoint was the percentage of subjects with hSBA titers ≥1:4 and ≥1:8 for each serotype at 28 days after vaccination.

- Other secondary endpoints included the percentage of subjects with hSBA titers ≥1:4, ≥1:8, and hSBA GMTs after the second vaccination, antibody responses 6 or 12 months after vaccination for subjects with and without a booster dose..

Safety Analysis:

The statistical analysis of safety was descriptive.

7.1.6.2 Results

Study Period

The first subject was enrolled on March 14, 2005 and the last subject completed the study on May 16, 2006.

7.1.6.2.1 Populations enrolled/analyzed

Across all groups 623 subjects were enrolled into the study. Of these, 413 toddlers from the age of 12 months to <36 months of age were randomized to MenACWY (206) or MenACWY(b)(4) (207). Approximately 411 toddlers were vaccinated with the first vaccine, 401 toddlers were vaccinated with the 2nd vaccination, while 394 toddlers completed the protocol. The reasons for study withdrawal included withdrawn consent (6); withdrawals due to AEs (4); withdrawals due to reasons that were unable to be classified (3); protocol deviations (2); lost to follow-up (2) and inappropriate enrollment (1); and maternal refusal to blood sampling (1).

Demography:

The mean age of subjects was 24.1 months in the Toddler MenACWY(b)(4) Group and 23.7 in the Toddler MenACWY Group. There were 46-48% males and 52-54% females across all 4 groups. The majority of the subjects were Caucasian (99-100%).

> *Reviewer Comment: The racial distribution in this study does not represent the racial distribution found in the US population.*

7.1.6.2.2 Immunogenicity outcomes

Table 52. V59P5. Percentage of Toddler Subjects with hSBA titers ≥1:8 Post 1-dose*

Serogroup	#1: Toddler 12-35m MenACWY(b)(4) %≥1:8 (95%CI) N=200	#2: Toddler 12-35m MenACWY %≥1:8 (95%CI) N=191
A	72% (65-78)	61% (53-68)
C	47% (40-54)	36% (29-44)
W-135	72% (65-78)	69% (62-76)
Y	60% (53-67)	57% (50-64)

Source: V59P7 CSR Table 11.4.1.3-2. * 4 weeks after 1-dose

The following table depicts the percentage of subjects in Groups 1 and 2 with hSBA titer ≥1:8, twenty-one days after a 6 month or 12 month booster.

Table 53. V59P5. Percentage of Toddler Subjects with hSBA titers≥1:8 Post Booster Dose of Same Vaccine

Serogroup	#1: MenACWY(b)(4) Toddler 12-35m *6 month Booster* %≥1:8 (95%CI) N=57	#1: MenACWY(b)(4) Toddler 12-35m *12 month booster* %≥1:8 (95%CI) N=56	#2: MenACWY Toddler 12-35m *6 month Booster* %≥1:8 (95%CI) N=56	#2: MenACWY Toddler 12-35m *12 month booster* %≥1:8 (95%CI) N=54
A	100% (94-100)	100% (94-100)	91% (80-97)	96% (87-100)
C	100% (94-100)	98% (90-100)	100% (94-100)	96% (87-100)
W-135	100% (94-100)	98% (90-100)	100% (94-100)	100% (93-100)
Y	100% (94-100)	100% (94-100)	100% (94-100)	100% (93-100)

Source: CSR V59P7 Table 11.4.1.3-2 and Addendum to CSR V59P7 Table 11.4.1.3-2

> *Reviewer Comment: The booster dose of the same vaccine at either 6 or 12 month results in comparable immune responses for the MenACWY(b)(4) and MenACWY groups.*

7.1.6.2.3 Safety outcomes

The safety population included 411 subjects 12-35 months of age who received the first study vaccination and had follow-up safety data and 401 subjects who received two study vaccinations.

Solicited Adverse Events:

Overall 68-74% of all subjects across the study experienced at least one local or systemic solicited adverse reaction in the seven days post-vaccination. As demonstrated in Table 54 below, 62% of toddler subjects exposed to 1 dose of MenACWY had at least one solicited adverse reaction, as compared to 56% of toddler subjects exposed to 1 dose of MenACWY(b)(4). The rates of subjects with solicited adverse reactions were 49%

in the ---(b)(4)------ group and 51% in the ----(b)(4)------ group after the second study vaccination.

Table 54. V59P5. Incidence (%) of Any, Local, and Systemic Reaction for the 7 days Post Vaccination in Toddlers

	Toddlers 12-35 Months			
	1st Vaccination		2nd Vaccination	
	#1: MenACWY (b)(4) N=205	#2: MenACWY N=206	#1: MenACWY(b)(4) N=200	#2: MenACWY N=201
Any	115 (56%)	127 (62%)	98 (49%)	103 (51%)
Local	78 (38%)	90 (44%)	75 (38%)	70 (35%)
Systemic	63 (31%)	78 (38%)	62 (31%)	61 (30%)

Source: V59P7 Table 12.2.3-1

Overall, 35% of subjects in the ----(b)(4)--------- arm and 44% in the ----(b)(4)------- arm experienced a local solicited adverse reaction. The most commonly reported local solicited adverse reaction was tenderness at the injection site, seen in 24% and 29% of subjects after the first dose of MenACWY(b)(4) or MenACWY, respectively and in similar percentages of subjects after the second dose. Erythema was reported in 17%-22% of toddler subjects after either the first and/or the second dose, while induration was reported in 10-13% of subjects.

Overall 30-38% of toddler subjects experienced a systemic solicited adverse reaction. The most frequently reported systemic solicited adverse reaction reactions in MenACWY exposed toddlers (1 or 2 doses) were irritability (20-25%); sleepiness (9-17%); and change in eating habits (11-16%). Fever was seen in 3-8% of MenACWY exposed toddlers after 1 or 2 doses. The percentage of subjects with individual systemic solicited adverse reactions was similar in the ----(b)(4)------ arm.

Reviewer Comment:
Across both toddler groups and after 1 or 2 doses, there does not appear to be a substantial difference in the rates of systemic or local reactogenicity.

Unsolicited Adverse Events:
Unsolicited adverse events were reported in 48% of subjects in the MenACWY group and in 57% in the MenACWY(b)(4) group The most frequently reported MedDRA System Organ Class (SOC) in which unsolicited adverse events were reported were infections and infestations (35-42%); the respiratory, thoracic and mediastinal disorders (3-15%); and general disorders and administration site conditions (5-11%); The most frequently reported unsolicited adverse event was upper respiratory infection, seen in 9% of subjects in both toddler groups.. Other frequently reported unsolicited adverse events

included otitis media (8-10% in toddlers); cough (6% MenACWY(b)(4) exposed toddlers, 2% MenACWY exposed toddlers,); and pyrexia (3% toddlers).

Reviewer Comment:
The unsolicited adverse events reported in the seven days post-vaccination were consistent with illnesses commonly observed in children.

Serious Adverse Events
Serious adverse events were reported in 13 (6% of) toddlers. Twelve SAEs reported in MenACWY exposed toddlers included 8 Varicella infections and 1 febrile convulsion. SAEs in MenACWY(b)(4) exposed toddlers included 6 Varicella infections; 3 gastroenteritis; 1 pneumonia; 1 otitis media; 1 Kawasaki infection; 1 Diabetes Mellitus; 1 enterocolitis; and 1 brain neoplasm.

Study Withdrawals/Deaths:
There was one AE leading to premature study withdrawal in the toddler MenACWY exposed group which was a febrile convulsion on study day 153, but no further information was provided in the CSR. There were three AEs leading to withdrawal in the toddler MenACWY(b)(4) exposed group: a subject with brain neoplasm diagnosed on study day 38; another subject with neurologic disease of the left arm three months after vaccination; and another subject with asthma requiring inhaled steroid therapy four months after vaccination. There were no deaths reported in the study.

Reviewer Comment:
No case narratives were provided for SAEs.

7.1.6.3 Comments & Conclusions
For purposes of this sBLA, this is a phase 2 study with objectives to evaluate MenACWY safety and immunogenicity in children 6 months through two years of age. The results support the selected ----(b)(4)----- vaccine formulation for phase 3 studies.

7.1.7 Trial #7: V59P8

7.1.7.1 Applicant's Protocol # V59P8 and Protocol Title
A Phase 2, Randomized, Single-blind, Controlled, Single-Center Study to Compare the Safety and Immunogenicity of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine with One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Children 2-10 Years of Age and an Open-label Study to Assess the Safety and Immunogenicity of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine Administered to Healthy Toddlers 12-23 Months of age.

Reviewer Comment:
This is a phase 2 study to evaluate the safety and immunogenicity of a single MenACWY dose in 2-10 years old children and a single MenACWY dose in toddlers 12-23 months. The dosing regimen is not directly applicable to the proposed 2-dose catch up series.

8 Overview of Efficacy Across Trials

Effectiveness of MenACWY vaccination against invasive meningococcal disease was inferred from a serological marker of protection, serum bactericidal antibody, using an assay with human complement source. Please see section 5.4.1 for further discussion.

Infant 4-dose primary immunization series:

Study V59P14 was the pivotal immunogenicity trial to infer effectiveness of a 4-dose MenACWY infant series, when administered at 2, 4, 6 and 12 months of age. DTaP-HBV-IPV, Hib, PCV7 and MMRV vaccines were administered concomitantly as appropriate for age. The primary endpoint was the percentage of US1a subjects who achieved an hSBA titer $\geq$1:8, measured one month after the 4th MenACWY dose. The primary objective was achieved if the lower limit of the 2-sided 95% CI for the endpoint described above was $\geq$ 80% for serogroup A and $\geq$ 85% for each of the remaining serogroups (C, Y and W-135). Of 154 subjects enrolled in US1a, 21% withdrew from the study, mainly due to voluntary withdrawal of parental consent, lost-to-followup or administrative reasons (e.g. loss of insurance).

Although the primary endpoint for each serogroup was met, the per-protocol immunogenicity and MITT populations might not constitute a randomized subset. The proportion of US subjects excluded from the toddler (4th dose) MenACWY MITT population ranged between 31% - 38% across study groups US1a, US1b, and US2. An additional 8% - 10% of the subjects were excluded from the MenACWY per-protocol populations. Twelve percent of US1 subjects prematurely withdrew or had a protocol deviation before receiving three MenACWY infant doses. Missing blood draws and incomplete infant and toddler MenACWY vaccinations series accounted for the majority of exclusions. The per-protocol and MITT populations for the 4th MenACWY dose (US1a) consisted of 91 and 107 participants, respectively. Bactericidal antibody responses following dose 3 was similar for three (C, Y, and W-135) of the four serogroups in the subjects who were included in the per protocol population after dose 4 and those who were excluded. Demographic data and baseline titers were similar between these two groups. However, the numbers of subjects tested for each serogroup are not consistent with the numbers for the same populations presented in the V59P14 CSR or in corresponding line listings within the ISE.

The applicant should explain why many subjects were not included in the dataset on which the first primary hypothesis was tested. In particular, they should clarify why a substantial number of MenACWY subjects were excluded due to incomplete vaccination series. Results related to the primary hypothesis may not be reliable because ignoring missing data can lead to incorrect inferences/biased estimates related to the immune response after the fourth dose of MenACWY vaccination. Further, the applicant should assess the impact of missing data on the results of testing the primary hypothesis and on the robustness of the results. The impact of missing data on bactericidal antibody responses measured after the third dose should also be assessed.

A subset of Latin American infants received three MenACWY doses at 2, 4 and 6

months of age (LA3) and a 4th dose at 16 months of age (LA3b). Serogroup-specific hSBA GMTs in LA3 participants after the 3rd MenACWY dose were 1-3 times higher compared to US1 participants; the 95% CIs for the GMTs were non-overlapping for all serogroups. After a 4th MenACWY dose, serogroup-specific hSBA GMTs in LA3b subjects were higher than corresponding hSBA antibody responses in US1a subjects, most likely due to age-related and geographic differences. Meningococcal hSBA antibody responses in Latin American subjects thus were not generalizable to a US population.

Catch-up vaccination series:
Study V59P21 was the main trial used to support the safety and immunogenicity of a 2-dose MenACWY series, when administered to US children at 7 – 9 months and at 12 months of age. The first MenACWY was given alone (study group 1 and 2); the second MenACWY dose was given alone (study group 2) or concomitantly with MMRV (or MMR+V) (study group 1). Other routine childhood vaccinations (e.g. PCV7, HepA) were permitted after the last scheduled blood sample was obtained. MenACWY hSBA antibody responses were measured 6 weeks after the 2nd dose. The proportion of enrolled subjects excluded from the MITT population ranged from 3% - 10% across groups, and an additional 9% - 19% of the subjects were excluded from the respective PP populations. Missing blood draws and incomplete vaccinations series accounted for the majority of exclusions.

Study V59P7 was a phase 2 study with objectives to evaluate a 2-dose MenACWY series in a subset of Finnish and Polish toddlers 12 to 24 months of age who received the second dose of MenACWY either one (n = 38), six (n = 37), or twelve (n = 39) months after the first dose and had serology evaluated ~ 21 days after the 2nd dose.

Study V59P9 was a phase 2 study with objectives to evaluate a 1or 2-dose MenACWY series in Canadian infants. One study group received MenACWY at 6 and 12 months of age (n = 64), and another study group received a single MenACWY dose at 12 months of age (n = 61). Pediatric vaccines were administered according to the Canadian vaccination schedule.

8.1.1 Efficacy Findings

According to the applicant, across the supportive studies V59P5, V59P7, and V59P9 92% - 100% of enrolled subjects were included in the respective MITT populations, while 85% - 96% were included in the respective PP populations.

Table 57. ISE. Percentage of subjects with hSBA ≥ 1:8 at 1 month after completing the age-specific proposed MenACWY vaccination schedule

Serogroup	4-dose Primary Infant series (US1a) V59P14[a]	2-dose Catch up series		
		Ages 7-12 months V59P21[c]	Ages 6-12 months V59P9[d]	Ages 12-59 months V59P7[e]
A	N = 84	N = 379	N = 50	N = 29
	94%	88%	84%	86%

	(87, 98)	(84, 91)	(71, 93)	(68, 96)
C	N = 86	N = 199	N = 55	N = 29
	98%	100%	100%	100%
	(92, 100)	(98, 100)	(94, 100)	(88, 100)
W	N = 85	N = 196	N = 40	N = 29
	100%	98%	100%	100%
	(96, 100)	(96, 100)	(91, 100)	(88, 100)
Y	N = 84	N = 198	N = 53	N = 29
	100%	96%	100%	100%
	(96, 100)	(93, 99)	(93, 100)	(88, 100)

[a] at 2, 4, 6, and 12 months of age (treatment Group US1a)
[c] 2-dose schedule at 7 – 9 months of age and 12 months of age
[d] 2-dose schedule at 6 and 12 months of age
[e] 2nd dose administered 6 months after the 1st dose
Source: Integrated Summary of Efficacy,table 3.2.4-7, page 122/130.

Table 58. ISE. hSBA GMTs (95% CIs) at 1 month after completing the age-specific proposed MenACWY vaccination schedule

Serogroup	4-dose Primary Infant series (US1a) V59P14[a]	2-dose Catch up series		
		Ages 7-12 months V59P21[c]	Ages 6-12 months V59P9[d]	Ages 12-59 months V59P7[e]
A	N = 84	N = 379	N = 50	N = 29
	77	37	44	59
	(55, 109)	(32, 42)	(29, 65)	(36, 96)
C	N = 86	N = 199	N = 55	N = 29
	227	180	302	252
	(155, 332)	(158, 205)	(224, 405)	(145, 438)
W	N = 85	N = 196	N = 40	N = 29
	416	119	220	601
	(288, 602)	(101, 139)	(155, 313)	(376, 959)
Y	N = 84	N = 198	N = 53	N = 29
	395	88	136	337
	(269, 580)	(73, 105)	(100, 185)	(205, 552)

[a] at 2, 4, 6, and 12 months of age (treatment Group US1a)
[c] 2-dose schedule at 7 – 9 months of age and 12 months of age
[d] 2-dose schedule at 6 and 12 months of age
[e] 2nd dose administered 6 months after the 1st dose

Source: Integrated Summary of Efficacy,table 3.2.4-8, page 123/130.

8.1.2 Efficacy Conclusions

Immunogenicity data from studies V59P14 and V59P21 are the most relevant to support MenACWY use in infants. Both studies had many limitations. While similar proportions of subjects in both trials met the criteria predictive of adequate immune response (hSBA $\geq$ 1:8), higher hSBA GMTs were achieved after a 4-dose primary infant immunization series than after a 2-dose series (7-9 months, 12months).

MenACWY vaccine containing particulate matter was used in studies V59P14 and V59P21. Assessments of the comparability of vaccine lot stability over time and available clinical immune responses was not provided in the sBLA, but are available in amendments submitted to the IND.

9 Overview of Safety Across Trials

The sponsor's Integrated Summary of Safety (ISS) includes safety data from a total of 6 studies, including the 3 pivotal clinical studies (V59P14, V59P21, and V59P23), and 3 supportive clinical studies (V59P5, V59P8, and V59P9). The ISS summarizes safety data on infant/toddler subjects who received MenACWY as a four-dose series (5563 subjects) and as a two-dose catch-up series (1985 subjects).

The percentage of infants who experienced any adverse solicited reaction was 96% for the four dose series and 78% for the two dose series. Local adverse reactions were observed in 80% of infants who received the four dose series and 49% who received two doses. Systemic solicited adverse reactions were noted in 89% of infants who received four doses and in 62% who received two doses. Any adverse reaction that was severe was observed in 19% of subjects who received four doses and in 10% who received two doses.

The most common local solicited adverse reaction in the MenACWY recipients in the 4 dose series was tenderness which was seen in 73% of MenACWY recipients, compared to 77% of controls; erythema was seen in 45% of MenACWY recipients and 51% of controls. For the 2-dose series, the most common local adverse reactions in the MenACWY recipients were tenderness and erythema, each seen in 32% of 2-dose catch-up series MenACWY recipients.

The most common systemic solicited adverse reaction for the MenACWY 4-dose series recipients was irritability, seen in 69% of subjects compared to 72% of controls. Fever ($\geq$38.0C) was seen in 26% of MenACWY recipient subjects and 24% of controls. Sleepiness (66% in MenACWY/66% control) and persistent crying (55% MenACWY/58% control) were seen frequently as well. The remaining individual solicited systemic reactions in the 4 dose series subjects were seen in 13-38% of subjects. For the MenACWY 2-dose catch-up series MenACWY recipients, irritability was seen in 45% of subjects and fever was seen in 13% of subjects. Sleepiness and persistent crying after the 2-dose series were seen in 29% and 22% of MenACWY subjects, respectively. The remaining systemic reactions after a 2 dose series were seen in 7-20% of MenACWY subjects.

> *Reviewer Comment: After both the 4-dose primary series and the 2-dose catch-up series, tenderness was and erythema were the most frequently seen local solicited adverse reaction, and irritability was the most common systemic solicited adverse reaction. The percentage of subjects with any solicited adverse reaction and with individual adverse reactions was similar between the two study arms. Therefore, administration of Menveo with routine childhood vaccinations did not appear to increase the percentage of subjects with solicited adverse reactions.*

Across all MenACWY studies, there were 13 serious adverse events (SAEs) that were considered to be related to MenACWY vaccination by the investigator.

Table 59. ISS. Serious Adverse Events (SAEs) in MenACWY Recipients Considered Related to Vaccination by the Investigator

Subject #/ V59-Study	SAE	Age/Race	Most recent vaccination
377053/P14	Febrile Convulsion	~12 mo male/ Caucasian US	8 days after 4th dose (with ProQuad)
717057/P14	Febrile Convulsion	~12 mo female Hispanic- Argentina	7 days after 4th dose (with ProQuad)
817196/P14	Febrile Convulsion	~12 mo female Hispanic- Colombia	3 days after 4th dose (with ProQuad)
0430016/P14	Febrile Convulsion	~8 mo male Caucasian- US	38 days after 3rd dose
367008/P14	Complex Partial Seizure	~5 mo female/ US	31 days after 2nd dose
0500010/P23	Epilepsy	7 mo female Hispanic- US	17 days after 3rd dose
1215028/P23	ADEM	~13mo male Caucasian- US	35 days after 4th dose
287010/P14	Kawasaki Disease	~ 7 mo male/ Caucasian- US	29 days after 3rd dose
3040129/P23	Kawasaki Disease	~12 week female/ Taiwan	20 days after 1st dose
4040204/P23	Kawasaki Disease	~10 week female Hispanic- Costa Rica	12 days after 1st dose
01062/P5	ITP	~12 mo male Caucasian- UK	7 days after 4th dose
01149/P5	SVT-3 episodes	~3 mo male Caucasian- UK	1st SVT: Prior to enrolling 2nd SVT: 36 hr after 1st dose 3rd SVT: 6 hrs after 2nd dose
1320002/P23	Groin Abscess	~9 mo male 'Other'- US	83 days after 3rd dose

Source: ISS, Section 2.2.2.1

Reviewer Comment:

1. *Three subjects experienced a febrile convulsion within 8 days after MenACWY vaccination. Each subject also received concomitant MMRV (ProQuad). In this reviewer's opinion, the event temporally follows vaccination, but could be due to Menveo or MMRV.*

2. *ADEM is a rare and isolated neurologic finding, and has been reported following meningococcal vaccination. It is this reviewer's opinion that it is not possible to rule out an association.*
3. *There were three cases of Kawasaki Disease (KD) listed in Table 59 that were considered related to vaccination by the investigator. On review of IND 11278 and the ISS, three additional cases were identified.*
    a. *V59P14 study (subject #287010-US site): This 7 month Caucasian male developed KD symptoms 29 days after his 3rd MenACWY dose. The investigator considered the KD adverse event related to vaccination, and the case was confirmed by expert opinion. It is unclear if there is a causal association with vaccination, despite a strong temporal association because the subject also received Rotateq vaccine. The Rotateq label (Merck Co., Inc.) was revised in June 2007 to include mention that KD rates, though not statistically significant, were higher among Rotateq vaccine than placebo recipients.*[1]
    b. *V59P23 study (subject #3040129-Taiwan): This 12 week female developed KD symptoms 20 days after her 1st MenACWY dose (3/26/10) with routine vaccines which included Infanrix-Hexa (DTaP, HBV, IPV, Hib), and Prevnar. The subject improved after treatment with intravenous immunoglobulin therapy (IVIG). The investigator did not consider the case related to MenACWY vaccination. Subsequently the subject received the 2nd dose (5/25/10) and 3rd dose (7/20/10) of MenACWY. However, on review of the cases, the applicant and the DMC considered the KD diagnosis related to vaccination.*
    c. *V59P23 study (subject #4040204-Costa Rica): This 10 wk Hispanic female developed KD symptoms 12 days after her 1st MenACWY dose, administered concomitantly with Infanrix-Hexa, and Prevnar. The subject was hospitalized after diagnosis and treated with IVIG, yet a follow-up echocardiogram 1 month later demonstrated coronary artery dilation which persisted for several months. The investigator did not consider this KD case related to vaccination, therefore the subject received dose #2 and #3 of MenACWY. Review of the case by the sponsor and the DMC at a later date resulted in an assessment of 'possibly related since it occurred within 6 weeks of vaccination.'*

In summary, all three of the cases are temporally related to administration of MenACWY, and other risk factors for development of KD were present in two cases [administration of Rotateq and race (Asian)]. While it is unclear if the administration of MenACWY contributed to the development of KD in these cases, the possibility of an association of KD and MenACWY administration cannot be ruled out.

---

1 http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142288.pdf

4. *As listed above there were three episodes of SVT in one subject who received two doses of MenACWY vaccination. While there appears to be a temporal relationship with vaccination, there are also several other factors that could have played a role in the development of SVT. The information provided is not sufficient to allow for this reviewer to make a clear association between MenACWY vaccination and SVT onset.*

There were no cases of KD in the control arms of the studies. The applicant stated that the number of study subjects with Kawasaki's disease was consistent with the background rate of Kawasaki's in the areas studied, though there were no cases observed in the control groups.

> *Reviewer Comment: The imbalance of cases of KD in the MenACWY arms compared to the control arm is concerning. However, the percentage of subjects who developed KD is very low (6/7548 or 0.08%). Therefore, it appears that the risk of developing KD after MenACWY may be small, and at this time, no change in the package insert for MenACWY is needed.*

A total of 12 deaths were reported across the 6 studies. Eight of these deaths occurred in study V59P23, three in study V59P14, and one in study V59_36.

Table 60. ISS: 12 Deaths after Vaccination*(9 MenACWY exposed and 3 unexposed)*

Subject #/ V59-Study Treatment Group	Death	Age/Race	Most recent vaccination/ comment
0480012/P23 MenACWY + RIV	Cardiac Arrest	~16 mo male Black- US	(b)(6) days since last dose
670004/P23 MenACWY + RIV	Cardiorespiratory Failure	3 mo female Hispanic- US	(b)(6) days after 1st dose, Recent hospitalization for bilateral pneumonia
837017/P14 MenACWY + RIV	Lung infection	~8 mo male Hispanic- Colombia	(b)(6) days after 3rd dose
1235006/P23 MenACWY + RIV	Bronchopneumonia	~6 mo female Hispanic- US	(b)(6) days after 2nd dose
5040234/P23 MenACWY + RIV	Respiratory failure	~4 mo male Hispanic- Guatemala	(b)(6) days after 1st dose
837212/P14 MenACWY + RIV	Sepsis	~5 mo female Black- Colombia	(b)(6) days after 2nd dose, Presence of Tetralogy of Fallot

7050001/P23 MenACWY + RIV	Septic shock	~3mo male Hispanic- Peru	(b)(6) days after 1st dose
6010098/P23 MenACWY + RIV	Sudden death	~2mo male Hispanic- Panama	(b)(6) days after 2nd dose; Found unresponsive; h/o GERD; Autopsy: Lung edema and pneumonitis
717021/P14 MenACWY + RIV	Auto accident	~17 mo male Hispanic- Argentina	(b)(6) days after 4th dose
133007/P36 *RIV only*	Cardiac Arrest	~3mo male Caucasian- US	(b)(6) days after 1st dose
6010134/P23 *RIV alone*	TAPVC with Pul. HTN*	~3 mo female Hispanic- Panama	(b)(6) days after 1st dose
7040057/P23 *RIV alone*	Head injury	~7mo female Hispanic- Peru	(b)(6) days after last dose

Source: ISS Section 2.2.1.1; *TAPVC with Pul .HTN= Total Anomalous Pulmonary Venous Connection with Pulmonary Hypertension

Reviewer Comment: In the opinion of this reviewer, none of the subject deaths listed in Table 60 appears to be related to vaccination. However, the 'sudden death' in Subject #6010098 (V59P23) has a close temporal relationship with vaccination, and the case narrative lacks sufficient detail to permit this reviewer to make an association between MenACWY vaccination and this subject's death.

9.1.1 Product-Product Interactions

Concomitant administration of DTaP-HBV-IPV, Hib, PCV7, MMRV (or MMR+V) and HepA vaccines with MenACWY was evaluated. Please see sections 7.1.1 and 7.1.3 for a description of the study design, immunogenicity outcomes, and conclusions.

9.1.2 Post-Marketing Experience

Please see package insert.

9.2 Safety Conclusions

The information provided in the BLA supplement is not adequate to assess the safety of Menveo when given as a 4-dose infant series, primarily due to an inability to verify, analyze independently, and resolve discrepancies in reported safety information in individual study reports. In addition, the number of study subjects who completed a four dose series of MenACWY was not able to be identified in study V59P23 or in the summarized data in the ISS. The interpretation of the data summarized in the ISS is limited, since not all studies were included in the ISS.

Three cases of Kawasaki disease were, in this reviewer's opinion, possibly related to administration of MenACWY. However, other risk factors for development of KD were present in two cases [administration of Rotateq and race (Asian)]. No cases occurred in the control group. While this imbalance in the number of cases is of concern, the overall

rate of KD in the MenACWY arm was very low and no changes to the package insert or additional studies are needed at this time.

10 Additional Clinical Issues

10.1 Directions for Use

10.2 Dose Regimens and Administration

10.3 Special Populations

n/a

10.4 Pediatrics

Presentation of the applicant's plan to fulfill Pediatric Research Equity Act (PREA) to Pediatric review committee (PeRC) deferred.

11.5 Other

12 Conclusions - Overall

The safety and immunogenicity data submitted in this supplemental application are not adequate to support extending the use of Menveo to children less than 2 years of age, primarily due to concerns regarding the completeness, reliability, and verifiability of the clinical data. The main deficiencies/concerns are as follows:

Safety

- In pivotal studies V59P14, V59P23 and V59P2, it was not possible to ascertain whether safety data were collected in a systematic manner. The applicant is not able to determine the extent to which AEs reported on diary cards were collected at the time of the visit/mailed to site, by verbal recall, and/or by review of clinical charts.
- In all studies, frequencies of certain solicited local and systemic AEs, particularly fever, in the MenACWY groups and corresponding control groups were unexpectedly low, based on the agency's experience with vaccines administered to infants/toddlers. Possibilities for underreported AE rates include recall bias, inaccurate temperature measurements, and overestimation of the population used as the denominator for calculating a given AE rate.
- In study V59P23, the number of study subjects who completed a four dose series of MenACWY was not able to be identified. From the datasets provided, we were not able to verify, analyze independently, and resolve discrepancies in reported safety information.

Immunogenicity:

- In study V59P14, a significant proportion of the exposed population dropped out or was excluded from the immunogenicity per-protocol population.
- During the review of this supplement, the agency became aware that translucent particles were observed in liquid CWY component packaged in ---(b)(4)----------. MenACWY vaccine used in the three trials was prepared by reconstituting lyophilized MenA glycoconjugate (packaged in a single dose vial) with liquid MenCWY glycoconjugates contained a -----(b)(4)----------.

Information submitted to the IND indicated that the particles in part consisted of ----------(b)(4)---------- ----------(b)(4)----------. No information regarding the investigation of particulates were provided in this sBLA.

Concomitant vaccine evaluation

- Except for pneumococcal serotype 6B, all endpoints for concomitantly administered vaccines were met. Immunogenicity evaluation of Prevnar co-administered with MenACWY was confounded by the control group (US1b) used for 4th dose comparisons. Routine vaccinations recommended by the ACIP at age 12 months were administered to US1b, but these subjects had received three doses MenACWY infancy (2, 4, and 6 months of age). Pneumococcal IgG GMCs in the control group might also have been reduced.

13 Recommendations

13.1 Approval or Non-approval Recommendation

The information provided by the applicant is not adequate to assess the safety and immunogenicity of Menveo in infants/toddlers. Final decisions for approval or non-approval are deferred pending the applicant's responses to the complete response letter.

13.2 Recommendations on Postmarketing Actions

Please see Dr. Niu's review.

13.3 Labeling

Labeling discussions are deferred pending resolution of the recommended questions to the applicant.

References

---

[i] MacNeil J. Epidemiology of Meningococcal Disease in Infants and Young Children. Presented at Advisory Committee on Imuunization Practices (ACIP) Meeting on October 21, 2009.

[ii] Center for Disease Control and Prevention (CDC). Active Bacterial Core surveillance (ABCs). http://www.cdc.gov/abcs/reports-findings/survreports/mening09.html. Accessed on 2/09/2012.

[iii] Kaplan SL, Schutze GE, Leake JAD, Barson WJ, Halasa NB, Byington CL, Woods CR, Tan TQ, Hoffman JA, Wald ER, Edwards KM, Mason EO. Multicenter Surveillance of Invasive Meningococcal Infections in Children. *Pediatrics*. October 2006;118(4):e979-e974.

[iv] CDC. Prevention and Control of Meningococcal Disease, Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54(no. RR-7)

[v] FDA. VRBPAC September 14-15, 1999. http://www.fda.gov/ohrms/dockets/ac/cber99.htm#Vaccines%20and%20Related%20Biological%20Products%20Advisory%20Committee. Accessed on 2/09/2012.

[vi] FDA. VRBPAC. April 6-7, 2011. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm241549.htm. Accessed on 2/09/2012.