DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Memorandum

DATE: January 28, 2010

TO: File, STN 125300

FROM: Margaret Bash M.D, MPH, Laboratory of Bacterial Polysaccharides

SUBJECT: Novartis Vaccines & Diagnostics, Inc
Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine
Clinical review for proposed indication in persons aged 11 to 55 years

THROUGH: Douglas Pratt, M.D., Chief, VCTB, DVRPA

TO: Willie Vann, Ph.D., Laboratory Chief, LBP
Committee Chair, OVRR/DBPAP

1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA #: 125300/0

1.1.2 Related IND #(s):
Meningococcal (*Neisseria meningitidis*) tetravalent oligosaccharide serogroups A, C, Y, W-135 conjugate (diphtheria toxin CRM197; *Corynebacterium diphtheriae*) vaccine ——b(4)—— : IND --b(4)---

1.1.3 Reviewer Name, Division and Mail Code:
Margaret C. Bash, MD, MPH
Division of Bacterial Parasitic and Allergenic Products
HFM-428

1.1.4 Submission Received by FDA: August 29, 2008

1.1.5 Review Completed: January 27, 2010

1.2 Product

1.2.1 **Proper Name**: Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine

1.2.2 **Proposed Trade Name:** MENVEO

1.2.3 **Product Formulation** (per 0.5 ml dose):

Composition	Quantity per 0.5 mL dose
CRM197-MenA conjugate	10 µg MenA, --(b)(4)-- µg CRM197
CRM197-MenC conjugate	5 µg MenC, --(b)(4)-- µg CRM197
CRM197-MenW conjugate	5 µg MenW, --(b)(4)-- µg CRM197
CRM197-MenY conjugate	5 µg MenY, --(b)(4)-- µg CRM197
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1.3 **Applicant:** Novartis Vaccines and Diagnostics, Inc.

1.4 **Pharmacologic Class**: Vaccine

1.5 **Proposed Indication**: MENVEO is a vaccine indicated for active immunization to prevent *Neisseria meningitidis* serogroups A, C, Y, and W-135.

1.6 **Proposed Populations**: Persons 11 through 55 years of age.

1.7 **Dosage Form(s) and Route(s) of Administration:** A single 0.5 mL dose for intramuscular injection

2 Table of Contents

3 Executive Summary

Background

BLA 125300/0 contains safety and immunogenicity data for a new quadrivalent meningococcal conjugate vaccine, MENVEO. This is the first licensing application for this vaccine worldwide although the applicant has developed a monovalent serogroup C conjugate vaccine Menjugate, using similar manufacturing methods, which is currently licensed in other countries, including the U.K., Canada, and Australia. Currently, two meningococcal vaccines are licensed for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, W-135, Y in the U.S. Menomune (Sanofi Pasteur Inc.) is a quadrivalent polysaccharide vaccine and Menactra (Sanofi Pasteur Inc,) is a polysaccharide-protein conjugate vaccine. Invasive meningococcal disease occurs in the U.S at a rate of 0.5 to 1.1/100,000 (1), and the relatively low prevalence of disease combined with the availability of currently licensed meningococcal vaccines precludes the conduct of studies to evaluate directly the efficacy of new meningococcal vaccines in prevention of clinical invasive disease. The approach used to evaluate safety and effectiveness of MENVEO to support licensure in the U.S. was to compare safety outcomes and serum bactericidal antibody responses after vaccination in comparison to the U.S. licensed vaccine Menactra (2).

The bactericidal activity of serum from vaccine recipients is considered an appropriate surrogate for evaluating vaccine effectiveness of meningococcal vaccines because complement mediated bacterial killing by bactericidal antibodies has been shown to be the primary mechanism of protection against meningococcal disease. Sero-epidemiologic studies by Goldschneider et. al., showed protection from disease in individuals whose sera killed the circulating strain when diluted 1:4 (2). In this application, bactericidal assays using an extrinsic source of human complement (hSBA) were used. Licensure of serogroup A and serogroup C meningococcal polysaccharide vaccines was originally supported by demonstrated clinical efficacy in preventing invasive meningococcal disease. In addition to serogroups A and C, the quadrivalent polysaccharide vaccine also contains serogroup Y and W-135 polysaccharides which were evaluated on the basis of demonstrating four-fold rise in SBA using exogenous rabbit complement (rSBA). Menactra was licensed in 2005 on the basis of immunologic (SBA) non-inferiority to Menomune. The SBA used an exogenous complement source that was either human (proportion with hSBA titer $\geq$1:8, 2-10 year old age group) or, when correlated to hSBA, baby rabbit complement (proportion with 4 fold rise in rSBA titer, 11-55 year old age group). The clinical studies of MENVEO were intended to evaluate immunogenicity and safety in comparison to U.S.-licensed meningococcal vaccines.

Safety

The total safety database for the proposed formulation and indicated age group consists of 6185 subjects from 5 studies. A total of 3579 adolescents aged 11 to 18 years, and 2606 adults aged 19 to 55 years from three pivotal (V59P13, V59P17, V59P18) and two supportive studies (V59P6 and V59P11) were evaluated for safety outcomes. For comparator vaccines, 1757 subjects provided safety data for Menactra, 209 provided safety data for Menomune, and 892

provided safety data for Tdap from vaccine co-administration studies. Two pivotal randomized blinded, controlled safety studies provided comparative safety data for the indication sought.

In study V59P13, a multi-center, observer-blind, randomized study in the United States, 2649 MENVEO subjects were evaluable for safety. In study V59P17, a multi-center, observer-blind randomized study in Columbia and Argentina, 1588 MENVEO subjects were evaluable for safety. The planned post vaccination period for each subject in both studies was 180 days.

In V59P18, a single center open label, multiple vaccination study in Costa Rica, safety of MENVEO was evaluated in 1620 healthy adolescents 11 to 18 years of age administered MENVEO either alone, or concomitantly with combined tetanus, reduced diphtheria, and acellular pertussis (Tdap) vaccine (GlaxoSmithKline [GSK], US-licensed Boostrix), and quadrivalent human papillomavirus [type 6, 11, 16, 18] (HPV) recombinant vaccine (Merck & Co.,GARDASIL). Data through 2 months following vaccination were evaluated for safety.

The safety profile of MENVEO in each individual study was similar to that observed by combining safety data across studies. Local and systemic reactogenicity occurred in a similar percent of subjects immunized with MENVEO or the U.S.-licensed comparator vaccine. Severe reactions occurred infrequently. Adverse events were more frequent in females and less common in the 35-55 year old age group. Geographic distribution, which largely corresponded to racial demographics (primarily Caucasian in U.S. studies and Hispanic in South/Central American studies), did not affect Adverse Event (AE) profiles.

Solicited adverse reactions in the primary U.S. safety study:
Using diary cards as memory aids, subjects self-reported in response to queries about the presence or absence of common vaccine reactions as solicited AEs. The percentages of subjects reporting all solicited AEs in the MENVEO group and in the Menactra group were: solicited AEs: 62% vs. 67%; local solicited AEs: 48% vs. 53%; systemic AEs 41% vs. 40%, respectively. The solicited events "use of analgesic/antipyretic medication" and "stayed at home due to vaccination" occurred in 21% of both vaccine groups.

Pain was the most frequently reported local solicited AE. While local AEs were reported in slightly fewer MENVEO recipients, severe local reactions were reported more frequently compared with Menactra (overall, 4% vs. 2%, respectively). The median duration of all severe local reactions were similar in the MENVEO and Menactra groups (2 days for severe pain in both vaccine groups; 4 days for erythema >50mm in both vaccine groups and 3 and 4 days in the MENVEO and Menactra groups, respectively, for induration >50mm).

Solicited systemic AEs were reported by 41% and 40% of the MENVEO and Menactra groups; the most commonly reported systemic solicited AEs were headache (28% and 27%, respectively), myalgia (17% in both vaccine groups), and malaise (11% in both vaccine groups). Severe headache was reported by 2% and 1%, respectively, while severe myalgia and malaise were reported by 1% in both vaccine groups.

Serious adverse events in the indicated age group:
Serious adverse events (SAE) occurred in <1% of subjects at any time during the studies in the MENVEO and Menactra groups (40 of 6185 subjects = 0.6% and 13 of 1757 subjects = 0.7% respectively). SAEs during month 1 occurred in 7 MENVEO recipients, 4 Menactra recipients and 1 Tdap recipient. None of the reports of these SAEs raised concerns regarding causality. Neurologic and psychiatric events were reviewed specifically: five MENVEO recipients and one Menactra recipient experienced one or more events of suicide attempt or intentional drug overdose between 10 and 156 days post vaccination. Three participants experienced seizure and one participant experienced syncope in the MENVEO group and one participant experienced auditory hallucinations in the Menactra group (occurred between 21 to 151 days post vaccination). These neurologic and psychiatric events varied widely in their presentations and temporal relationship to vaccination, and were not considered by this reviewer to raise concerns regarding causality.

Pregnancy, or intention to become pregnant was an exclusion criterion for the clinical studies reviewed in this application. However, among the 5209 women enrolled in the studies, 37 pregnancies occurred among 4115 MENVEO recipients (7 spontaneous abortions, no congenital anomalies) and 6 pregnancies occurred among 1013 Menactra recipients (no spontaneous abortions, one congenital anomaly [hydrocephalus] that resulted in neonatal death). The estimated dates of conception for the seven MENVEO subjects with adverse pregnancy outcomes, were 5 days prior to vaccination (1 subject), 6 to 17 weeks post vaccination (5 subjects), and 6 months post vaccination (1 subject). The Menactra subject's estimated date of conception was approximately 15 weeks post immunization. The rates of adverse fetal outcomes (19% for MENVEO and 17% for Menactra) are similar to those identified in the clinical studies of GARDASIL (23.3% among pregnancies that occurred in GARDASIL recipients and 24.1% among pregnancies that occurred in control or placebo recipients). The safety of MENVEO has not been established in pregnant women and MENVEO should be administered to a pregnant woman only if clearly needed. Novartis has agreed to monitor pregnancy outcomes by establishing a pregnancy registry.

Immunogenicity and Inferred Effectiveness
Pivotal immunogenicity data to support lot consistency and non-inferiority to Menactra were provided in study V59P13. Immunogenicity was evaluated on subsets of the per protocol population for each serogroup. Laboratory assessments were blind to immunization group, and differences in subset populations were evaluated during the review, but were not assessed by this reviewer as having a meaningful impact on the immunogenicity endpoints. All primary end-points comparing pairwise the three lots of MENVEO for the four serogroups were met (equivalence based on hSBA GMTs for lot consistancy), thus providing clinical evidence supporting consistency of manufacture. Immunogenicity data for the three lots were therefore combined for noninferiority comparisons to Menactra.

Effectiveness of MENVEO was inferred from immunogenicity as assessed by evaluation of serum bactericidal activity (hSBA) in response to immunization with MENVEO compared to the currently licensed meningococcal conjugate vaccine, Menactra. Non-inferiority of hSBA responses to MENVEO compared to Menactra was shown for all four serogroups for individuals

11-18 years of age and 19 – 55 years of age using a composite endpoint of seroresponse rates, defined as follows: for subjects with hSBA titer <1:4 at baseline, seroresponse was a postvaccination hSBA titer ≥ 1:8; for subjects with hSBA titer ≥ 1:4 at baseline, seroresponse was a post vaccination hSBA titer of at least 4 times the baseline titer.

All secondary end-points (based on seroresponse, geometric mean titer [GMT] and %≥1:8 in 11-55 year age groups) also met pre-specified non-inferiority criteria for each serogroup. Additional exploratory analyses were requested during the review, such as analysis of non-inferiority using non-interpolated titers, and an analysis excluding two study sites that may have been unblinded to study group. Exploratory analyses also indicated similar hSBA responses in comparison to Menactra.

Pre-defined criteria for superior immune responses required that (1) non-inferiority was achieved and (2) that the lower limit of the 2 sided 95% confidence interval around the difference in proportions (MENVEO – Menactra) or ratio of GMTs (MENVEO/Menactra) was greater than 0% or 1.0 respectively. This criteria was met for the following endpoints: seroresponse in 11 to 18 year age groups for serogroups A, W and Y; seroresponse in 19 to 55 year age groups for serogroups C, W, and Y; seroresponse in the 11 to 55 year age groups for serogroups C, W and Y; proportion ≥1:8 in 11-55 year age groups for serogroups W and Y. The clinical significance of statistically significantly higher immune responses is unknown as there are no clinical data demonstrating differences in meningococcal disease prevention due to higher post-immunization immune responses. During clinical development, CBER conveyed to Novartis that an immune response that is determined to be statistically significantly higher than another immune response would not be interpreted or used as evidence of superior protection from meningococcal disease. Explicit or implicit superiority claims based on the immunogenicity data reviewed are not appropriate for labeling purposes.

In general the hSBA responses to MENVEO observed in studies V59P18 and V59P6 were consistent with those of the pivotal immunogenicity study V59P13. Concomitant administration of MENVEO with Boostrix and GARDASIL did not interfere with the immune response to MENVEO, tetanus, diphtheria or pertussis toxin (GARDASIL responses following the three dose series will be evaluated under a labeling supplement due to their later availability). The geometric mean antibody titers (GMTs) to two pertussis antigens, FHA and pertactin, were lower in subjects in the concomitant administration group than in those that received Boostrix alone. This assessment was conducted in the context of GARDASIL also administered to the concomitant group, and data are not adequate to evaluate the effect of MENVEO on the immune responses to pertussis antigens. Data are insufficient to evaluate vaccine interactions when MENVEO is administered one month before or one month following Boostrix. Further evaluation of the effect of MENVEO on U.S. recommended adolescent vaccines will be undertaken as a postmarketing commitment.

Recommendations

The available safety and immunogenicity data for MENVEO support a recommendation for approval of this vaccine administered as a single dose to individuals 11 to 55 years of age for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 or Y.

No safety signals were noted that should be specifically examined in post marketing studies. The database size is too small to detect rare adverse events. A postmarketing safety surveillance study, as recommended by CBER's Office of Biostatistics and Epidemiology (OBE), is warranted. In addition a well-designed pregnancy registry is needed given that the vaccine is likely to be used in women of child-bearing age. Further evaluation of the effect of MENVEO on U.S recommended adolescent vaccines should be undertaken as a postmarketing commitment.

1. Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54 (No. RR-7).

2. Vaccines and Related Biological Products Advisory Committee: 9/15/1999. http://www.fda.gov/ohrms/dockets/ac/cber99.htm (3544t2.rtf).

3. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I: The role of humoral antibodies. J Exp Med 1969;129:1307--26.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

N. meningitidis causes disease in all regions of the world. Invasive disease presents primarily as meningitis and or rapidly progressive sepsis. The case fatality rate is 10% overall and approaches 25% in adolescents even in the face of rapid and aggressive medical treatment. Sequelae occur in 10% to 20% of survivors and include hearing loss, neurologic disability, digit or limb amputation and skin scarring. Currently, meningococcal vaccines are licensed for individuals 2 years of age and older. Immunization of all adolescents and other populations at high risk for infection is recommended in the US using polysaccharide or polysaccharide-protein conjugated vaccines that protect against serogroups A, C, Y and W-135.

Antibodies that kill *N. meningitidis* in the presence of active complement (complement mediated bactericidal activity) can protect against meningococcal disease. Functional serologic assays are used to assess the ability of meningococcal vaccines to induce bactericidal antibodies. The source of complement, bacterial strain and other assay parameters can affect the assay results and these assays can be difficult to standardize. Conjugate vaccines have been licensed on the basis of comparison to existing licensed meningococcal vaccines, and bactericidal assays were used to show non-inferiority of the immune responses.

Serogroup B *N. meningitidis* accounts for roughly one third of meningococcal disease in the U.S. and is responsible for epidemics of disease in some parts of the world. The group B polysaccharide capsule is poorly immunogenic even when conjugated to a protein and so is not included in the currently licensed U.S. quadrivalent vaccines.

4.2 Regulatory Background Information

In 1999, FDA proposed to the Vaccine and Related Products Advisory Committee, and the Committee agreed, that serum bactericidal antibody serve as an appropriate immunologic measure to estimate protective efficacy for the licensure of meningococcal conjugate vaccines in adults. A pre-IND meeting with Novartis was held in June 2003 to discuss the licensure strategy (non-inferiority to Menomune and later Menactra), evaluation of dose and schedule, and b(4) BB IND b(4) was established in September 2003 under which clinical investigations of Novartis' quadrivalent meningococcal polysaccharide conjugate vaccine (MENVEO, referred to as MenACWY in this review) were conducted.

Results of the studies V59P2 and V59P4 were submitted to CBER to support the choice of the 10-5-5-5 µg dose formulation b(4) (S0009 dated 3 September 2004). CBER recommended a reevaluation b(4) in the same age group in which the dose-ranging and the formulation-finding trials had been conducted (toddlers) (5 November 2004 telephone conference). MenACWY vaccine, b(4), was subsequently evaluated in toddlers, infants and adolescents, and a formulation without adjuvant was selected for further development.

In 2006, an End of Phase 2 (EOP2) meeting addressed:

- Basis for licensure in the different age groups (infants and older age groups);
- Size and composition of the proposed total safety database;
- Design of pivotal clinical trials;
- Design of the clinical lot-to-lot consistency trial;

- Confirmation of acceptability of the use of drug substances manufactured at Novartis' facility in Rosia, Italy for phase 3 trials;
- Confirmation of product specifications.

CBER provided comments and requested clarification on the clinical development plan, but the justification for the GMT ratio (0.5, 2.0) as the lot equivalence criterion was accepted. CBER recommended adding MenACWY immunogenicity as a co-primary objective in study V59P11, along with immunogenicity against each of the pertussis antigens separately, and advised Novartis that the use of a non-US licensed formulation of Boostrix™ would limit the study's applicability for U.S. licensure. MenACWY immunogenicity was left as a secondary objective in this protocol. CBER also indicated that the number of planned subjects (450) aged 56 to 65 years in study V59P17 was insufficient to gain approval for that age group.

At the EOP2 meeting and in further follow-up discussions with the Agency, the following trials were proposed as pivotal for registration in the 11 to 55 years of age group:

- V59P13 – A US-based non-inferiority trial comparing MenACWY to Menactra, with a co-primary objective of demonstrating lot-to-lot consistency between three lots of MenACWY, conducted in subjects aged 11 to 55 years
- V59P18 – A safety and immunogenicity study evaluating noninterference between MenACWY and Tdap, either given concomitantly or sequentially, conducted in adolescents aged 11 to 18 years in Costa Rica
- V59P17 – A study evaluating safety of MenACWY in comparison with Menactra (subjects aged 19 to 55 years) and Menomune (subjects aged 56 to 65 years), conducted in Colombia and Argentina.

A separate meeting with CBER on 25 April 2007 addressed serology issues:

- The rationale and techniques for screening and qualifying human complement for use in the hSBA.
- CBER requested, and Novartis provided interpolated data for V59P5 and V59P6 using the T_0 time point (all data currently provided this way) vs T_{60} time point as well as noninterpolated data using the T_0 time point vs T_{60} time point. Subsequent review of these data indicated that the choice of T_0 as the baseline bacterial count for calculating 50% kill, and the use of interpolated titers would not adversely affect the interpretation of hSBA immunogenicity data.

Study V59P18, reporting on the effect of concomitant and sequential vaccine administration, was ongoing at the time of this submission. Data collected and analyzed up to study day 61 were submitted initially, and the complete study report was submitted February 24, 2009. Per agreement with CBER at the time of the pre-BLA meeting, complete safety follow-up data were submitted during the review period of the BLA, but concomitant administration immunogenicity data regarding GARDASIL will be reviewed as a labeling supplement.

5 Clinical Data Sources and Review Strategy

5.1 Material Reviewed

125300/0.0 (8/29/2008): **2.2** Introduction; **2.5** Clinical overview; **2.7** Clinical summary; **5.3.1.4** hSBA – Serum Bactericidal Assay for the Determination of Complement Fixing Antibodies against Neisseria Meningitidis Serogroups A, C, W135, Y; **5.3.5.1** Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (V59P6, V59P11, V59P13, V5917, V59P18); **5.3.5.3** Integrated Summary of Efficacy and Integrated Summary of Safety.

125300/0.2 (12/5/2008): **5.3.5.1.3** Study V59P18 Safety Update.

125300/0.3 5.3.5.1.3 (12/19/2008): Study V59P13 Reanalysis excluding sites 44 &50, Assay Variability Response, Statistical Analysis Effect of Assay as Variable.

125300/0.5 (2/6/2009): **5.3.5.1.** V59P13 study report addendum, additional assessments; V59P17 Study report addendum, Statistical Methods Interim Analysis Plan, Individual Efficacy Response Data, Additional Assessments.

125300/0.6 (2/24/2009): **5.3.5.1** V59P18 Clinical Study Report.

125300/0.7 (3/9/2009): **1.9** Pediatric Administrative Information.

125300/0.15 (8/21/2009): **1.11.3** Efficacy Information Amendment "Response to Clinical and Statistical Questions"; **5.3.1.4.1** Determination of Antibodies Against Neisseria Meningitidis Bacteria of the Sergroups A, C, W-135, Y in Human Sera Using SBA SOP 222582 – Standard Operating Procedure; **5.3.5.1.12** Study V59P13 Analysis Plan for Protocol.

125300/0.19 (01/15/2010): 1.11.4 Multiple Module Information (Novartis Positions on USPI); **1.14.1.3** Draft Labeling Text.

5.2 Review Strategy

The clinical study reports provided safety and immunogenicity data to evaluate the reactogenicity, safety and immunogenicity of MenACWY in comparison to the currently licensed quadrivalent meningococcal conjugate vaccine Menactra.

Clinical study V59P13 provided pivotal lot consistency, immunogenicity and safety data for the indication sought.

V59P18 provided an evaluation of MenACWY administered concomitantly with Boostrix and GARDASIL. An interim report was submitted initially and the complete study report was submitted during the review of this BLA. This study was reviewed for safety and immunogenicity of MenACWY and concomitant administration of Boostrix only. GARDASIL data will be reviewed subsequently as a labeling supplement.

V59P17 provided pivotal safety data for MenACWY administered to healthy adults and supportive immunogenicity data.

V59P11 was reviewed for safety only. Inadequate assay validation was provided for the pertussis serology, and a non-U.S formulation of Boostrix was used.

V59P6 was a phase 2 study comparing the b(4) formulations. Study participants that received the b(4) formulation contributed to the safety database.

Studies not related to the proposed indication (age group and current formulation) were not reviewed except for summary information regarding Serious Adverse Events.

5.3 Table of Clinical Studies

Table 1. Clinical Studies

Study Number	Location	Objectives	Design	Vaccine	# of Sub-jects	Population	# Injec-tions	Status; Report
Studies for Proposed Indication:								
V59P6	US	Safety and Immune response to 1 dose MenACWY vs Menomune	Single-Blind Randomized Controlled Phase 2 Multi-center	MenACWY 10-5-5-5ug (b)(4) IM MenACWY 10-5-5-5ug (b)(4) IM Menomune SC	164 151 209	Healthy Subjects 11-17y	One	Complete Full
V59P11	Italy	Safety and Immune response of MenACWY with and without Boostrix vs Boostrix alone	Observer-blind Randomized Controlled Phase 3 Multi-center	MenACWY 10-5-5-5µg (b)(4) IM (+Boostrix™ [EU]) MenACWY 10-5-5-5µg (b)(4) IM (+ Saline) Boostrix™ [EU] IM (+ Saline)	359 357 353	Healthy Subjects 11-17y and 19-25y	One	Complete Full
V59P13	US	Consistency of 3 lots MenACWY and Safety and Immune Response vs Menactra	Observer-Blind Randomized Controlled Phase 3 Multi-Center	MenACWY 10-5-5-5ug (b)(4) IM Menactra IM	2649 875	Healthy Subjects 11-17y and 19-55y	One	Complete Full
V59P17	Argentina Columbia	Safety and Immune response of menACWY vsl Menomune or Menactra	Observer-blind Randomized Controlled Phase 3 Multi-center	MenACWY 10-5-5-5ug (b)(4) IM Menactra IM (19-55y) Menomune SC (56-65y)	1817 889 109	Healthy Subjects 19-55y 56-65y	One	Complete
V59P18		Safety and Immune response of MenACWY with and without Boostrix and GARDASIL	Open Label Randomized Controlled Phase 3 Single-Center	MenACWY 10-5-5-5µg (b)(4) IM +Boostrix™+ GARDASIL ™ MenACWY 10-5-5-5µg (b)(4) IM → Boostrix™ → GARDASIL ™ Boostrix™ →MenACWY 10-5-5-5µg (b)(4) IM → GARDASIL ™				Complete

Other Studies								
V59P1 Non-IND	Switzer-land	Safety and Immune response 2 Formulations vs Mencevax	Open label Randomized Controlled Phase 1 Single-center	MenACWY 10-10-10-10ug (b)(4) IM menA+CWY 10-10-10-10ug (b)(4) IM Mencevax SC	30 30 30	Healthy 18-45	One	Complete Full
V59P1E1 Non-IND	Switzer-land	Safety and Immune response Persistence and memory	Open label Controlled Phase 2 Single- center	1/10th dose Mencevax IM	15 prior Men AC WY 14 prior PS	Healthy 18-45 Vrom V59P1	One	Complete Full
V59P2 Non-IND	Finland Ger-many	Safety and Immune response Dose ranging	Observer blind Randomized Controlled Phase 2 Multi-center	MenACWY 10-10-10-10µg (b)(4) IM MenACWY 0-10-10-10µg (b)(4) IM MenACWY 10-5-5-5µg (b)(4) IM MenACWY 5-5-5-5µg (b)(4) IM MenACWY 2.5-2.5-2.5-2.5µg (b)(4) IM Menjugate™ IM	109 106 103 101 104 97	Healthy 12-16 months	One or two	Complete Full
V59P2E1	Finland	Safety and immune reponse of Mencevax 6 months after menACWY	Open-label Controlled Phase 2 Single -center	Mencevax SC	94 prior Men AC WY 25 new	Healthy 22-24 months	One	Complete Full
V59P2E2 Non-IND	Finland	Safety and Immune response of mencevax 12 months after 1 or 2 doses of MenACWY	Open-label Controlled Phase 2 Single center	Mencevax SC	175 prior Men AC WY 62 new	Healthy 24-28 months	One	Complete Full

V59P3 Non-IND	Switzer-land	Safety and Immune Respnse of MenACWY b(4) vs Mencevax	Observer-blind Randomized Controlled Phae 1 Single-center	MenACWY 10-10-10-10µg b(4) IM MenACWY 10-10-10-10µg b(4) IM Mencevax™ IM	30 30 30	Healty 18-45y	One	Complete Full
V59P4	US	Safety and Immune response Dose ranging MenACWY b(4) vs Menomune	Double-blind Randomized Controlled Phase 2 Multi-center	MenACWY 10-10-10-10µg b(4) IM MenACWY 5-5-5-5µg b(4) IM MenACWY 5-5-5-5µg b(4) IM Menomune SC	81 79 75 80	Healthy 12-16 months 3-5y	One	Complete Full
V59P5	UK Canada	Safety and Immune Response Schedule finding Persistence boosting and memory	Open label Randomized Controlled Phase 2 Multi-center	MenACWY 10-5-5-5µg b(4) with 10-5-5-5 µg b(4) Boost IM MenACWY 10-5-5-5µg b(4) no Boost IM MenACWY 10-5-5-5µg b(4) IM followed by 1/5 Menomune SC MenACWY 10-5-5-5µg b(4) with 10-5-5-5 µg b(4) Boost IM MenACWY 10-5-5-5µg b(4) IM followed by 1/5 Menomune SC Menjugate with MenACWY 10-5-5-5µg b(4) Boost IM	229 49 98 135 45 45	Healthy 2 months	1, 3 or 4	Complete Full
V59P7	Finland Poland	Safety and Immune Response MenACWY b(4) vs. Mencevax	Observer-blind Randomized Controlled Phase 2	MenACWY 10-5-5-5µg b(4) IM MenACWY 10-5-5-5µg b(4) IM Mencevax™ IM	205 331 81	Healthy 12-35 months 36-59	2	Complete Full

			Multi-center	followed by MenACWY 10-5-5-5µg b(4) IM		months		
V59P8	US	Safety and Immune Response MenACWY vs. Menomune	Single-blind Randomized Controlled in Children Open label in toddlers Phase 2 Single-center	MenACWY 10-5-5-5µg b(4) IM MenACWY 10-5-5-5µg b(4) (+ PnC) IM MenACWY 10-5-5-5µg b(4) (+ DTaP) IM Menomune SC	453 71 73 310	Healthy 2-10 years 6-12 months	One	Complete Full
V59P9	Canada	Schedule finding and safety and Immune Response of 1 or 2 doses MenACWY	Open-label Partially randomized Controlled Phase 2 Multi-center	MenACWY 10-5-5-5µg b(4) IM Menjugate™ followed by MenACWY 10-5-5-5µg b(4) IM	125 50	Healthy 6-12 months	1 or 2	Complete Full
V59P14	US Argentina Columbia	Safety and Immune Response MenACWY with US routine vaccines vs routine vaccines followed by MenACWY	Open-label Randomized Phase 3 Multi-center	MenACWY 10-5-5-5µg b(4) IM (+ Routine Vaccines) Routine Vaccines Only Followed by MenACWY 10-5-5-5µg b(4) IM	3035 1521	Healthy 2 months	2 or 3 infant 1 or 2 toddler	Ongoing No CSR submitted
V59P16	UK	Safety and Immune Response Memory B cell response to MenACWY at 2 and 4 months	Open-label Randomized Phase 2 Single-center	MenACWY 10-5-5-5µg b(4) IM	216	Healthy 2 months	3	Ongoing No CSR submitted

5.4 Good Clinical Practices and Data Integrity

5.4.1 BIMO Inspection Summary

Background

Four clinical investigator inspections (V59P13 study sites) were performed in support of this Biologics License Application (BLA). Study subject population, geographic distribution, field resource considerations, and specific review committee concerns were among the factors used to select the inspected sites. The inspections focused on the pivotal U.S. safety and immunogenicity study (V59P13) and the comparison of information from the BLA to source documents at four clinical sites.

Summary

The bioresearch monitoring inspections of four clinical sites did not reveal problems that impact the data submitted in the application.

6 Clinical Studies

6.1 Indication

Active immunization of individuals 11 through 55 years of age to prevent invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y

6.2 Trial 1 (NCT00450437)

6.2.1 Protocol Number and Title:

Protocol V59P13: A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age.

6.2.1.1 Rationale/Objectives

Study V59P13 was undertaken as a pivotal study to compare the safety and immunogenicity of MenACWY to the currently U.S licensed meningococcal conjugate vaccine Menactra. Study V59P13 also evaluated clinical immune responses of three independent lots of MenACWY to evaluate lot consistency.

Immunogenicity

Primary Objectives (1 month after a single injection)

- To show consistency of immune response for three lots of MenACWY, measured by serum bactericidal activity geometric mean titer directed against *N. meningitidis* serogroups A, C, W-135, and Y using human complement (hSBA GMTs) in healthy subjects 11 to 18 years of age. This end-point must be met to combine data from the three lots for further analysis;

- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra™, defined as the percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y in healthy adolescents 11 to 18 years of age;

- To compare the immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with seroresponse directed against *N. meningitidis* serogroups A, C, W-135,and Y in healthy adults 19 to 55 years of age.

Seroresponse: For subjects with hSBA titer <1:4 at baseline, seroresponse is a postvaccination hSBA titer ≥ 1:8; for subjects with hSBA titer ≥ 1:4 at baseline, seroresponse is a postvaccination hSBA titer of at least 4 times the baseline.

Secondary Objectives (1 month after a single injection)

- To assess consistency of immune response for three lots of MenACWY, as measured by the percentage of subjects with seroresponse, hSBA titer ≥ 1:4 and ≥1:8, directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy adolescents 11 to 18 years of age);

- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with seroresponse directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55 years of age);

- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, defined as the percentage of subjects with hSBA ≥ 1:4 and ≥ 1:8, directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55 years of age);

- To compare immunogenicity of a single injection of MenACWY (3 lots combined) to that of a single injection of Menactra, as measured by hSBA GMTs directed against *N meningitidis* serogroups A, C, W-135, and Y (healthy subjects 11 to 55years of age).

Safety

Primary Objective

To compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY to the percentage of subjects presenting at least one severe systemic reaction to Menactra during the first 7 days (days 1 to 7) following a single injection administered to healthy subjects (11 to 55 years of age).

Secondary Objective

To describe and compare the safety profile following a single injection of MenACWY (3 lots combined) to that following a single injection of Menactra administered to healthy adolescents or adults (11 to 55 years of age) defined as the percentage and number of subjects with: immediate hypersensitivity reactions (within 30 minutes) following vaccination; local and systemic reactions during the period study day 1 to 7; adverse events (AEs) reported during the period study day 1 to 29; medically significant AEs reported during the period study day 30 to 180; serious adverse events (SAEs) reported from study day 1 to 180.

6.2.1.2 Design Overview

Study V59P13 was a randomized, controlled, observer blind multicenter study conducted in the U.S. Subjects were administered either MenACWY or Menactra intramuscularly (IM) by an

unblinded study vaccine administrator. The subjects were blinded to the study vaccine given. All safety follow-up performed by the investigator and study staff was also blinded. Blood was drawn before vaccination, at day 1, and after vaccination, at day 29 (window:+14 days). From day 29 to day 180 only safety was collected.

6.2.1.3 Population

6.2.1.3.1 Study Period

The study period was from March 1, 2007 to January 16, 2008

6.2.1.3.2 Study Sites and Recruitment

Study participants were recruited at 44 centers in the US. A total of 3539 subjects 11 to 55 years of age were randomized at a 1:1:1:1 ratio to one of four vaccine groups (MenACWY Lot 1, Lot 2, Lot 3, or Menactra). Randomization was stratified by center and age so that 2180 adolescents (11 to 18 years of age), 413 adults (19 to 34 years of age) and 946 adults (35 to 55 years of age) were enrolled (Table 2).

Table 2*. V59P13 Planned and Actual Enrollment

Vaccine Group	Subjects enrolled (planned) and actual	Subjects enrolled (planned) and actual		
		11-18	19-34	35-55
MenACWY Lot 1	(2574) 2663	(525) 548	(100) 104	(233) 235
MenACWY Lot 2		(525) 548	(100) 98	(233) 241
MenACWY Lot 3		(525) 544	(100) 106	(233) 239
Menactra	(858) 876	(525) 540	(100) 105	(233) 231

*From V59P13 Table 9.1-1 (CSR) Table 11.1-1 (CSR) and Study Synopsis (p. 3 of 17)

6.2.1.3.3 Inclusion Criteria

- Male and female individuals 11 to 55 years of age
- Written informed consent (18 to 55 years old), or
- Written assent and/or informed consent by parent or legal guardian (11 to 17 years old),
- Available for all visits and telephone calls scheduled for the study;
- In good health (by medical history, physical exam and judgment of the investigator).

6.2.1.3.4 Exclusion Criteria

- Unwilling or unable to give written informed assent or consent
- Perceived to be unreliable or unavailable for the duration of the study
- Previous or suspected disease caused by *N. meningitidis*;
- Household and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
- Previously immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (exception: receipt of OMP-

containing Hib vaccines was permitted);
Prior military service;

- Received investigational agents or vaccines within 90 days prior to enrollment or expected to receive an investigational agent or vaccine prior to completion of the study;
- Received any licensed vaccines within one month prior to enrollment or anticipated receipt of a licensed vaccine within 28 days after vaccination (exception: influenza vaccine administered up to 15 days prior to study vaccination and at least 15 days after study vaccination);
- Received a live viral vaccine within 60 days prior to enrollment;
- Significant acute or chronic infection within the 7 days prior to enrollment or fever (≥ 38°C) within 3 days prior to enrollment;
- Serious acute, chronic or progressive disease such as: history of cancer (excluding minor nonmelanoma skin cancer); complicated diabetes mellitus; advanced arteriosclerotic disease; autoimmune disease; HIV infection or AIDS; blood dyscrasias; congestive heart failure; renal failure; severe malnutrition. (Note: Subjects with mild asthma were eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids were not eligible for enrollment).
- Pregnant or breastfeeding mothers (urine pregnancy test at entry, sensitive to 20 IU β-hCG)
- Female of childbearing potential and sexually active with a male partner, without acceptable birth control measures at least 30 days before study entry and continuing through 180 days after the last vaccine dose.
- Epilepsy, progressive neurological disease, or history of Guillain-Barré Syndrome;
- History of anaphylaxis, serious vaccine reactions, or allergy to any vaccine component;
- Known or suspected impairment/alteration of immune function, either congenital, acquired or resulting from (for example): receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose >1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy); receipt of immunostimulants; receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study.
- Bleeding diathesis, or condition associated with a prolonged bleeding time;
- Down's syndrome or other known cytogenic disorders;
- Leaving the area of the study site before the end of the study period;
- Any condition that, in the opinion of the investigator, could interfere with the evaluation of the study objectives.

6.2.1.3.5 Concomitant Vaccines and Medications

Other than study vaccines, no other vaccines were to be given within 1 month prior to 28 days after vaccination (influenza vaccine could be administered up to 15 days prior and after 15 days following study vaccination).

All over the counter or prescription medications were recorded on the case report form. Analgesics or antipyretics were not routinely administered, but their use within the first 7 days following immunization was recorded.

6.2.1.4 Products Mandated by the Protocol

The investigational MenACWY vaccine was obtained by mixing the lyophilized MenA component (lot numbers Z008011, Z009011, and Z010011 for the Lot 1, Lot 2, and Lot 3 groups respectively) with the MenCWY full liquid vaccine (lot numbers Z79P40I1, Z79P41I1, and Z79P42I1 respectively) just before injection. The vaccine was administered intramuscularly.

MenACWY Composition after Reconstitution

Composition	Quantity per 0.5 mL dose
CRM197-MenA conjugate	10 µg MenA, --(b)(4)-- µg CRM197
CRM197-MenC conjugate	5 µg MenC, --(b)(4)-- µg CRM197
CRM197-MenW conjugate	5 µg MenW, --(b)(4)-- µg CRM197
CRM197-MenY conjugate	5 µg MenY, --(b)(4)-- µg CRM197
------b(4)----------	--b(4)---
--b(4)---	--b(4)---
--b(4)---	--b(4)---
------b(4)----------	--b(4)---
--b(4)---	--b(4)---

Licensed meningococcal ACWY polysaccharide-protein conjugate vaccine Menactra (manufactured by Aventis Pasteur Inc., Swiftwater, PA) was supplied as a single 0.5 mL injection (administered by IM injection in the left deltoid area) formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y, and W-135 polysaccharides (4 ug each) conjugated to approximately 48 µg of diphtheria toxoid protein carrier.

Menactra Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide (PS)	4 µg
Serogroup C polysaccharide (PS)	4 µg
Serogroup Y polysaccharide (PS)	4 µg
Serogroup W135 polysaccharide (PS)	4 µg
Diphtheria toxoid protein total	48 µg
(Each PS is conjugated to diphtheria toxoid)	
Sodium phosphate	--b(4)---
Sodium chloride	--b(4)---

6.2.1.5 Study Endpoints

6.2.1.5.1 Safety Endpoints

Primary
MenACWY was considered noninferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference ($P_{MenACWY}$ minus $P_{Menactra}$) was less than 6%. ($P_{MenACWY}$ and $P_{Menactra}$ are the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days after vaccination with MenACWY [3 lots combined] and Menactra, respectively).

Secondary
Descriptive analysis of the proportion of study participants, by age and vaccine group, experiencing solicited local and systemic adverse reactions (all, mild, moderate and severe), unsolicited adverse events and serious adverse events was reported.

6.2.1.5.2 Immunogenicity Endpoints

Primary

- Immunogenicity of the 3 lots of MenACWY was considered equivalent if for each serogroup and each pair of vaccine lots, the two-sided 95% confidence interval (CI) of the ratio of the GMTs 1 month after the vaccination was within the interval [0.50, 2.0].
- Immunogenicity of MenACWY (3 lots combined) was considered noninferior to Menactra in the 11 to 18 year old and 19 to 55 year old groups, for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with seroresponse for that serogroup (MenACWY minus Menactra) was greater than -10%. A MenACWY serogroup was considered to have a statistically significant higher immune response compared with that same serogroup of Menactra if the lower limit of the two-sided 95% CI around the difference in percentage of seroresponders (MenACWY minus Menactra) was greater than 0, i.e., the CI did not include zero.

The success criterion for this study was based upon all three co-primary objectives: lot-to-lot consistency for the three MenACWY lots (required for subsequent co-primary end-points), and seroresponse noninferiority of MenACWY as compared with Menactra for the 11 to 18 and 19 to 55 year old groups.

Secondary

- Immunogenicity of the three lots of MenACWY was equivalent if for each serogroup and each pair of vaccine lots, the two-sided 95% CI on the difference in proportions of responders (seroresponse, hSBA titer ≥ 1:8, or hSBA titer ≥ 1:4) was within the interval [-10%, 10%].
- Immunogenicity of MenACWY (3 lots combined) was noninferior to the immunogenicity of Menactra, in the 11 to 55 years group, for any of the four

serogroups, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with: (a) seroresponse; (b) hSBA ≥ 1:8 (or hSBA ≥ 1:4) for that serogroup (MenACWY minus Menactra) was greater than -10%. A statistically significant superior immune response of MenACWY compared with Menactra was identified if the lower limit of the two-sided 95% CI around the difference in percentage of (a) seroresponse; (b) hSBA ≥ 1:8 (or hSBA ≥ 1:4) (MenACWY minus Menactra) was greater than 0, i.e., the CI did not include zero.

- Immunogenicity response of MenACWY (3 lots combined) was considered noninferior to the immunogenicity of Menactra, in the 11 to 55 yoa group, if the lower limit of the two-sided 95% CI around the ratio of hSBA GMTs between MenACWY and Menactra (MenACWY/Menactra) at 1 month after vaccination was above 0.5.

6.2.1.6 Surveillance and Monitoring

6.2.1.6.1 Safety Monitoring

Study personnel observed subjects for 30 minutes post-vaccination. Subjects were given a diary card and instructed on reporting AEs. Subjects were contacted by telephone on study day 3. During visit 2 (study day 29), subjects were examined and interviewed. The diary cards were collected and a worksheet was provided for study days 30 to 180. On study day 180 (study days 165 to 195), the subjects were contacted by telephone to review and record any safety information.

Local and systemic solicited and unsolicited adverse events were recorded on a diary card by subjects or parents or guardians for study days 1-7. Solicited AEs were local pain, erythema, induration, temperature, chills, nausea, malaise, myalgia, arthralgia, headache and rash.

Adverse events necessitating a physician's visit or resulting in premature study withdrawal were monitored days 8-29.

Medically significant AEs that required a physician visit, Emergency Department visit or lead to study withdrawal were monitored from day 30 to 180 (excluding preplanned visits, medical office visits or ER visits for routine medical care and common acute conditions such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections gastroenteritis superficial skin infections and contact dermatitis).

Serious Adverse Events (SAEs) were monitored from day 1 – 180 and until resolution and/or the cause was identified.

Reviewer note: The exclusion from reporting of "common acute conditions" is potentially subjective and could exclude reporting of events that are initially thought to fit this category. The study was observer blind and randomized so any potential for under-reporting would likely affect both vaccine groups equivalently.

6.2.1.6.2 Immunogenicity

Blood was drawn before vaccination (at day 1), and 4 weeks after vaccination (at day 29; window:+14 days).

6.2.1.7 Statistical Considerations

See study safety and immunogenicity endpoints 6.2.1.5. Secondary safety objectives were evaluated descriptively. Safety analyses were based on the Safety population. Primary immunogenicity analyses were based on the Per-Protocol Population, Immunogenicity (see definitions below).

Definition of populations to be analyzed:
Enrolled population: contained all subjects enrolled and randomized in the study. This population was used for the analysis of demographics and all subject listings.

Exposed population: Subjects who actually received a study vaccination. In case of an error in administration, the subject was included in the vaccination group for the treatment received.

Safety population: All subjects who received the study vaccination and had post-baseline safety data. This population was used for the analysis of local and systemic reactions and other adverse events. Subjects were included in the group for the vaccination actually received.

Intention-to-treat (ITT) population, Immunogenicity: all subjects in the enrolled population who actually received a study vaccination and provided at least one evaluable serum sample before or after vaccination. Subjects were included in the vaccine group they were assigned during randomization. The size of the ITT population was summarized but was not used to evaluate any of the objectives.

Modified Intention-to-treat (MITT) population, Immunogenicity: all subjects in the ITT population who actually received a study vaccination and provided at least one evaluable serum sample both before and after vaccination. The MITT population was summarized and used to evaluate only the primary endpoints.

Per protocol (PP) population, Immunogenicity: all subjects in the MITT population who provided evaluable serum samples (titer results were available) both before and after vaccination and had no major protocol deviation, as defined prior to unblinding. This population was used to evaluate all the primary, secondary, and tertiary immunogenicity objectives. A "major" deviation was defined as a protocol deviation that was considered to have a significant impact on the immunogenicity results of the subject. All protocol deviations were identified prior to the analysis (e.g., visit out of window, unmet inclusion/exclusion criteria, forbidden concomitant medications).

6.2.2 Results

6.2.2.1 Populations Enrolled/Analyzed

A total of 3539 subjects were enrolled and randomized at a 1:1:1:1 ratio to receive one injection of MenACWY (lot 1, lot 2, or lot 3) or Menactra. A total of 2649 subjects were administered MenACWY and 875 Menactra. 15 subjects were enrolled but not vaccinated, and 131 additional were excluded from the immunogenicity analysis due to major protocol deviations.

Major protocol deviations were distributed proportionally across the immunization groups: 49 did not meet entry criteria, 9 received the wrong vaccine or an incorrect dose, 24 received excluded concomitant medications, 88 had no blood draw at visit 2, 39 had no blood draw at visit 1, 16 had a visit 2 blood draw outside the day 24 to day 56 window, 9 received a previous meningococcal vaccine, 2 had blood left at room temperature for an extended time, 4 received other vaccines, 1 had previous meningococcal infection.

No pre-identified immunogenicity subset was used in this study; all subjects were to have blood drawn which could potentially have been used for analysis. The protocol did specify that a randomly selected group of subjects be chosen for analysis of serogroups A, W, and Y (all available samples for all subjects were tested for serogroup C). The protocol-specified selection was performed by the b(4) who provided the randomization for the study. The subsets for hSBA testing are shown in Table 3. The disposition of subjects selected for hSBA testing by age groups is shown in Table 4 and Table 5.

Reviewer note: The original plan for subset selection for hSBA testing had potential for unblinding the vaccine group of some sera. This problem was addressed by the sponsor when recognized and was submitted in the SAP with a revised subset plan (developed after enrollment had been completed).

Table 3*. Number of Subjects by Vaccine Group and Testing Allocation

Age Group	Vaccine Group	C only	AC	ACWY
11-18	MenACWY	435	36	1104
	Menactra	145	65	315
19-55	MenACWY	-	474	525
	Menactra	-	13	320

*from Table 17-2 (p. 32 of 84) Clinical Responses S0015

Table 4*. Accounting of Subjects From Selection for Testing to Resulting PP Population, Ages 11 to 18

	A		C		W		Y	
Reason	**ACWY**	**Menactra**	**ACWY**	**Menactra**	**ACWY**	**Menactra**	**ACWY**	**Menactra**
Selected	1140	380	1575	525	1104	315	1104	315
Missing at least 1 blood draw	43	17	63	20	42	16	42	16
No valid result, sample ID discrepancy, sample sent too late, etc.	6	0	12	0	23	7	10	1
Total MITT	1091 (96%)	363 (96%)	1500 (95%)	505 (96%)	1039 (94%)	292 (93%)	1052 (95%)	298 (95%)
Other major protocol deviation	16	4	17	4	15	4	16	4
Total PP	1075 (94%)	359 (94%)	1483 (94%)	501 (95%)	1024 (93%)	288 (91%)	1036 (94%)	294 (93%)

*from Table 17-4 (p. 35 of 84) Clinical Responses S0015

Table 5*. Accounting of Subjects From Selection for Testing to Resulting PP Population, Ages 19 to 55

	A		C		W		Y	
Reason	**ACWY**	**Menactra**	**ACWY**	**Menactra**	**ACWY**	**Menactra**	**ACWY**	**Menactra**
Selected	999	333	999	333	525	320	525	320
Missing at least 1 blood draw	14	4	14	4	8	4	8	4
No valid result, sample ID discrepancy, sample sent too late, etc.	7	6	9	9	27	22	7	8
Total MITT	978 (98%	) 323 (97%)	976 (98%)	320 (96%)	490 (93%)	294 (92%)	510 (97%)	308 (96%)
Other major protocol deviation	15	2	15	2	6	2	7	2
Total PP	963 (96%)	321 (96%)	961 (96%)	318 (96%)	484 (92%)	292 (91%)	503 (96%)	306 (96%)

*from Table 17-5 (p. 35 of 84) Clinical Responses S0015

6.2.2.2 Safety Outcomes

The primary safety objective, to compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY to that observed in the Menactra group during the first 7 days following a single injection administered to healthy subjects 11 to 55 years of age, was met: the upper limit of the 95% CI of the vaccine group difference was 2%, below the criterion set, i.e., <6% (Table 6).

Table 6*. Primary Safety Analysis: Percentage of Subjects With at Least One Severe Systemic Reaction, Days 1 to 7, Age 11 to 55

Systemic Reaction	Number (%), 95%CI of Subjects with Solicited Reaction		MenACWY minus Menactra Vaccine Group
	11 – 55 years	11 – 55 years	Difference, 95%
	MenACWY	Menactra	CI
	N=2649	N=875	
Severe	94 (4%)	24 (3%)	1% (-1%, 2 %)

*from Table 12.2-1 (p. 91 of 712) CSR V59P13

6.2.2.2.1 Immediate Reactions

No anaphylaxis or immediate hypersensitivity reactions occurred during 30 minute observation following vaccination.

6.2.2.2.2 Solicited Local and Systemic Reactions

The percentages of subjects reporting all solicited AEs and local solicited AEs were lower in the MenACWY group than in the Menactra group (solicited AEs: 62% vs. 67%, respectively; local solicited AEs: 48% vs. 53%, respectively), while they were similar for the systemic solicited AEs and other indicators of reactogenicity (systemic: 41% vs. 40%, respectively; use of analgesic/antipyretic medication and stayed at home due to vaccination: 21% in both vaccine groups).

Pain, the most frequently reported local solicited AE, was reported by a lower percentage of MenACWY recipients than in the Menactra group during days 1 to 7 (42% vs. 48%, respectively, $P < .001$) and days 1 to 3 (41% vs. 48%, respectively, $P < .001$). Pain was slightly more frequent following MenACWY during days 4 to 7 (12% vs. 9%, respectively, $P = .012$). Severe local reactions were more frequent in the MenACWY group (overall, 4% vs. 2%, respectively, Table 7), primarily differences in erythema and induration were observed. Most local reactions were experienced during the first three days post vaccination. Six subjects in the MenACWY group (08/1063, 20/1024, 38/1078, 44/1168, 53/1036, and 56/1085) reported erythema > 50 mm which lasted from five to eight days, two subjects in the MenACWY group (35/1043 and 44/1168) reported induration > 50 mm which lasted five and six days, one subject in the MenACWY group (15/1029) reported severe pain for seven days. The median duration of all severe local reactions were similar in the MenACWY and Menactra groups (2 days for severe pain in both vaccine groups; 4 days for erythema >50mm in both vaccine groups and 3 and 4 days in the MenACWY and Menactra groups, respectively, for induration >50mm)

Solicited systemic AEs were similar in the MenACWY and Menactra groups (41% and 40%, respectively, $P = .32$) (Table 8). The most commonly reported systemic solicited AEs were headache (28% and 27%, respectively), myalgia (17% in both vaccine groups), and malaise (11% in both vaccine groups). Severe headache was reported by 2% and 1%, respectively, while severe myalgia and malaise were reported by 1% in both vaccine groups. Most systemic solicited AEs were reported in the first three days post vaccination. All cases of severe headache

were transient and lasted four days or less, except for one subject in the MenACWY group (19/1024), who reported severe headache for five days. The majority of cases of severe myalgia were transient and lasted from one to four days; three subjects in the MenACWY group (15/1029, 53/1019, and 56/1155) reported severe myalgia which lasted from eight to 15 days. All cases of severe malaise were transient and lasted four days or less.

Table 7*. Local Reactions: Overall and by Severity, Age 11 to 55

Type of Reaction	Severity	Number (%) of Subjects with Local Reaction	
		MenACWY N=2642	Menactra N=875
Any Local Reaction	Any	1275 (48%)	467 (53%)
	Severe	95 (4%)	17 (2%)
Pain	Any	1105/2641 (42%)	424 (48%)
	Severe	19/2641 (0.7%)	7 (0.8%)
Erythema	Any	414 (16%)	126 (14%)
	>50mm	64 (2.4%)	10 (1.1%)
Induration	Any	324 (12%)	88 (10%)
	>50mm	45 (1.7%)	5 (0.6%)

*from Table 12.2.3-1 (p. 97 of 712) CSR V59P13

Table 8*. Summary of Reactogenicity – Systemic Reactions and Other Indicators of Reactogenicity, Overall and by Severity, Age 11 to 55

Type of Reaction	Severity	Number (%) of Subjects with Systemic Reaction	
		MenACWY N=2643	Menactra N=875
Systemic Reaction	Any	1086 (41%)	350 (40%)
	Severe	94 (4%)	24 (3%)
Chills	Any	168 (6%)	50 (6%)
	Severe	10 (<1%)	1 (<1%)
Nausea	Any	260 (10%)	65 (7%)
	Severe	14 (1%)	5 (1%)
Malaise	Any	279 (11%)	99 (11%)
	Severe	25 (1%)	10 (1%)
Myalgia	Any	452 (17%)	149 (17%)
	Severe	29 (1%)	7 (1%)
Arthralgia	Any	197 (7%)	54 (6%)
	Severe	11 (<1%)	3 (<1%)
Headache	Any	731 (28%)	237 (27%)
	Severe	49 (2%)	12 (1%)
Rash	Any	69 (3%)	20 (2%)
Fever ≥ 38°C	Any	32 (1%)	6 (1%)
	Severe (≥ 39°C)	9 (<1%)	1 (<1%)
Any Other Reaction			
Analgesic/ Antipyretic Med.	Used	533 (20%)	178 (20%)
Stayed Home		69 (3%)	17 (2%)

*from Table 12.2.3-3 (p. 100 of 712) CSR V59P13

6.2.2.2.3 Unsolicited Adverse Events, Including Serious Adverse Events

The percentages of subjects reporting unsolicited AEs requiring a physician's visit, emergency room visit, or premature withdrawal were similar between the MenACWY and Menactra groups during days 1 to 29 (19% and 20%, respectively, none of which reported an AE leading to withdrawal). During days 30 to 180, unsolicited medically significant AEs were reported for 10% and 7% in the MenACWY and Menactra groups, respectively. None that occurred after day 29 were assessed as possibly or probably related by study personnel.

Overall, the percentage of subjects experiencing any unsolicited AE was similar between the MenACWY and Menactra groups (26% and 24%, respectively). The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was "infections and infestations" (6% in both vaccine groups), followed by "injury and poisoning" (4% and 5%, respectively), while

"respiratory thoracic and mediastinal disorder", "muscular and connective tissue and bone disorders", "nervous system disorder", and "general disorders and administration site conditions" were all affected in 3% to 4% of the subjects in the two vaccine groups. All other SOCs were affected in no more than 2% of subjects.

In total, 207 subjects reported at least one unsolicited AEs considered possibly related by study investigators (6% in both vaccine groups). The most commonly experienced possibly or probably related unsolicited AEs were injection site erythema and injection site pruritis, reported each by 21 subjects (0.8%) in the MenACWY group and 2 subjects (0.2%) in the Menactra group. The other most commonly reported possibly or probably related unsolicited AE reported was headache, reported by 14 subjects (0.5%) in the MenACWY group and 4 subjects (0.5%) in the Menactra group.

Severe possibly or probably related unsolicited AEs were reported by 12 (0.5%) subjects in the MenACWY group and by 2 subjects (0.2%) in the Menactra group. Six severe possibly or probably related AEs reported by subjects in the MenACWY group (03/1020, 15/1029, 44/1227, 53/1019, 56/1085, and 56/1155) lasted from seven to 58 days (Severe headache and nausea with moderate local and systemic reactions; severe local pain and myalgia; severe depression; severe myalgia and URI; severe erythema and urticaria with left arm swelling; severe malaise, myalgia, arthralgia).

Unsolicited AEs reported by 1% or more of subjects within the first 29 days were headache, pharyngolaryngeal pain (both reported by 1.5% in both vaccine groups) and diarrhea, reported by 0.6% in the MenACWY and 1.3% in the Menactra group. These were mostly mild to moderate in severity.

No deaths occurred during this study. A total of 28 subjects reported SAEs, (Table 9). Four SAEs occurred in MenACWY recipients within study days 1-30 (drug overdose, seizure, Meckel's diverticulum, and depression). Two SAEs occurred in Menactra recipients during study days 1-30 (intervertebral disk protrusion and fall with trauma). Three seizures occurred in MenACWY recipients during the 6 months post vaccination: 1) simple complex partial seizure occurred in a 17 year old female on day 22; evaluation revealed a normal MRI and a right temporoparietal focus on EEG; 2) generalized tonic-clonic seizure occurred in a 17 year old male on day 35 following 2 days of sleep deprivation; neurologic evaluation was non-focal with a normal MRI and CT and a diagnosis of juvenile myoclonic epilepsy was assessed; 3) generalized seizure occurred in a 40 year old female 151 days after vaccination following sleep deprivation; MRI, CT and lumbar puncture were normal, but a photoconvulsive response with photic stimulation was noted on EEG. (*CSR V59P13;14.3.3 p.670 of 712*).
Reviewer's note: Review of narratives of these events did not suggest causality

A total of 18 pregnancies occurred, 15 (0.98% of the vaccinated females 11 to 55 years old) in the MenACWY group and three (0.6% of the vaccinated females 11 to 55 years old) in the Menactra group. Pregnancy outcomes are reviewed for all studies in the Human Reproductive Safety section of this review (7.5.3).

Table 9*. Listing of Subjects with SAEs by Treatment Group

Subject No.	Age	Preferred Term	Onset (Study Day)	Duration (days)	Outcome	Hospital-ization	Relatedness
MenACWY							
02/1034	31	Road Traffic Accident	51	---a	AE Persist	Yes	None
10/1050	16	Myoclonic Epilepsy	36	<1	Recovered		None
13/1014	16	Multiple Drug Overdose Intentional	2	3	Recovered	Yes	None
19/1030	15	Intentional Overdose	58	<1	Recovered		None
20/1024	11	Appendicitis	148	3	Recovered	Yes	None
23/1008	17	Simple Partial Seizures	22	5	Recovered	Yes	None
34/1055	12	Vitello-Intestinal Duct Remnant	22	3	Recovered	Yes	None
35/1074	12	Depression Suicidal	11	6	Alive w/seq	Yes	None
37/1077	12	Road Traffic Accident	160	4	Recovered	Yes	None
44/1072	40	Meningitis Viral	108	23	Recovered	Yes	None
		Pneumonia	109	3	Recovered	Yes	None
44/1110	40	Epilepsy	152	3	Alive w/seq	Yes	None
45/1042	17	Tonsillitis	114	16	Recovered	Yes	None
45/1074	13	Epiphysiolysis	103	121b	Recovered	Yes	None
45/1080	34	Pulmonary Embolism	159	3	Recovered	Yes	None
45/1093	19	Dystonia	91	<1	Recovered	Yes	None
47/1057	40	Chest Pain	152	1	Recovered	Yes	None
53/1085	14	Clavicle Fracture	74	1	Recovered	Yes	None
53/1145	17	Suicide Attempt	112	4	Recovered	Yes	None
		Accidental Overdose	134	1	Recovered	Yes	None
		Suicide Attempt	149	3	Recovered	Yes	None
		Suicide Attempt	157	3	Recovered	Yes	None
53/1291	16	Traumatic Brain	118	10	Alive w/seq	Yes	None
		Injury					
53/1299	16	Ligament Rupture	142	1	Recovered	Yes	None
54/1013	17	Staphylococcal Infection	73	1	Recovered	Yes	None
54/1016	18	Road Traffic Accident	165	<1	Recovered	Yes	None

56/1007	27	Overdose	122	5	Recovered	Yes	None
		Respiratory Failure	122	5	Recovered	Yes	None
		Suicide Attempt	122	9	Recovered	Yes	None
Menactra							
22/1032	15	Therapeutic Agent Toxicity	121	1	Recovered	Yes	None
44/1091	38	Intervertebral Disc Potrusion	11	4b	Recovered	Yes	None
45/1029	22	Burns Second Degree	44	28	Alive w/seq	Yes	None
		Circulatory Collapse	44	<1	Recovered	Yes	None
		Syncope Vasovagal	44	<1	Recovered	Yes	None
46/1061	26	Fall	17	86	Recovered	Yes	None
53/1297	18	Dislocation of Sternum	69	2	Recovered	Yes	None

*from Table 12.3.1.2-1 (p. 105 of 712) CSR V59P13

6.2.2.3 Immunogenicity Outcomes

The Per Protocol population of both vaccine groups was 96% of the enrolled population. Baseline and other demographic characteristics were similar between the vaccine groups, both in the 11 to 18 year old MenACWY population (analyzed for lot-to-lot consistency) and in the overall enrolled population.

All three primary immunogenicity objectives were met:

- The primary lot-to-lot consistency objective was met: the two-sided 95% CI on the ratio of the GMTs (Lot 1/Lot 2, Lot 1/Lot 3, and Lot 2/Lot 3) was within the interval [0.5, 2.0] for all four serogroups and all three pairs of vaccine lots in the 11 to 18 MenACWY age group. (Table 10).
- Non-inferiority of immune response to MenACWY in the 11 to 18 age group: the lower limit of the 95% CI around the difference of the percentage of seroresponders (MenACWY minus Menactra) was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups A, W, and Y (Table 11).
- Non-inferiority of immune response to MenACWY in the 19 to 55 age group: the lower limit of the 95% CI around the difference of the percentage of seroresponders (MenACWY minus Menactra) was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups C, W, and Y (Table 11).

The two secondary immunogenicity lot-to-lot consistency objectives were not met:

- The two-sided 95% CI of the difference in the proportions of seroresponders was within the interval [-10%, 10%], set as the success criterion for the secondary lot-to-

lot consistency objective for all three pairs of MenACWY vaccine lot groups (Lot 1 minus Lot 2, Lot 1 minus Lot 3, and Lot 2 minus Lot 3) for serogroup C (statistical power 80%), while it was outside this range for at least one pair of MenACWY lots for serogroups A (statistical power 49%), W (statistical power 49%), and Y (statistical power less than 39%).

- The two-sided 95% CI on the difference in the proportion of subjects with hSBA titer ≥ 1:8 at day 29 was within the interval [-10%, 10%] for each of the three pairs of MenACWY vaccine lots for serogroups C, W, and Y (statistical power greater than 90%) but it was outside this range for one of the three pairs of MenACWY lots for serogroup A (statistical power 49%).

All three secondary immunogenicity noninferiority objectives were met:

- In the 11 to 55 age group, the lower limit of the two-sided 95% CI around the difference in the percentages of seroresponders between the MenACWY and Menactra groups was greater than -10% (noninferiority criterion) for all four serogroups and it was greater than 0% (superiority criterion) for serogroups C, W, and Y.
- In the 11 to 55 age group, the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with hSBA titer ≥ 1:8 was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (superiority criterion) for serogroups W and Y.
- The lower limit of the two-sided 95% CI around the ratio of hSBA GMTs between the MenACWY and Menactra groups was above 0.5 (noninferiority criterion) for all four serogroups.

Table 10*. Primary Lot to Lot Consistency Objective: hSBA GMT Vaccine Group Ratios at Day 29, Ages 11 to 18 Years, PP Population

		Day 29 GMT vaccine group ratios (95% CI)
A	Lot 1 / Lot 2	0.89 (0.68, 1.16)
	Lot 1 / Lot 3	0.95 (0.73, 1.23)
	Lot 2 / Lot 3	1.06 (0.81, 1.38)
C	Lot 1 / Lot 2	1.33 (1, 1.77)
	Lot 1 / Lot 3	1.2 (0.9, 1.6)
	Lot 2 / Lot 3	0.9 (0.68, 1.2)
W	Lot 1 / Lot 2	0.79 (0.63, 0.97)
	Lot 1 / Lot 3	1.06 (0.86, 1.31)
	Lot 2 / Lot 3	1.35 (1.09, 1.67)
Y	Lot 1 / Lot 2	0.79 (0.61, 1.02)
	Lot 1 / Lot 3	0.91 (0.7, 1.18)
	Lot 2 / Lot 3	1.16 (0.89, 1.5)

*from Table11.4.1.1-1 (p. 79 of 712) CSR V59P13

Reviewer note: hSBA serogroup W GMTs for each lot were higher than hSBA serogroup W GMT for Menactra.

Table 11*. Primary Immunogenicity Objective: Percentage of Seroresponders at day 29, Ages 11 to 18 and 19 to 55, PP Population

			11-18			19-55		
			MenACWY	**Menactra**	**Vaccine Group Difference (95% CI)**	**MenACWY**	**Menactra**	**Vaccine Group Difference (95% CI)**
A	Baseline titer	<1:4	75% 780/1039	66% 230/347	9% (3%, 15%)	67% 582/875	67% 191/283	-1% (-7%, 5%)
		≥ 1:4	58% 21/36	67% 8/12	-8% (-35%, 24%)	70% 62/88	71% 27/38	-1% (-17%, 18%)
	Overall		75% 801/1075	66% 238/359	**8% (3%, 14%)**	67% 644/963	68% 218/321	**-1% (-7%, 5%)**
C	Baseline titer	<1:4	79% 771/977	79% 260/331	0% (-5%, 6%)	71% 425/596	62% 133/214	9% (2%, 17%)
		≥ 1:4	68% 345/506	62% 105/170	6% (-2%, 15%)	61% 223/365	51% 53/104	10% (-1%, 21%)
	Overall		75% 1116/1483	73% 365/501	**2% (-2%, 7%)**	67% 648/961	58% 186/318	**9% (3%, 15%)**
W	Baseline titer	<1:4	94% 570/609	83% 150/180	10% (5%, 17%)	82% 131/160	71% 67/94	11% (0%, 22%)
		≥ 1:4	47% 193/415	28% 30/108	19% (9%, 28%)	35% 112/324	26% 52/198	8% (0%, 16%)
	Overall		75% 763/1024	63% 180/288	**12% (6%, 18%)**	50% 243/484	41% 119/292	**9% (2%, 17%)**
Y	Baseline titer	<1:4	81% 510/630	54% 95/176	27% (19%, 35%)	66% 173/263	52% 83/160	14% (4%, 23%)
		≥ 1:4	47% 192/406	22% 26/118	25% (16%, 34%)	45% 108/240	27% 39/146	18% (9%, 28%)
	Overall		68% 702/1036	41% 121/294	**27% (20%, 33%)**	56% 281/503	40% 122/306	**16% (9%, 23%)**

*from Table 11.4.1.1-2 (p. 81 of 712) CSR V59P13

6.2.2.4 Comments and Conclusions

6.2.2.4.1 Study Design and Population

Study V59P13 was a blinded, randomized and controlled study. Possible unblinding of two sites was reported, but analysis of safety and immunogenicity data excluding those sites did not alter the study outcomes. The exclusion of common acute medical problems from safety reporting is unlikely to affect the study conclusions because study personnel involved in assessing safety

were blinded to study group. An original protocol plan for designating sera for specific serogroup SBA testing could have led to unblinding of the laboratory for some sera. This was recognized by the applicant prior to completion of the sample allocation, and a revised allocation plan was incorporated into the statistical analysis plan.

6.2.2.4.2 Safety

The primary safety objective demonstrated that MenACWY was noninferior to Menactra in terms of severe systemic reactions(i.e., the upper limit of the two-sided 95% CI of the difference in the percentage of subjects experiencing at least one severe reaction was below 6%). Some solicited reactions were reported less frequently in the MenACWY group, but report of severe reactions, while infrequent occurred more often than following Menactra. Overall, the safety profile of MenACWY was similar to that of Menactra for solicited local and systemic reactions, unsolicited adverse events and SAEs.

6.2.2.4.3 Immunogenicity

All 20 protocol-specified analyses performed for the primary objectives (four serogroups, three pairs of lots for GMT ratios, and four serogroups, two age groups for the MenACWY vs. Menactra comparison) met the protocol-specified criteria for or lot-to-lot consistency, and for non-inferiority in comparison to Menactra.

6.3 Trial 2 (NCT00474487)

6.3.1 Protocol Number and Title:

Study V59P17: A Phase 3, Randomized, Observer-blind, Controlled, Multicenter Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune™) when One Dose is Administered to Healthy Subjects 56-65 Years of Age.

6.3.1.1 Rationale/Objectives

Study V59P17 was conducted to evaluate the safety and immunogenicity of a single dose of MenACWY in healthy adults.

Primary Objective

Safety

To compare the percentage of subjects presenting at least one severe systemic reaction to MenACWY with the percentage presenting at least one severe systemic reaction to Menactra during the first 7 days (days 1 to 7) following a single dose administered to healthy subjects (19 to 55 years of age).

Secondary Objectives

Immunogenicity

- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse, human Serum Bactericidal Assay (hSBA) ≥ 1:4 or ≥ 1:8 directed against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, in healthy subjects 19 to 55 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, as measured by hSBA geometric mean titer (GMT) response against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, in healthy subjects 19 to 55 years of age.
- To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menomune, defined as percentage of subjects with hSBA ≥ 1:4 or ≥ 1:8 or a seroresponse against *N meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, in healthy subjects 56 to 65 years of age.
- To compare the immunogenicity of a single dose MenACWY with the immunogenicity of a single dose of Menomune, as measured by hSBA GMTs against *N meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, in healthy subjects 56 to 65 years of age.

Safety

To describe and compare the percentages of subjects in the MenACWY and Menactra vaccine groups and the MenACWY and Menomune vaccine groups when administered to healthy adults aged 19 to 55 years and aged 56 to 65 years, respectively, in terms of:

- Immediate hypersensitivity reactions (within 30 minutes) following vaccination,
- Local and systemic reactions during study days 1 to 7,
- AEs reported during study days 1 to 29,
- Medically significant AEs reported during study days 30 to 180,
- Serious adverse events (SAEs) reported from study day 1 to 180.

6.3.1.2 Design Overview

This was a phase 3, observer-blind, multicenter, randomized, controlled study in healthy subjects (19 to 65 years of age). Approximately 2500 healthy subjects 19 to 55 years of age were to be randomly assigned to receive either MenACWY or Menactra.

Immunogenicity testing was carried out for the first 200 subjects of the 19 to 34 years of age subgroup and for the first 200 subjects of the 35 to 55 years subgroup; these subjects were randomized in a 1:1 ratio. The remaining subjects in both age groups were randomized in a 2:1 ratio. Subjects in the 56 to 65 year subgroup were randomized in a 2:1 ratio (MenACWY:Menomune), and the initial 225 subjects were tested for immunogenicity.

After vaccination, the subjects were monitored in the clinic for 30 minutes to assess any signs or symptoms of anaphylaxis, local injection site reactions, and systemic reactions. An independent,

external Data Monitoring Committee (DMC) was established to monitor safety by reviewing scheduled analyses.

The trial was designed as an observer-blind study. Because the syringes of the study and control vaccines had a different appearance, and reconstitution and administration methods, study personnel that performed the safety assessments were different from those who performed the vaccinations. Sponsor and subjects were blinded to treatment.

6.3.1.3 Population

Approximately 2500 healthy subjects 19 to 55 years of age were to be randomly assigned to receive either MenACWY or Menactra.

6.3.1.3.1 Study Period

23 May 2007 to 26 Feb 2008

6.3.1.3.2 Study Sites and Recruitment

Three study sites: Buenos Aires, Argentina; Cali Colombia; Bogota, Colombia.

6.3.1.3.3 Inclusion Criteria

- 19 to 65 years of age
- Provided written informed consent
- Available for all visits and telephone calls for the study
- Judged to be in good health by medical history, physical assessment

6.3.1.3.4 Exclusion Criteria

- unwilling or unable to give written informed consent to participate in the study;
- perceived to be unreliable or unavailable for the duration of the study period;
- previous or suspected disease caused by *N. meningitidis*;
- household contact with and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
- previously immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (Exception: Receipt of Outer Membrane Protein [OMP]-containing *Haemophilus influenzae* type b [Hib] vaccines was permitted);
- received any investigational agents or vaccines within 90 days prior to enrollment or expected to receive an investigational agent or vaccine prior to the completion of the study;
- received any licensed vaccines within 1 month prior to enrollment or for whom receipt of a licensed vaccine was anticipated within 1 month after vaccination (Exception: Influenza vaccine could have been administered up to 15 days prior to study vaccination and at least 15 days after study vaccination);
- received a live viral vaccine within 60 days prior to enrollment;

- experienced a significant acute or chronic infection within the 7 days prior to enrollment (for example, requiring systemic antibiotic treatment or antiviral therapy) or fever (≥ 38°C) within 3 days prior to enrollment.

6.3.1.3.5 Concomitant Vaccines and Medications

All prescription medication and antibiotics, including nonstudy vaccines, taken by the subjects were documented on the "Concomitant Medications" Case Report Form (CRF).

Concomitant vaccines: No concomitant vaccines were administered during visit 1. Normal routine or catch-up vaccinations appropriate for this age group, and recommended vaccines for high-risk situations not otherwise excluded by the protocol inclusion/exclusion criteria were allowed if given at least 1 month after study vaccination (exception: influenza vaccine administered up to 15 days prior to or at least 15 days after study vaccination).

6.3.1.4 Products Mandated by the Protocol

Adults were randomized to received MenACWY, Menactra or Menomune.

MenACWY: One 0.5 mL dose of MenACWY was administered by IM injection in the left deltoid area. (Composition as in V59P13 shown in section 6.2.1.4)
Menactra: One 0.5 mL dose of Menactra was administered by IM injection in the left deltoid area. (Composition as shown in V59P13 section 6.2.1.4)
Menomune: One 0.5 mL dose of Menomune was administered by SC injection in the left upper arm.

Table 12. Menomune Composition

Composition	Quantity per 0.5 mL dose
Serogroup A polysaccharide	50 µg
Serogroup C polysaccharide	50 µg
Serogroup W-135 polysaccharide	50 µg
Serogroup Y polysaccharide	50 µg
Lactose	2.5 to 5 mg
Liquid diluent: water for injection	qs to 0.5 mL

6.3.1.5 Study Endpoints

6.3.1.5.1 Safety Endpoints

MenACWY considered noninferior to Menactra with respect to severe systemic reactions if the upper limit of the 2-sided 95% CI of the difference ($P_{MenACWY}$ minus $P_{Menactra}$) was less than 6%.

Descriptive analysis of reactogenicity, and adverse events reported throughout the study period.

6.3.1.5.2 Immunogenicity Endpoints (all secondary)

To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with seroresponse, hSBA ≥ 1:4 or ≥ 1:8 directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 19 to 55 years of age.

To compare the immunogenicity of a single dose of MenACWY with the immunogenicity of a single dose of Menomune, defined as percentage of subjects with hSBA ≥ 1:4, hSBA ≥ 1:8, or seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 56 to 65 years of age.

6.3.1.6 Surveillance/Monitoring

6.3.1.6.1 Safety Monitoring

All subjects were observed for 30 minutes after vaccination for immediate reactions including signs of anaphylaxis or local and systemic reactions. During visit 1 (day 1), subjects were given a diary card and were instructed on how to complete it for days 1 to 29. On day 3 (days 3 to 5), study personnel contacted subjects via telephone to identify any medical problems and to remind them to record reaction data, any other medical problems, and use of concomitant medications. On day 29, (days 29 to 43), all subjects completed a medical office visit including measurement of oral temperature and examination of previous injection site. The diary card was collected. Subjects were given a worksheet and instructed on how to complete it for days 30 to 180. On day 180 (days 152 to 208), study site personnel contacted all subjects by telephone to assess their health status and review any safety information recorded on the worksheet. At the discretion of the investigator, home or office visits could be performed instead of telephone calls.

6.3.1.6.2 Immunogenicity

For the immunogenicity subset, a blood sample (20 mL) was obtained at visit 1 (day 1), prior to administration of study vaccine, and at visit 2 (day 29) for assessment of bactericidal antibody titers against each serogroup in the presence of human complement (hSBA).

6.3.1.7 Statistical Considerations

For all of the four serogroups, the lower limit of the 2-sided 95% confidence interval (CI) around the difference (MenACWY – comparator [Menactra or Menomune, as applicable]) in the percentage of subjects with seroresponse had to be greater than –10% to demonstrate noninferiority for that serogroup. The immunogenicity endpoint for assessing noninferiority was the percentage of subjects with seroresponse for *N meningitidis* serogroups A, C, Y and W-135 at 1 month after vaccination. The primary dataset for this analysis was the PP population.

For GMT endpoints: For any of the four serogroups, the lower limit of the 2-sided 95% CI around the ratio of hSBA GMTs between MenACWY and the comparator vaccine, 1 month after vaccination, was to be above 0.5 to demonstrate noninferiority for that serogroup.

All safety analyses were carried out using the safety population.

6.3.2 Results

6.3.2.1 Populations Enrolled/Analyzed

See Table 13. Population definitions are as in V59P13 (section 6.2.2.1)

A total of 17 subjects were enrolled who did not satisfy the entry criteria (MenACWY: 8 subjects; Menactra: 9 subjects). Two subjects (MenACWY subjects) developed withdrawal criteria without being withdrawn from the study. Three Menactra subjects received the wrong vaccine or an incorrect dose. Overall, 17 subjects received an excluded concomitant medication (MenACWY: 13 subjects; Menactra: 3 subjects; Menomune: 1 subject).

The majority of subjects were Hispanic (71% to 76%). Baseline demographic characteristics were balanced between MenACWY and comparator groups.

Table 13*. Number of subjects Enrolled and Analyzed

Vaccine Group	**Number (%) of Subjects**			
	MenACWY (Group I)	**Menactra** (Group II)	**Menomune** (Group III)	**Total**
Enrolled population				
19-55 years	1606 (100%)	899 (100%)	—	2505 (100%)
56-65 years	217 (100%)	—	109 (100%)	326 (100%)
Total Subjects	1823 (100%)	899 (100%)	109 (100%)	2831 (100%)
ITT population				
19-55 years	199 (12%)	198 (22%)	—	397 (100%)
56-65 years	85 (39%)	—	42 (39%)	127 (100%)
PP population				
19-55 years	183 (11%)	184 (20%)	—	367 (100%)
56-65 years	84 (39%)	—	41 (38%)	125 (100%)
Safety population				
19-55 years	1588 (99%)	882 (98%)	—	2470 (100%)
56-65 years	216 (100%)	—	109 (100%)	325 (100%)

*from Table 11.1-1 (p. 60 of 405) CSR V59P17

6.3.2.2 Safety Outcomes

Table 14*. Primary Safety Analysis: Percentage of Subjects with at Least One Severe Systemic Reaction, Days 1 to 7, Age 19 to 55

Systemic Reaction	Number (%), 95%CI of Subjects with Solicited Reaction		MenACWY minus Menactra Vaccine Group Percent Difference (95% CI)	Primary Safety Objective Criterion Upper 95%CI limit < 6%
	19 – 55 years MenACWY N=1588	19 – 55 years Menactra N=882		
Severe	95 (6%)	46 (5%)	1% (-1, 3)	Met

*from Table 12.2-1 (p. 64 of 405) CSR V59P17

6.3.2.2.1 Immediate Reactions

None

6.3.2.2.2 Solicited Local and Systemic Reactions

Solicited local reactions by age group and by severity are shown in Table 15.

Table 15*. Local Reactions – Overall and by Severity, Age 19 to 55 and 56 to 65

Age group	Type of Reaction	Severity	Number (%) of Subjects with Local Reaction	
			MenACWY N=1588	Menactra N=882
19 to 55 years	Any Local Reaction	Any	729 (46%)	439 (50%)
		Severe	60 (4%)	37 (4%)
	Pain	Any	632 (40%)	392 (44%)
		Severe	41 (3%)	29 (3%)
	Erythema	Any	207 (13%)	105 (12%)
		> 50mm	17 (1%)	7 (1%)
	Induration	Any	179 (11%)	115 (13%)
		> 50mm	13 (1%)	10 (1%)
			MenACWY N=216	Menomune N=109
56 to 65 years	Any Local Reaction	Any	92 (43%)	44 (40%)
		Severe	12 (6%)	2 (2%)
	Pain	Any	69 (32%)	34 (31%)
		Severe	8 (4%)	2 (2%)
	Erythema	Any	41 (19%)	13/108 (12%)
		> 50mm	6 (3%)	0
	Induration	Any	39 (18%)	17/108 (16%)
		> 50mm	4 (2%)	0

*from Table 12.2.3-1 (p. 70 of 405) CSR V59P17

The percentages of subjects reporting solicited AEs were balanced between the vaccine groups and within each age group, with 60% of MenACWY subjects and 64% of Menactra subjects experiencing any reaction in the 19 to 55 age group and 57% of MenACWY and Menomune subjects in the 56 to 65 age group. Overall, the incidence rates of systemic reactions were balanced between vaccine groups and within each age stratification (19 to 55 years: 39% MenACWY and 43% Menactra 56 to 65 years: 39% MenACWY and 40% Menomune). Most systemic reactions were mild or moderate in severity. All systemic reactions were transient; (median durations ranged from 1 to 6 days).

19 to 55 years age group: the most frequently reported systemic reactions were headache (27% MenACWY and 29% Menactra), malaise (19% MenACWY and 21% Menactra), and myalgia (12% MenACWY and 15% Menactra). All other systemic reactions were reported in < 10% of subjects in both vaccine groups. Systemic reactions classified as severe were reported for 6% overall in the MenACWY group and 5% in the Menactra group. The most frequently reported severe reactions were headache (3% for MenACWY and Menactra) and malaise (3% MenACWY and 1% Menactra).

56 to 65 years age group: the most frequently reported systemic reactions were headache (24% MenACWY and 28% Menomune), malaise (23% MenACWY and 18% Menomune), and myalgia (18% MenACWY and 10% Menomune). Systemic reactions classified as severe were reported for 6% overall in the MenACWY group and 8% in the Menomune group. The most frequently reported severe reactions were malaise (4% MenACWY and 6% Menomune) and headache (3% MenACWY and 5% Menomune

Use of analgesic/antipyretic medication was balanced between vaccine and age groups (19 to 55 years: 16% MenACWY and 17% Menactra; 56 to 65 years: 12% MenACWY and 13% Menomune).

6.3.2.2.3 Unsolicited Adverse Events, Including Serious Adverse Events

One death occurred (*note: outside the age indication of this application*): MenACWY subject withdrew due to an AE during days 30 to 180 (subject 82/1658: death due to hypovolaemic shock, assessed by investigators as unrelated):

> "A 58-year-old woman was vaccinated with Men ACWY on 13 Aug 2007. During the 6-month follow-up phone call to the subject (visit 3) on 11 Jan 2008, the subject's mother told the investigator that the subject had died on -b(6)---- due to renal disease. Upon review of medical chart, the diagnosis was changed to hypovolemic shock. In Nov 2007, the subject presented with kidney stones and a "double J" stent was placed. After placement, the subject complained of abdominal pain and was evaluated and hospitalized for observation. On 26 Nov 2007 (105 days after vaccination), the subject presented to the hospital with dyspnea, cough and fever. Chest X-Ray showed pleural fluid and signs of consolidation. On 30 Nov 2007, the subject was hospitalized and referred to the intensive care unit. Abdominal CT showed perinephric abscess and air in the retroperitoneal space. On 1 Dec 2007, the retroperitoneal abscess was drained by puncture. The subject did not show clinical improvement and a nephrectomy was performed on the same day. The subject developed hypotension post-surgery and required blood transfusions, IV liquids, colloids, pressors and vasoactive drugs. The subject began bleeding through surgical incision, and a laparotomy was done. There was no intra-abdominal bleeding but the subject

continued bleeding through the surgical incision. The subject progressed to hypovolemic shock and died on -b(6)--. The investigator considered the event as not related to the investigational product."

The incidence of SAEs was < 1% for the 19 to 55 years age group and one occurred in the 56 to 65 years age group (Table 16). One SAE (subject 90/1289: spontaneous abortion) was considered by investigators as possibly related to the study vaccine.

Table 16*. Listing of Subjects with Serious Adverse Events by Treatment Group

Subject No.	Age	Preferred Term	Onset (Study day)	Duration (days)	Outcome	Hospitali-zation	Relatedness
MenACWY							
71/1402	30	Abortion spontaneous	142	< 1	Recovered	No	None
71/1491	48	Syncope	65	8	Recovered	Yes	None
71/1595	33	Appendicitis	96	3	Recovered	Yes	None
81/1105	49	Deep vein thrombosis	36	15	Recovered	Yes	None
81/1307	25	Nephrectomy	117	2	Recovered	Yes	None
82/1382	31	Pelvic inflammatory disease	4	12	Recovered	Yes	None
82/1658	58	Hypovolaemic shock	106	7	Death	Yes	None
90/1030	25	Abortion spontaneous	111	4	Recovered	No	None
90/1149	24	Arthropod sting	115	4	Recovered	No	None
90/1171	38	Upper limb fracture	102	3	Alive with sequelae	Yes	None
90/1225	43	Haematuria	78	8	Recovered	Yes	None
90/1289	34	Abortion spontaneous	45	3	Recovered	No	Possibly
Menactra							
71/1020	55	Ankle fracture	125	49	Recovered	Yes	None
71/1370	31	Angioedema	4	1	Recovered	Yes	None
71/1395	48	Herpes zoster	29	13	Recovered	No	None
		HIV infection	38	cont'd	AE persists	No	None
71/1505	47	Intervertebral disc protrusion	71	13	Alive with sequelae	Yes	None
90/1041	24	Abdominal pain	72	1	Recovered	Yes	None
90/1276	23	Cellulitis	129	9	Recovered	Yes	None
90/1285	37	Urticaria	109	3	Recovered	Yes	None
90/1422	24	Generalised oedema	31*	< 1-29	Recovered	Yes	None
		Generalised oedema	61*	< 1-30	Recovered	Yes	None
Menomune							
90/1562	65	Pyometra	125	17	Recovered	Yes	None

*from Table 12.3.1.2-1 (p 86 of 405) CSR V59P17

Pregnancies
A total of 16 pregnancies were reported in this study, 13 in the MenACWY group and three in the Menactra group. Pregnancy outcomes are reviewed in the Human Reproductive Safety section (7.5.3) of this review.

In the 19 to 55 years age group, the percentage of subjects experiencing any unsolicited AE was 24% in the MenACWY group and 27% in the Menactra group; in the 56 to 65 years age group the percentage of subjects experiencing any unsolicited AEs was slightly higher for MenACWY (33%) compared to Menomune (26%).

The most commonly reported unsolicited AEs reported by more than 1% of MenACWY subjects during days 1 to 29 were balanced by SOC between the vaccine groups. The most frequently reported unsolicited AEs in both age groups were headache (19 to 55 years: 3% MenACWY and Menactra; 56 to 65 years: 3% MenACWY and 2% Menomune), and malaise (19 to 55 years: 2% MenACWY and 1% Menactra; 56 to 65 years: 3% MenACWY and 2% Menomune). In total, 270 subjects reported unsolicited AEs considered by investigators as possibly or probably related (19 to 55 years: 9% MenACWY and Menactra; 56 to 65 years: 15% MenACWY and 10% Menomune). The SOCs most commonly affected by possibly or probably related AEs were as follows:

- General disorders and administration site conditions:
  - 19 to 55 years: 4% MenACWY and 2% Menactra;
  - 56 to 65 years: 6% MenACWY and 4% Menomune, and
- Nervous system disorders:
  - 19 to 55 years: 3% MenACWY and Menactra;
  - 56 to 65 years: 5% MenACWY and 4% Menomune.

Table 17*. All and Possibly Related Adverse Events Reported in at Least 1% of MenACWY Subjects, Days 1 to 29, Age 19 to 55

	Preferred Term	Number (%) of Subjects with Unsolicited AEs	
		MenACWY N=1588	Menactra N=882
All AEs	Headache	44 (3%)	24 (3%)
	Malaise	26 (2%)	7 (1%)
	Nasopharyngitis	26 (2%)	12 (1%)
	Injection site pain	19 (1%)	5 (1%)
	Myalgia	17 (1%)	8 (1%)
Possibly Related AEs	Headache	31 (2%)	16 (2%)
	Injection site pain	19 (1%)	5 (1%)
	Malaise	16 (1%)	3 (< 1%)

*from Table 12.2.3-7 (p. 82 of 405) CSR V59P17

Table 18*. All and Possibly Related Adverse Events Reported in at least 1% of MenACWY, Days 1 to 29, Age 56 to 65

	Preferred Term	Number (%) of Subjects with Unsolicited AEs	
		MenACWY N=216	Menomune N=109
All AEs	Malaise	7 (3%)	2 (2%)
	Headache	6 (3%)	2 (2%)
	Myalgia	5 (2%)	2 (2%)
	Chills	4 (2%)	1 (1%)
	Dizziness	4 (2%)	2 (2%)
	Back pain	3 (1%)	0
	Diarrhea	3 (1%)	0
	Injection site erythema	3 (1%)	0
	Injection site pain	3 (1%)	0
	Nasopharyngitis	3 (1%)	1 (1%)
	Pain in extremity	3 (1%)	0
	Rash	3 (1%)	0
	Viral infection	3 (1%)	0
Possibly Related AEs	Dizziness	3 (1%)	2 (2%)
	Headache	3 (1%)	2 (2%)
	Injection site erythema	3 (1%)	0
	Injection site pain	3 (1%)	0
	Malaise	3 (1%)	2 (2%)
	Rash	3 (1%)	0

*from Table 12.2.3-8 (p. 83 of 405) CSR V59P17

6.3.2.3 Immunogenicity Outcomes

Noninferiority to Menactra

All immunogenicity outcomes were secondary. The protocol-specified noninferiority immunogenicity objectives in subjects aged 19 to 55 years were met for all four serogroups in the analysis of hSBA seroresponse and hSBA GMTs. In the analysis of the percentages of subjects with hSBA titer ≥ 1:8, the protocol-specified criterion was met for serogroups A, W, and Y, but not for serogroup C.

The lower limit of the two-sided 95% CI around the difference of the percentage of overall seroresponders (MenACWY minus Menactra) was greater than -10% (noninferiority criterion) for all four serogroups and greater than 0% (statistical superiority criterion) for serogroups W and Y.

The lower limit of the two-sided 95% CI around the difference in the percentage of subjects with hSBA titer ≥ 1:8 was greater than -10% (noninferiority criterion) for all serogroups except serogroup C (lower limit of the two-sided 95% CI for serogroup C was -11%) and greater than 0% (statistical superiority criterion) for serogroups W and Y.

The lower limit of the two-sided 95% CI around the ratio of hSBA GMTs (MenACWY: Menactra) was above 0.5 (noninferiority criterion) for all four serogroups and above 1.0 (statistical superiority criterion) for serogroup Y.

Reviewer's note: There are no clinical data demonstrating differences in meningococcal disease prevention due to higher post-immunization immune responses.

Noninferiority to Menomune
In the analysis of hSBA seroresponse, the protocol-specified noninferiority immunogenicity objectives in the comparison of the immunogenicity of MenACWY with that of Menomune after a single injection administered to subjects aged 56 to 65 years were met for serogroups A, C, and Y, but not for serogroup W. In the analysis of the percentages of subjects with hSBA titer ≥ 1:8 and in the analysis of hSBA GMTs, the protocol-specified criterion was met for all four serogroups.

The lower limit of the two-sided 95% CI around the difference of the percentage of overall seroresponders (MenACWY minus Menomune) was greater than-10% (noninferiority criterion) for all four serogroups except serogroup W (lower limit of the two-sided 95% CI for serogroup W: -11%) and greater than 0% (statistical superiority criterion) for serogroups A and Y.

The lower limit of the two-sided 95% CI around the difference in the percentage of subjects with hSBA titer ≥ 1:8 was greater than -10% (noninferiority criterion) for all serogroups and greater than 0% (statistical superiority criterion) for serogroups A and Y.

The lower limit of the two-sided 95% CI around the ratio of hSBA GMTs (MenACWY: Menactra) was above 0.5 (noninferiority criterion) for all four serogroups and above 1.0 (statistical superiority criterion) for serogroups A, C, and Y.

6.3.2.4 Comments and Conclusions

6.3.2.4.1 Study Design and Population

This study was conducted in Argentina and Columbia. The population of 56-65 year old participants does not contribute to the indication sought in this application.

6.3.2.4.2 Safety

The percentages of subjects reporting solicited AEs (i.e., local and systemic reactions collected during the 7 days after vaccination) were comparable between the vaccine groups within each age group. Overall, the solicited reactions were of short duration. The solicited reactions were mostly mild or moderate in severity. One SAE (spontaneous abortion) was reported in a

MenACWY recipient that was considered by investigators to be possibly related to the study vaccine because of temporal relation to vaccination.

6.3.2.4.3 Immunogenicity

hSBA seroresponse and GMTto MenACWY met the non-inferiority criteria for all four serogroups and %≥1:8 met non-inferiority criteria for serogroups A, C and Y.

6.4 Trial 3 (NCT00518180)

6.4.1 Protocol # and Title:

Study V59P18: A Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (HPV, GARDASIL®) in Healthy Adolescents

6.4.1.1 Rationale/Objectives

Study V59P18 was conducted to evaluate the safety and immunogenicity of MenACWY when administered as a single dose to healthy adolescents alone or concomitantly with Tdap (Boostrix) and GARDASIL.

Immunogenicity Objectives

Primary

- Demonstrate that the immune response to MenACWY, when given concomitantly with Tdap and HPV is not inferior to the immune response when MenACWY is administered alone as measured by the percentage of hSBA seroresponders.
- Demonstrate that the immune response to MenACWY, as measured by the percentage of hSBA seroresponders, when given one month after Tdap, is not inferior to the immune response when MenACWY is administered alone.
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with anti-diphtheria and anti-tetanus toxin ≥1.0 IU/mL, and anti-PT,,anti-FHA, and anti-PRN GMCs, when given concomitantly with MenACWY and HPV, is not inferior to the immune response when Tdap is administered alone.

Secondary

- *Demonstrate that the immune response to the HPV vaccine given concomitantly with MenACWY and Tdap is not inferior to the immune response to HPV administered alone. (Note: HPV responses to be reviewed under a later labeling supplement)*
- Demonstrate that the immune response to Tdap, as measured by the percentage of subjects with anti-diphtheria and anti-tetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, anti-PRN GMCs, when administered one month after MenACWY is not inferior to the immune response to Tdap administered alone.
- Assess the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥1:4, when given: (a) concomitantly with Tdap and HPV; and

(b) when given one month after Tdap.
- Assess the anti-diphtheria and anti-tetanus GMCs and the percentage of subjects with a 4-fold rise in antibody titer over baseline against PT, FHA, PRN.

Safety Objectives
- Assess the safety profile following a single injection of MenACWY given alone one month after Tdap, compared with the safety profile following a single injection of MenACWY given alone one month before Tdap.
- Assess the safety profile following a single injection of MenACWY given alone or concomitantly with Tdap and HPV vaccine.
- Assess the safety profile following a single injection of HPV given alone or concomitantly with Tdap and MenACWY.

6.4.1.2 Design Overview

The trial was an open-label single center study conducted in Costa Rica; both the study personnel and the subjects knew which vaccine was administered.

Subjects were randomized 1:1:1 ratio to receive:
- MenACWY concomitantly with Tdap and HPV at study month 0 followed by two injections of HPV at month 2 and 6 (MenACWY+Tdap+HPV group);
- MenACWY at study month 0 followed by one injection of Tdap at month 1, followed by three injections of HPV at months 2, 4, and 8 (MenACWY → Tdapgroup);
- Tdap at month 0 followed by one injection of MenACWY at month 1, followed by three injections of HPV at months 2, 4, and 8 (Tdap → MenACWY group).

Randomization was stratified by gender and age group (11 to 14 years; 15 to18 years).

6.4.1.3 Population

A total of 1620 subjects 11 to 18 years of age planned, 540 in each of the three vaccine groups.

6.4.1.3.1 Study Period

July 19, 2007 to September 30, 2008

6.4.1.3.2 Study Sites and Recruitment

Instituto de Atencion Pediatrica, San Jose, Costa Rica

6.4.1.3.3 Inclusion Criteria

- Male or female individuals 11 to 18 years of age
- Written assent and, if applicable, parents or legal guardians written informed consent
- Pre-sexual debut (oth male and female) with no intention of becoming sexually active during the study period,
- Available for all visits and telephone calls scheduled for the study,
- In good health by medical history, physical assessment, and clinical judgment

- Had received five doses of pediatric DTP/DTaP before their seventh birthday (if fourth dose was administered on or after the 4th birthday, no fifth dose was needed).

6.4.1.3.4 Exclusion Criteria

- Unwilling or unable to give written informed assent or consent
- Perceived to be unreliable or unavailable for the duration of the study
- Previous or suspected disease caused by *N. meningitidis*;
- Household and/or intimate exposure to an individual with culture-proven *N. meningitidis* infection within 60 days prior to enrollment;
- Previously immunized with a meningococcal vaccine or vaccine containing meningococcal antigen(s) (licensed or investigational) (exception: receipt of OMP-containing Hib vaccines was permitted);
- Prior human papillomavirus (HPV) vaccine;
- Received any investigational agents or vaccines within 90 days prior to enrollment or expected to receive prior to completion of the study;
- Received any licensed vaccines within one month prior to enrollment or anticipated receipt within 28 days after vaccination (exception: influenza vaccine up to 15 days prior to study vaccination and at least 15 days after study vaccination);
- Received a live viral vaccine within 60 days prior to enrollment;
- Significant acute or chronic infection within the 7 days prior to enrollment (i.e. requiring systemic antibiotic treatment or antiviral therapy) or fever (≥ 38°C) within 3 days prior to enrollment;
- Serious acute, chronic or progressive disease such as: history of cancer (excluding minor nonmelanoma skin cancer); complicated diabetes mellitus; advanced arteriosclerotic disease; autoimmune disease; HIV infection or AIDS; blood dyscrasias; congestive heart failure; renal failure; severe malnutrition. (Note: Subjects with mild asthma were eligible for enrollment. Subjects with moderate or severe asthma requiring routine use of inhaled or systemic corticosteroids were not eligible for enrollment).
- Epilepsy, progressive neurological disease, or history of Guillain Barré Syndrome;
- History of anaphylaxis, serious reactions, or allergy to any vaccine component;
- Condition that was a contraindication to vaccination as indicated in the package inserts (including latex allergy)
- Known or suspected impairment/alteration of immune function, either congenital or acquired or resulting from (for example): receipt of immunosuppressive therapy within 30 days prior to enrollment (any systemic corticosteroid administered for more than 5 days, or in a daily dose >1 mg/kg/day prednisone or equivalent during any of 30 days prior to enrollment, or cancer chemotherapy); receipt of immunostimulants; receipt of parenteral immunoglobulin preparation, blood products, and /or plasma derivatives within 90 days prior to enrollment and for the full length of the study.
- Bleeding diathesis, or condition that may be associated with prolonged bleeding time;
- Down's syndrome or other known cytogenic disorders;
- Leaving the area of the study site before the end of the study period;
- Any condition that, in the opinion of the investigator, could interfere with the

evaluation of the study objectives.

6.4.1.3.5 Concomittant Vaccines and Medications

All prescription medication and non-prescription medication (with the exception of mineral supplements and vitamins) were recorded for 7 days after each vaccination. All prescription medications were recorded from the day of the first vaccination through 30 days after the last vaccination. Prescription medications taken to treat medically significant AEs were recorded from 30 days after the last vaccination through the follow up phone call 6 months after the last study vaccination.

A complete DTP vaccine history from birth was recorded on entry into the study using, wherever possible, national vaccination cards.

The use of prophylactic antipyretics/analgesics was strongly discouraged. If antipyretics were given on the day of injection for treatment of fever, the temperature was retaken and recorded 4 hours after the antipyretic dose to see if further treatment was necessary. This information was recorded on the subject's diary card and on the appropriate CRF pages.

6.4.1.4 Products Mandated by the Protocol

Test Product, Dose, Mode of Administration, Lot Number:
MenACWY conjugate vaccine, lot Z79P40I1, expiry date: Feb 2008. A 0.5 mL injectable solution, administered by intramuscular injection (IM) in the right deltoid area. (See 6.2.1.4)

Reference Therapy, Dose, Mode of Administration, Lot Number:
1) HPV vaccine (Merck & Co. GARDASIL), lot 0515U, expiry date: 10 Feb 2010. A 0.5 mL injectable solution was administered IM in the upper anterolateral area of the thigh.

HPV Vaccine (GARDASIL) Composition

Composition	Quantity per 0.5 mL dose
HPV 6 L1 protein	20 mcg
HPV 11 L1 protein	40 mcg
HPV 16 L1 protein	40 mcg
HPV 18 L1 protein	20 mcg

Other ingredients included amorphous aluminum hydroxyphosphate sulphate adjuvant (225 micrograms aluminum), sodium chloride, L-histidine, Polysorbate 80, sodium borate.

2) Tdap vaccine (GSK US-licensed Boostrix, available commercial lots). A 0.5 mL injectable solution was administered IM in the left deltoid area.

Tdap Vaccine (US-licensed Boostrix) Composition

Composition	Quantity per 0.5 mL dose
Tetanus toxoid (T)	5 Lf
Diphtheria toxoid (d)	2.5 Lf
Inactivated PT	8 µg
Filamentous hemagglutinin (FHA)	8 µg
Pertactin (PRN)	2.5 µg

Other ingredients included NaCl (4.5 mg), aluminum adjuvant (not more than 0.39 mg aluminum by assay), ≤100 mcg of residual formaldehyde, and ≤ 100 mcg of polysorbate 80 (Tween 80).

6.4.1.5 Study Endpoints

6.4.1.5.1 Safety Endpoints

Descriptive measures of safety :solicited local and systemic reactions, other unsolicited AEs.

6.4.1.5.2 Immunogenicity Endpoints

Primary:

- Concomitant noninferiority for MenACWY: lower limit of the two-sided 95% confidence interval (CI) of the difference in the percentages of seroresponders for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone) to be > -10%;
- Concomitant noninferiority for Tdap:
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with -(b)(4)- anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY+HPV+Tdap minus Tdap alone) to be > -10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, anti-PRN GMCs (MenACWY+HPV+Tdap / Tdap alone) to be > 0.67.
- Sequential noninferiority for MenACWY: lower limit of the two-sided 95% CI of the difference in the percentages of seroresponders for each serogroup (Tdap → MenACWY→HPV minus MenACWY alone) to be > -10%.

Secondary:

- Concomitant noninferiority for HPV
  - lower limit of the two-sided 95% CI of the difference in the percentages for anti-HPV seroconversion for each HPV type as measured by -(b)(4)- (MenACWY+Tdap+HPV minus HPV alone) to be > -5%.
  - lower limit of the two-sided 95% CI of the anti-HPV GMT ratio (MenACWY+Tdap+HPV / HPV alone) to be > 0.5 for each HPV type.
- Sequential noninferiority for Tdap
  - lower limit of the two-sided 95% CI around the difference of the percentages of subjects with -b(4)- anti-D toxin and anti-T toxin ≥ 1.0 IU/mL (MenACWY → Tdap →HPV minus Tdap alone) to be >-10%;

- lower limit of the two-sided 95% CI for the vaccine group ratios of the anti-PT, anti-FHA, and anti-PRN GMCs (MenACWY → Tdap →HPV / Tdap alone) to be >0.67.

- Concomitant and sequential noninferiority for MenACWY (criteria non pre-specified in the study protocol):
  - lower limit of the two-sided 95% CI of the difference in the percentages for hSBA ≥1:8 and ≥ 1:4 for each serogroup (MenACWY+HPV+Tdap minus MenACWY alone; Tdap → MenACWY→HPV minus MenACWY alone) to be >-10%;
  - lower limit of the two-sided 95% CI for the vaccine group ratio of the hSBA GMTs (MenACWY+HPV+Tdap / MenACWY alone; Tdap → MenACWY→HPV /MenACWY alone) to be >0.5.

The antidiphtheria and antitetanus GMCs and the percentage of subjects with at least a 4- fold rise in antibody titer over baseline against PT, FHA, and PRN, secondary endpoints for the assessment of both concomitant and sequential administration of Tdap, were evaluated descriptively.

6.4.1.6 Surveilance/Monitoring

6.4.1.6.1 Safety Monitoring

The subjects remained in the clinic for 30 minutes following vaccination to assess for immediate reactions. Safety assessments were similar to studies V59P13 and V59P17 (Table 19):

Table 19. Safety Assessments

Immediate reactions: Signs or symptoms of anaphylaxis, local injection site and systemic reactions	30 minutes after each vaccination
Stayed home due to reaction?	For 7 days after each vaccination
Antipyretics/Analgesics used?	For 7 days after each vaccination
Temperature: Oral temperature	For 7 days after each vaccination
Local reactions: Pain, erythema, induration *were reported as an AE if persisting beyond day 7*	For 7 days after each vaccination
Systemic reactions: Chills, nausea, malaise, myalgia, arthralgia, headache, and rash *were reported as an AE if persisting beyond day 7*	For 7 days after each vaccination
All Adverse Events	For 7 days after each vaccination
Adverse Events: AEs that required a medical office visit, consultation and/or results in premature withdrawal from the study.	From visit 1 through 30 days after last vaccination
Medically significant AEs: AEs requiring Emergency Room visit, or leading to a subject's withdrawal, or hospitalizations with the exclusion of pre-planned medical office visits or ER visits for routine medical care and common acute conditions such as upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, contact dermatitis. *(Note, the excluded conditions above were NOT collected or recorded in CRFs.)*	Throughout the study including 6-month follow up period for subjects who terminate

6.4.1.6.2 Immunogenicity

Blood samples (20 mL) for serological evaluations were collected from all subjects at visit 1 (day 1) prior to administration of study vaccines, at one month after the first vaccination (in all study groups), at one month after the second vaccination (for subjects receiving Tdap one month after MenACWY and those receiving MenACWY one month after Tdap), and at one month after the third HPV vaccination (all three study groups).

6.4.1.7 Statistical Considerations

Analysis of Safety
The analyses of safety were performed on all subjects who received at least one injection and provided post baseline safety data.
For each solicited local and systemic reaction, differences between the vaccine groups were analyzed using Pearson's chi-square test or Fisher's Exact test where appropriate, due to small expected cell sizes.

Noninferiority Immunogenicty Analysis
The percentage of subjects with hSBA seroresponses were computed at one month after vaccination with MenACWY.

hSBA GMTs were computed using an ANOVA model with vaccination group, gender, and age group as factors.

The percentage of subjects with –b(4)– anti-D and anti-T antibodies antibody concentrations ≥ 1.0 IU/mL, were calculated for each antigen at one month after vaccination with Tdap.

Anti-PT, anti-FHA and anti-PRN antibody response GMC were computed using an ANCOVA model with vaccine group, gender, and age group as fixed effects and the log10 transformed prevaccination ELISA concentrations as covariate.

Anti-HPV seroconversion was computed for each HPV type at one month after the third HPV vaccination.

Anti-HPV-6, anti-HPV-11, anti-HPV-16, and anti-HPV-18 GMTs, were computed for each HPV type, at one month after the third HPV vaccination, using an ANOVA model with vaccination group, gender, and age group as factors.

6.4.2 Results

6.4.2.1 Populations Enrolled/Analyzed

A total of 1620 subjects were enrolled and randomized at a 1:1:1 ratio. Baseline and other demographic characteristics of the enrolled population were similar between the three vaccine groups. There were three PP populations: one for the analysis of the MenACWY objectives, one for the Tdap objectives, and one for the HPV objectives. Since the MenACWY and Tdap MITT

and PP population of each vaccine group did not differ by more than 4%, all immunogenicity analyses were carried out using the PP populations. The MITT and PP populations for the analysis of the HPV objectives differed by 17% to 21%; therefore, all HPV immunogenicity analyses were performed both for the MITT and PP populations. The main immunogenicity analyses were performed on the PP population (Table 20).

Table 20*. Planned and Actual Enrollment and Analyses

Populations Analyzed: Numbers of Subjects (and Percentages)				
		MenACWY + Tdap + HPV	**MenACWY → Tdap → HPV**	**Tdap → MenACWY → HPV**
Enrolled		540	541	539
ACWY	MITT	507 (94%)	508 (94%)	481 (89%)
	PP	496 (92%)	490 (91%)	461 (86%)
Tdap	MITT	503 (93%)	484 (89%)	498 (92%)
	PP	492 (91%)	458 (85%)	487 (90%)

*from Table 11.1-1 (p. 70 of 839) CSR V59P18

6.4.2.2 Safety Outcomes

6.4.2.2.1 Immediate Reactions

6.4.2.2.2 Solicited Local and Systemic Reactions

Tdap was generally more reactogenic then MenACWY (69% of subjects reported solicited reactions to MenACWY vs. 82% to Tdap, both administered alone). Higher rates of any solicited reaction following concomitant vaccination of MenACWY, Tdap, and HPV were reported when compared with MenACWY alone; percentages reporting solicited reactions following Tdap administered alone and concomitantly were similar. There was no evidence of a negative impact on the reactogenicity profile of either MenACWY or Tdap when given sequentially.

Higher percentages of subjects reported solicited local reactions to MenACWY (69%) and Tdap (82%) when administered alone than when respectively administered one month after Tdap (64%) and MenACWY (70%).

The most frequently reported local reaction to MenACWY and Tdap was pain (range, 45% [MenACWY alone] to 71% [Tdap alone]) with no apparent difference among subjects administered MenACWY alone, sequentially, or concomitantly. Most solicited local reactions were experienced during the 3 days immediately following vaccination. Local reactions ≥ 100 mm were rare in all groups (erythema or induration ≥ 100 mm were reported in four MenACWY recipients and in two Tdap recipients) (Table 21).

Table 21*. Effect of Concomitant and Sequential Administration on Local Reactions to MenACWY and Tdap, Overall and by Severity

Type of Reaction	Severity	Number (%) of Subjects					
		MenACWY + Tdap +HPV (I) N=540		MenACWY → Tdap→HPV (II) N=541		Tdap → MenACWY → HPV (III) N=539	
		Visit 1	Visit 1	Visit 1	Visit 2	Visit 2	Visit 1
Injection Site Evaluated		MenACWY	Tdap	MenACWY	Tdap	MenACWY	Tdap
Pain	Any	263 (49%)	367 (68%)	246 (45%)	310/510 (61%)	239/502 (48%)	383 (71%)
	Severe	16 (3%)	42 (8%)	8 (1%)	31/510 (6%)	16/502 (3%)	29 (5%)
Erythema	Any	68 (13%)	78 (14%)	66 (12%)	38/510 (7%)	64/502 (13%)	70 (13%)
	>50mm	6 (1%)	2 (<1%)	3 (1%)	1 (<1%)	6/502 (1%)	1 (<1%)
Induration	Any	68 (13%)	90 (17%)	70 (13%)	64/510 (13%)	63/502 (13%)	110 (20%)
	>50mm	11 (2%)	10 (2%)	6 (1%)	4 (1%)	5/502 (1%)	9 (2%)

*from Table 12.2.3-1 (p. 108 of 839) CSR V59P18

The most commonly reported solicited systemic reactions after receiving MenACWY or Tdap were headache (36% to 40% after vaccination at visit 1; 25% and 27% after vaccination at visit 2), myalgia (19% to 27% after vaccination at visit 1; 16% after vaccination at visit 2), and malaise (20% to 25% after vaccination at visit 1; 18% after vaccination at visit 2), most of which were reported in the 3 days immediately following vaccination. Generally higher percentages reported each systemic reaction to Tdap alone than MenACWY alone with highest rates observed after Tdap, MenACWY, and HPV concomitant administration (Table 22).

The percent of subjects reporting any severe systemic reaction was 9% in the concomitant group and 7% in the MenACWY or Tdap alonegroups at visit 1, mainly severe headache (6% in the concomitant group versus 4% following MenACWY or Tdap alone).

Table 22*. Summary of Reactogenicity – Number (%) of Subject with Systemic Reactions and Other Indicators of Reactogenicity After MenACWY and Tdap Vaccination, Overall and by Severity

Type of Reaction	Severity	MenACWY + Tdap + HPV	MenACWY → Tdap → HPV	Tdap → MenACWY → HPV	MenACWY → Tdap→ HPV	Tdap → MenACWY → HPV
		Visit 1	Visit 1	Visit 1	Visit 2	Visit 2
		MenACWY + Tdap + HPV N=540	MenACWY N=541	Tdap N=539	Tdap N=510	MenACWY N=502
Systemic Reaction	Any	312 (58%)	274 (51%)	309 (57%)	218 (43%)	214 (43%)
	Severe	50 (9%)	38 (7%)	37 (7%)	33 (6%)	33 (7%)
Chills	Any	77 (14%)	66 (12%)	70 (13%)	42 (8%)	45 (9%)
	Severe	7 (1%)	6 (1%)	2 (<1%)	1 (<1%)	6 (1%)
Nausea	Any	88 (16%)	72 (13%)	82 (15%)	42 (8%)	64 (13%)
	Severe	8 (1%)	4 (1%)	2 (<1%)	5 (1%)	5 (1%)
Malaise	Any	133 (25%)	110 (20%)	115 (21%)	91 (18%)	88 (18%)
	Severe	15 (3%)	7 (1%)	6 (1%)	9 (2%)	14 (3%)
Myalgia	Any	146 (27%)	104 (19%)	142 (26%)	81 (16%)	82 (16%)
	Severe	17 (3%)	7 (1%)	11 (2%)	7 (1%)	8 (2%)
Arthralgia	Any	94 (17%)	62 (11%)	76 (14%)	52 (10%)	52 (10%)
	Severe	12(2%)	3 (1%)	6 (1%)	3 (1%)	1 (<1%)
Headache	Any	217 (40%)	194 (36%)	200 (37%)	125 (25%)	138 (27%)
	Severe	31 (6%)	23 (4%)	24 (4%)	13 (3%)	18 (4%)
Rash	Any	21(4%)	17 (3%)	20 (4%)	15 (3%)	13 (3%)
Fever (≥38°C) [c]	Any	27 (5%)	19 (4%)	17 (3%)	25 (5%)	30 (6%)
	Severe (≥39°C)	4 (1%)	4 (1%)	5 (1%)	6 (1%)	6 (1%)
Analgesic/Antipyretic Med. Used		110 (20%)	83 (15%)	96 (18%)	58 (11%)	49 (10%)
Stayed Home		52/513 (10%)	39/509 (8%)	39/502 (8%)	25/496 (5%)	24/484 (5%)

*from Table 12.2.3-4 (p. 113 of 839) CSR V59P18

6.4.2.2.3 Unsolicited Adverse Events, Including Serious Adverse Events

There were no deaths in this study.

Twelve SAEs were reported by eleven subjects; none were assessed by study investigators as related to the study vaccines (Table 23). One subject (01/1451) withdrew due to two SAEs (Cushing's Syndrome and Pituitary Tumour Benign).

Table 23*. Listing of Subjects with SAEs by Vaccination Group

Subject No.	Age Sex	Preferred Term	Onset (Study Day)	Duration (days)	Out-come	Hospit al-ization	Related-ness	Days post vaccination
MenACWY + Tdap + HPV								
01/1451	12 F	Cushing's Syndrome	17	-	AE Persist	Yes	None	16d post MenACWY + Tdap+HPV
01/1451	12 F	Pituitary Tumour Benign	17	59	Recov-ered	Yes	None	16d post MenACWY + Tdap+HPV
MenACWY → Tdap → HPV								
01/1127	13 F	Abortion Spontaneous	187	7	Recov-ered	Yes	None	150d post study termination
01/1259	14 F	Haemorrhagi c ovarian cyst	181	2	Recov-ered	Yes	None	21d post 2nd HPV
01/2379	15 F	Bezoar	222	7	Recov-ered	Yes	None	106d post 2nd HPV
01/1406	14 F	Behcet's Syndrome	203	4	Recov-ered	Yes	None	44d post 2nd HPV
01/1411	11 F	Appendicitis	56	3	Recov-ered	Yes	None	26d post Tdap
01/4097	17 M	Appendicitis	133	1	Recov-ered	Yes	None	60d post 1st HPV
01/4181	15 M	Testicular torsion	250	2	Recov-ered	Yes	None	112d post 2nd HPV
Tdap → MenACWY → HPV								
01/2035	15 F	Abortion Spontaneous	271	<1	Recov-ered	No (ER visit)	None	20d post 3rd HPV
01/2315	18 F	Road Traffic Accident	113	<1	Recov-ered	No (ER visit)	None	35d post 1st HPV
01/3449	12 M	Hydronephro sis	168	8	Alive w/seq	Yes	None	54d post 2nd HPV

*from Table 12.3.1.2-1 (p. 120 of 839) CSR V59P18

Overall, unsolicited AEs were reported by similar percentages across the three vaccine groups (28% to 29%) (Table 24). The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was "infections and infestations" (12% to 13% of the subjects across the three vaccine groups). In total, 109 subjects reported unsolicited AEs considered possibly or probably related by study investigators (range, 6% to 8% per vaccine group). Severe possibly or probably related unsolicited AEs were reported by nine subjects, six of these nine were cases of headache.

Table 24*. Overview of All and Possibly Related Adverse Events Reported by More Than 1% of Subjects by Descending Frequency, Overall (From Day 1 until End of Study)

Preferred Term	Number (%) of Subjects with Adverse Events					
	All			At Least Possibly Related		
	MenACWY + Tdap + HPV	MenACWY → Tdap → HPV	Tdap → MenACWY → HPV	MenACWY + Tdap + HPV	MenACWY → Tdap → HPV	Tdap → MenACWY → HPV
	N=540	N=541	N=539	N=540	N=541	N=539
Headache	17 (3%)	16 (3%)	26 (5%)	13 (2%)	11 (2%)	20 (4%)
Dysmenorrhoea	24 (4%)	15 (3%)	15 (3%)	0	0	0
Upper Respiratory Tract Infection	21 (4%)	20 (4%)	12 (2%)	0	0	0
Malaise	5 (1%)	9 (2%)	15 (3%)	4 (1%)	8 (1%)	13 (2%)
Influenza	15 (3%)	8 (1%)	13 (2%)	0	0	0
Tonsillitis	13 (2%)	7 (1%)	11 (2%)	0	0	0
Abdominal Pain	3 (1%)	5 (1%)	12 (2%)	0	0	0
Myalgia	2 (<1%)	3 (1%)	10 (2%)	1 (<1%)	1 (<1%)	9 (2%)
Nausea	2 (<1%)	5 (1%)	8 (1%)	1 (<1%)	3 (1%)	8 (1%)
Pain	6 (1%)	6 (1%)	7 (1%)	6 (1%)	5 (1%)	6 (1%)
Hypersensitivity	7 (1%)	3 (1%)	6 (1%)	0	0	0
Acne	3 (1%)	7 (1%)	2 (<1%)	0	0	0
Colitis	3 (1%)	7 (1%)	1 (<1%)	0	0	0
Chills	1 (<1%)	0	6 (1%)	1 (<1%)	0	6 (1%)
Pharyngotonsillitis	2 (<1%)	1 (<1%)	6 (1%)	0	0	0
Cough	4 (1%)	6 (1%)	3 (1%)	0	0	0

*from Table 12.2.3-7 (p. 118 of 839) CSR V59P18

6.4.2.3 Immunogenicity Outcomes

Of three co-primary immunogenicity objectives, one was met and two were partially met:

The MenACWY immunogenicity analyses included two co-primary noninferiority objectives, both measured in terms of hSBA seroresponse at one month after a single injection of vaccine, administered concomitantly, sequentially, or alone (Table 25):

- Noninferiority of the immune response to MenACWY when administered concomitantly with Tdap and HPV, compared with the immune response to MenACWY when administered alone, was demonstrated for all four serogroups.
- Noninferiority of the immune response to MenACWY when administered one month after Tdap, compared with the immune response to MenACWY when administered alone, was demonstrated for serogroups A, C, and Y, but not for serogroup W.

Among subjects lacking bactericidal antibodies at baseline (baseline hSBA titer < 1:4), the percentage of seroresponders in the sequential administration group was 90%. One month after MenACWY, 95% of subjects receiving MenACWY one month after Tdap had an hSBA titer ≥ 1:8 for serogroup W versus 99% of subjects receiving MenACWY one month before Tdap.

Table 25*. Primary Immunogenicity Objective: Percent of Subjects (95% CI) whith hSBA Seroresponse, PP Population

	Variable		MenACWY + Tdap + HPV (I) (95% CI)	MenACWY→ Tdap→HPV (II) (95% CI)	Tdap → MenACWY → HPV (III) (95% CI)	Vaccine Group Differences (95% CI)	
						Concomit-ant (I - II)	Sequential (III - II)
A	Baseline titer	<1:4	N=457 80% (76, 83)	N=456 81% (77, 85)	N=415 87% (84, 90)	-1% (-7, 4)	6% (1, 11)
		≥ 1:4	N=37 84% (68, 94)	N=30 87% (69, 96)	N=43 81% (67, 92)	-3% (-20, 16)	-5% (-22, 14)
	Overall		N=494 80% (76, 84)	N=486 82% (78, 85)	N=458 87% (83, 90)	-2% (-6, 3)*	5% (1, 10)**
C	Baseline titer	<1:4	N=336 90% (86, 93)	N=355 88% (84, 91)	N=319 90% (86, 93)	1% (-3, 6)	2% (-3, 7)
		≥ 1:4	N=158 69% (61, 76)	N=132 74% (66, 81)	N=138 69% (60, 76)	-5% (-15, 5)	-5% (-16, 5)
	Overall		N=494 83% (79, 86)	N=487 84% (81, 88)	N=457 84% (80, 87)	-1% (-6, 3)*	-1% (-6, 4)*
W	Baseline titer	<1:4	N=256 96% (93, 98)	N=259 99% (97,100)	N=224 90% (86, 94)	-3% (-6, -1)	-9% (-14, -6)
		≥ 1:4	N=231 55% (48, 62)	N=215 59% (52, 65)	N=234 41% (35, 48)	-4% (-13, 6)	-17% (-26, -8)
	Overall		N=487 77% (73, 80)	N=474 81% (77, 84)	N=458 65% (61, 70)	-4% (-9, 1)*	-16% (-21, -10)
Y	Baseline titer	<1:4	N=360 91% (88, 94)	N=362 91% (87, 94)	N=333 90% (87, 93)	1% (-4, 5)	0% (-5, 4)
		≥ 1:4	N=133 59% (51, 68)	N=125 58% (48, 66)	N=127 46% (38, 56)	2% (-10, 14)	-11% (-23, 1)
	Overall		N=493 83% (79, 86)	N=487 82% (79, 86)	N=460 78% (74, 82)	0% (-4, 5)*	-4% (-9, 1)*

*from Table 11.4.1.1-2 (p. 78 of 839) CSR V59P18

The Tdap immunogenicity analyses comprised one co-primary noninferiority objective:

- Noninferiority of the immune response to Tdap when administered concomitantly with MenACWY and HPV, compared with the immune response to Tdap when administered alone, was demonstrated for diphtheria, tetanus, and the PT pertussis antigen, but not for FHA and PRN (Table 26).

Table 26*. Primary Immunogenicity Objective, Tdap: Effect of Concomitant Vaccination on Immunogenicity for Diphtheria, Tetanus, and Pertussis Antigens (Postvaccination Results), PP Population

		MenACWY+ Tdap + HPV (I) (95% CI)	MenACWY→ Tdap → HPV (II) (95% CI)	Tdap → MenACWY→ HPV [a] (III) (95% CI)	Vaccine Group Difference (I - III) (95% CI)	Vaccine Group Ratio (I/III) (95% CI)
		N=492	**N=458**	**N=487**		
Diphtheria % ≥1.0 IU/mL		100% (99, 100)	100% (99, 100)	98% (96, 99)	2% (1, 4)**	NA
GMC		*25 (23-27)*		*6.38 (6.28-7.42)*		*3.65 (3.26-4.09)*
Tetanus % ≥1.0 IU/mL		100% (99, 100)	100% (99, 100)	100% (99, 100)	0% (-1, 1)*	NA
Pertussis antigen						
PT	GMC	**N=479** 51 (47, 55)	**N=451** 79 (72, 87)	**N=477** 63 (58, 69)	NA	0.8 (0.72, 0.9)*
FHA	GMC	**N=489** 342 (310, 376)	**N=457** 1106 (989, 1238)	**N=485** 511 (464, 563)	NA	0.67 (0.58, 0.76)
PRN	GMC	**N=492** 819 (727, 923)	**N=458** 1563 (1390, 1758)	**N=487** 1197 (1061, 1350)	NA	0.68 (0.58, 0.81)

*from Table 11.4.1.1-4 (p. 81 of 839) and Table 14.2.1.18 (p. 259 of 839) CSR V59P18

Reviewer note: anti-diphtheria GMCs up to 4 fold greater following receipt of MenACWY with Tdap assumed secondary to Diphtheria CRM carrier protein of MenACWY.

The antipertussis GMCs for all pertussis antigens when Tdap was administered concomitantly and when it was administered alone were PT: 51 and 63, respectively; FHA: 342 and 511, respectively; PRN: 819 and 1197, respectively.

All secondary MenACWY and Tdap noninferiority immunogenicity objectives were met:

- Noninferiority of the immune responses to MenACWY, as measured by the hSBA GMTs and hSBA titer ≥ 1:8 and ≥ 1:4, when given: (a) concomitantly with Tdap and HPV; and (b) when given one month after Tdap, was demonstrated for all four serogroups using all selected endpoints.
- Noninferiority of the immune response to Tdap, as measured by the percentage of subjects with antidiphtheria and antitetanus toxin ≥1.0 IU/mL, and anti-PT, anti-FHA, and anti-PRN GMCs, when administered one month after MenACWY was demonstrated for all antigens using all selected endpoints.

6.4.2.4 Comments and Conclusions

6.4.2.4.1 Study Design and Population

The study was conducted at a single center in Costa Rica. The study was open label, and so neither safety nor immunogenicity were blinded. hSBA assays were performed in groups by study visit, so the hSBA for sequential administration of MenACWY (one month after Tdap) were conducted at a different time than the concomitant and separate groups. Evaluation of concomitant administration of Tdap with MenACWY was evaluated in the context of co-administration of GARDASIL in the concomitant group.

Reviewer's note: The study design limits the applicability and generalizability of this concomitant vaccine trial to the general U.S population. The data are also insufficient to evaluate the effect of MenACWY on interference of immune responses to the pertussis antigens fimbrae and pertactin.

6.4.2.4.2 Safety

The safety profile of MenACWY was comparable when MenACWY was administered alone, concomitantly with Tdap and HPV, or one month after Tdap. Similarly, the safety profile of Tdap was comparable when Tdap was administered alone and concomitantly with MenACWY and HPV. Overall, reactogenicity after Tdap was higher than after MenACWY. In neither instance was the reactogenicity of one diphtheria-containing vaccine (Tdap or MenACWY) enhanced when administered after the other. No unexpected or otherwise clinically significant AEs related to the vaccines administered were reported in this study.

6.4.2.4.3 Immunogenicity

The immunogenicity end-points for coadministration of MenACWY with Tdap were met for meningococcal antigens, Diphtheria, tetanus and pertussis toxin angtigens. Interference with immune responses to pertactin and fimbrae antigens was observed, but the relevance of the observed difference in GMTs is not known.

6.5 Trial 4 (NCT00329901)

6.5.1 Protocol Number and Title:

Study V59P11: A Phase 3, Multi-Center, Observer Blind, Controlled, Randomized Study to Compare the Immunogenicity and Safety of the Concomitant Administration of a Combined Tetanus, Reduced Diphtheria and AcellularPertussis (Tdap) Vaccine (GSK Boostrix®) and Novartis (formerly Chiron) Meningococcal ACWY Conjugate Vaccine, With Either One Dose of Boostrix®, or One Dose of Novartis Meningococcal ACWY Conjugate Vaccine in Healthy Subjects Aged11-25 Years

6.5.1.1 Rationale/Objectives

Study V59P11 was conducted to evaluate the safety and immunogenicity of MenACWY administered alone or concomitantly with Tdap vaccine

6.5.1.2 Design Overview

Subjects were randomized at a 1:1:1 ratio to receive concomitant administrations of either Tdap and MenACWY vaccines, or Tdap vaccine with saline placebo, or MenACWY with saline placebo. Subjects were administered each of the concomitant vaccines in different arms. Blood was drawn before vaccination, at day 1 and after vaccination, at day 29. From day 30 to day 181, only safety was collected.

This study administered a European formulation of Tdap. The assays used for evaluation of pertussis antigens were not considered adequate for the purpose of evaluating concomitant vaccine administration.

Reviewer note: This study contributes to the safety data base for MenACWY ***administered to adolescents and adults and was reviewed as part of the Integrated Summary of Safety only.***

6.5.1.3 Population

A total of 999 evaluable subjects (333 for each vaccination group) were planned to be enrolled. A total of 1072 subjects were enrolled and randomized to receive Tdap vaccine and MenACWY vaccine (333 subjects planned, 361 actually enrolled), Tdap vaccine and saline placebo (333 subjects planned, 354 actually enrolled), or MenACWY and saline placebo (333 subjects planned, 357 actually enrolled).

6.5.1.3.1 Study Period

April 18, 2006 to May 8, 2007

6.5.1.3.2 Study Sites and Recruitment

14 study sites located in Italy

6.5.1.4 Products Mandated by the Protocol

MenACWY conjugate vaccine, lot V79P39D1, expiry date: August 2007

6.6 Trial 5 (NCT00450437)

6.6.1 Protocol Number and Title:

Study V59P6: A Phase 2, Randomized, Single-blind, Controlled, Multicenter Study to Compare the Safety and Immune Response of One Dose of Chiron Meningococcal ACWY Conjugate Vaccine ——b(4)—— With the Safety and Immune Response of One Dose of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune®) Administered to Healthy Adolescents 11 to 17 Years of Age

6.6.1.1 Rationale/Objectives

Study V59P6 was conducted to evaluate the safety and immunogenicity of a single dose of MenACWY b(4) in healthy adolescents.

6.6.1.2 Design Overview

This trial was a phase 2, randomized, single-blind, controlled, multicenter study to evaluate the safety and immune response at 1 month and 12 months following vaccination with one dose of either MenACWY+ or MenACWY- conjugate vaccine or Menomune® in healthy adolescents 11 to 17 years of age. According to the original protocol, healthy adolescents were to be enrolled and randomized to MenACWY+ or Menomune vaccination groups. Due to the addition of a third study group after enrollment began, the study was divided into two stages: the first stage randomized subjects to MenACWY+ or Menomune in a 1:1 ratio; the second stage randomized subjects to MenACWY- or Menomune in a 4:1 ratio. Enrollment in stage 2 was to commence after enrollment in stage 1 was completed.

Reviewer note: Subjects enrolled in phase 2, who received MenACWY-, contribute to the total safety database for** MenACWY **for the indication sought. This study is reviewed as part of the Integrated Summary of Safety.

6.6.1.3 Population

A total of 490 subjects were to be enrolled according to the protocol, 300 in stage 1 (150 subjects each in MenACWY+ and Menomune groups) and 190 in stage 2 (152 subjects in the MenACWY- group and 38 subjects in the Menomune group). A total of 524 subjects were actually enrolled, 334 in stage 1 and 190 in stage 2. A convenience subset of subjects enrolled at Site 01 (Group Health Cooperative, Seattle, WA) was to be identified for additional study. These subjects were to provide an additional blood sample at 12 months after vaccination so that meningococcal capsule-specific memory B-cells could be studied in this population.

During stage 2, 151 MenACWY- and 39 Menomune subjects were analyzed for safety, and 150 MenACWY- and 39 Menomune subjects were analyzed for immunogenicity (MITT).

6.6.1.3.1 Study Period

October 29, 2004 to march 31, 2006

6.6.1.3.2 Study Sites and Recruitment

U.S. study sites

7 Overview of Safety Across Trials

7.1 Safety Database

Overview of integrated MenACWY safety data (Table 27):
A total of 6185 subjects provided safety data on MenACWY for the analysis (3579 adolescents aged 11 to 18 years, and 2606 adults aged 19 to 55 years) from three pivotal (V59P13, V59P17, V59P18) and two supportive studies (V59P6 and V59P11). For comparator vaccines, 1757 subjects provided safety data for Menactra, 209 provided safety data for Menomune, and 892 provided safety data for Tdap.

Table 27*. Overview of Studies That Provide MenACWY Safety Data

Region	Study	Age range	Vaccines	Number of Subjects Exposed	Planned Duration of Study (days) for Each Subject
US	V59P13 phase 3	11-55 y	MenACWY	2649	180
			Menactra	875	
Latin America (Argentina/ Columbia)	V59P17 phase 3	19-65 y [b]	MenACWY	1600 subjects 19-55; 217 subjects 56-65	180
			Menactra	889 subjects 19-55	
			Menomune	109 subjects 56-65	
Latin America (Costa Rica)	V59P18 phase 3	11-18 y	MenACWY + Tdap[c]+ HPV	540	211
			MenACWY followed by Tdap	541	271
			Tdap followed by ACWY	539	
US	V59P6 phase 2	11-17 y	MenACWY	151	360
			MenACWY adjuvanted	164	
			Menomune	209	
Europe (Italy)	V59P11 phase 3	11-25 y	MenACWY	357	181
			Tdap + MenACWY	359	
			Tdap	353	

*from Table 1.1.2-1 (p. 17 of 128) Integrated Summary of Clinical Safety (ISCS)

In addition, SAEs were reviewed for studies that enrolled subjects outside the 11 to 55 year range or received other formulations (dose b(4)).

7.2 Methods

Safety monitoring, definitions of relatedness as determined by study investigators and severity, and solicited AEs were generally the same for all studies contributing to the safety database for this indication except rash was not solicited in studies V59P6 and V59P11.

7.3 General Discussion of Safety Endpoints

Studies V59P13 and V59P17 provide the most relevant information regarding reactogenicity and solicited and unsolicited AEs because of the blinded study design used for these two studies. SAEs from all studies were reviewed for evidence of or suggestion of causality.

7.4 Significant/Potentially Significant Events

7.4.1 Deaths

No deaths occurred among subjects within the proposed indication of 11 to 55 years.

Two deaths occurred in vaccinees outside of the proposed indication, neither assessed as related to the MenACWY vaccine:

- Subject 837017, in study V59P14: 8 month old infant who succumbed to a serious lung infection (67 days after third immunization);
- Subject 821658, in study V59P17: 58 year old woman with a perinephric abscess from kidney stones who succumbed to hypovolemic shock (approximately 4 months after immunization).

7.4.2 Other Potentially Significant Events

Serious adverse events (SAE) occurred in 1% of subjects at any time during the studies in the MenACWY and Menactra groups (40 of 6185 subjects = 0.6% and 13 of 1757 subjects = 0.7% respectively). Less than 1% of subjects had an SAE during month 1; SAEs during months 2 to 6 occurred at an incidence of 1% or less. One SAE in subjects 11 to 55 years of age was considered by study investigators as possibly related to vaccine: spontaneous abortion that occurred on day 44 in study V59P17. The event was considered possibly related to the vaccine because of temporal association.

SAEs reported by more than one total MenACWY subject each were: spontaneous abortion (7 subjects), appendicitis and road traffic accident (3 subjects each), and suicide attempt (5 subjects including intentional drug overdose). SAE diagnoses: hepatitis, femur fracture, trauma, myoclonic epilepsy, intentional drug overdose, intentional overdose, appendicitis, simple partial seizures, vitello-intestinal duct remnant, suicidal depression, trauma, viral meningitis, epilepsy, tonsillitis, epiphisiolysis, pulmonary embolus, dystonia, chest pain, clavicle fracture, suicide attempt, suicide attempt, traumatic brain injury, ACL rupture, Staphylococcal infection, trauma, suicide attempt, ankle fracture, angioedema, HSV and HIV, spontaneous abortion, syncope, lumbar disc, DVT, nephrectopy, PID, spontaneous abortion, wasp sting, elbow fracture, hematurea, spontaneous abortion.

7.4.3 Dropouts

Overall, the proportion of subjects who withdrew or were lost to follow-up was low and evenly distributed across vaccine groups (Table 28 and Table 29).

Table 28*. Subject Disposition and Reasons for Withdrawal: Comparing Vaccines Pooled Across Studies Within the 11 to 18 Year Age Group

Age (yr)	Subject Disposition		ACWY Alone	ACWY + Concomitant Vaccines	Total ACWY	Menactra	Menomune	Tdap
11-18	Total exposed: n		2680	899	3579	539	209	892
	Total ongoing: n (%)		495 (18)	501 (56)	996 (28)	0	0	488 (55)
	Total completed: n (%)		2094 (78)	352 (39)	2446 (68)	524 (97)	203 (97)	349 (39)
	Premature Withdrawal	AE	0	1 (<1)	1 (<1)	0	0	0
		Withdrew consent	36 (1)	24 (3)	60 (2)	2 (<1)	1 (<1)	31 (3)
		Lost to follow up	47 (2)	14 (2)	61 (2)	12 (2)	5 (2)	19 (2)
		Other	8 (<1)	7 (1)	15 (<1)	1 (<1)	0	5 (<1)

*from Table 1.2-3 (p. 31 of 128) ISCS

Table 29*. Subject Disposition and Reasons for Withdrawal: Comparing Vaccines Pooled Across Studies Within 19 to 34 and 35 to 55 Year Age Groups

		19 to 34 Age Group		35 to 55 Age Group	
Subject Disposition		ACWY	Menactra	ACWY	Menactra
Total exposed: n		1145	569	1461	649
Total ongoing: n (%)		0	0	0	0
Total completed: n (%)		1124 (98)	563 (99)	1454 (100)	644 (99)
Premature Withdrawal	AE	0	0	0	0
	Withdrew consent	0	1 (<1)	0	0
	Lost to follow up	21 (2)	5 (<1)	7 (<1)	4 (<1)
	Other	0	0	0	1 (<1)

*from Table 1.2-4 (p. 32 of 128)

7.5 Other Safety Findings

There were no episodes of anaphylaxis or immediate hypersensitivity reactions within 30 minutes following vaccination. Three episodes of syncope occurred in the 11-18 year age group (one in MenACWY and 2 in the Menactra group). One episode of vaso-vagal syncope occurred in the 19 to 34 year only MenACWY group.

7.5.1 Local and Systemic Events

The overall incidence of solicited reactogenic events was similar between groups that received MenACWY (either alone or with a concomitant vaccine) and those that received Menactra (Table 30). There was a slightly higher percentage of Menactra subjects with at least one solicited local reaction compared with MenACWY subjects, and there was a slightly higher percentage of MenACWY subjects with a systemic reaction when compared with Menactra. Most solicited events occurred during the first 3 days after vaccination. Severe solicited local or systemic reactions within the first 7 days after vaccination were similar between MenACWY and Menactra (8% vs 6%).

Table 30. Summary of Individual Signs of Reactogenicity: Total MenACWY Compared With Menactra in Pooled Studies: Days 1 to 7; Pooled Age Groups

Reaction	Category	Total MenACWY N=6185 n (%)	Menactra N=1757 n (%)
LOCAL REACTIONS			
Pain	Any	2524 (41)	816 (46)
	Severe	100 (2)	36 (2)
Erythema	Any	926 (15)	231 (13)
	>50 mm	97 (2)	17 (1)
Induration	Any	775 (13)	203 (12)
	>50 mm	86 (1)	15 (1)
SYSTEMIC REACTIONS			
Chills	Any	545 (9)	120 (7)
	Severe	53 (1)	6 (<1)
Nausea	Any	625 (10)	142 (8)
	Severe	47 (1)	9 (1)
Malaise	Any	961 (16)	285 (16)
	Severe	107 (2)	22 (1)
Myalgia	Any	1130 (18)	280 (16)
	Severe	104 (2)	17 (1)
Arthralgia	Any	580 (9)	130 (7)
	Severe	61 (1)	10 (1)
Headache	Any	1881 (30)	491 (28)
	Severe	203 (3)	38 (2)
Rash	Any	160 (3)	42 (2)
Fever	38°C - 38.9°C	125 (2)	27 (2)
	39°C - 39.9°C	30 (<1)	8 (<1)
	≥40°C	6 (<1)	2 (<1)
OTHER REACTIONS			
Stayed home	Yes	268 (4)	63 (4)
Analgesic/ antipyretic use	Yes	1066 (17)	326 (19)

The reactogenicity (any solicited AE) of MenACWY alone was less than that of Tdap alone (69% and 82% respectively). Local reactions were reported in 52% and 74% for MenACWY and Tdap, respectively.

Reactogenicity was lower in the subjects aged 35 to 55 years: at least one solicited AE in MenACWY subjects was reported by 67%, 65%, and 56% for 11 to 18 year-old, 19 to 34 year-old, and 35 to 55 year-old age groups, respectively. Geographic location (U.S. versus South or Central America) did not affect reported reactogenicity.

Pooled across age groups and studies, 11% more female MenACWY subjects reported at least one local, systemic, or other reaction than male subjects (female, 69%; male, 58%). The difference in incidence of any reaction was similar in local (10% difference; female, 52%; male 42%), systemic (11% difference; female, 49%; male 38%), and other reactions (difference 7%: female, 22%; male 15%). The same higher reporting pattern by females was also observed for Menactra subjects. MenACWY female vs male differences in local reactions were due primarily to injection site pain (46% vs 34%, respectively) and induration (14% vs 11%). The incidence of erythema was the same (15%) for female and male subjects. The same pattern was observed for Menactra. MenACWY female vs male differences in systemic reactions were due primarily to more female reporting of headache (11% difference; female, 35%; male 24%) and myalgia (4% difference; 20% vs 16%, respectively), malaise (4% difference; 17% vs 13%), and nausea (4% difference; 12% vs 8%). Again, the pattern was also observed for Menactra. In other reactions, more female than male MenACWY subjects stayed at home (7% difference; 20% vs 13%); there was no noteworthy difference in analgesic/antipyretic use.

Unsolicited AEs were reported during the first month after vaccination in 17% and 20% of MenACWY and Menactra subjects; 1% of subjects in each group experienced severe unsolicited AEs. Headache was the one unsolicited AE reported in more than 1% of subjects during month 1 postvaccination (2% in each vaccine group). In total, 6% of MenACWY subjects and 7% of Menactra subjects reported unsolicited AEs assessed as possibly or probably related to the vaccine within month 1 postvaccination; most started within 1 to 7 days postvaccination.

7.5.2 Concomitant Immunization Safety

In the examination of the effect of concomitant Tdap and HPV vaccine with MenACWY vaccination, the incidence of systemic reactogenic events was, as expected, slightly higher than when MenACWY was given alone. However, the administration of Tdap vaccination one month before MenACWY did not change the incidence or severity of reactogenic events after MenACWY. MenACWY given after Tdap was comparable to MenACWY given alone.

7.5.3 Human Reproduction and Safety

In study V59P13, 18 pregnancies were reported, 15 (0.98% of the vaccinated females 11 to 55 years of age) in the MenACWY group and three (0.6% of the vaccinated females 11 to 55 years of age) in the Menactra group. Of the 15 pregnancies in the MenACWY group, one resulted in miscarriage (08/1006), and four resulted in therapeutic abortion (09/1078, 10/1009, 48/1011, and 54/1003). The remaining 10 MenACWY pregnancy outcomes were all live born deliveries.

Reviewer note: One therapeutic abortion was for fetal demise at 14 to 17 weeks gestation and would be more appropriately included as a spontaneous abortion (incomplete).

Of the three pregnancies in the Menactra group originally reported in the full CSR, one resulted in therapeutic abortion (45/1029), and one resulted in liveborn delivery (07/1021: this child upon further evaluation was found to have been born with hydrocephalus and died shortly after birth; refer to details below). A third Menactra pregnancy resulted in live born delivery after the original database lock (subject 42/1024).

Subject 08/1006, MenACWY Lot 2, a 38-year-old Asian female, had a miscarriage; this subject was vaccinated on March 22, 2007. The last menstrual period was reported to have occurred 19 days before study day 1, and conception was estimated at 5 days before immunization (March 17, 2007). Miscarriage occurred on May 7, 2007. Hypertension and migraine were indicated in the subject's medical history records. The subject had previous history of spontaneous abortions. The subject completed the protocol.

Additional reports of spontaneous abortion

Subject 901289 was a 34-year-old female who received one vaccination of MenACWY on 19 JUL 07. A urine pregnancy test was negative on that day. On 01 SEP 07 (44 days after vaccination), the subject was seen in clinic for vaginal bleeding and low abdominal pain for the previous 20 hours. At that time, her serum B-HCG of 2248 mIU/mL (consistent with a fourth or fifth week of pregnancy) and ultrasound showed neither a gestational sac nor evidence of an adnexal solid mass or cyst. Subject was discharged on the same day with a diagnosis of spontaneous abortion. On 04 SEP 07, the serum B-HCG was found to be 543 mIU/mL, ultrasound still showed no adenexal solid mass or cyst, and she was diagnosed with a complete spontaneous abortion. Subject reported a history of a previous normal intrauterine pregnancy with a normal delivery. The investigator assessed the event as serious based on the criteria of medically significant and possibly related to study vaccine due to temporal association of vaccination and SAE.

Subject # 011127 was a 14-year-old adolescent female who was randomized to Group II. Investigational vaccine MenACWY was given on 6AUG2007 and Boostrix (Tdap) on 11SEP2007. The subject was hospitalized on 8FEB2008 for uterine activity and found to have been pregnant. She had a spontaneous abortion during hospitalization. She was 19 weeks pregnant at that time with a last menstrual period of 20SEP2007. Laboratory findings were: haemoglobin 9,9; VDRL not reactive, blood type O+. The subject received therapy with Primogyn and underwent uterine curettage due to retained placenta retention. The subject was discharged on the same day. The pathology report showed a male fetus of 20 weeks, of 390 grams weight inside the yolk sac and attached to the placenta by the umbilical cord. No external malformations were present. The decidua and hypersecretory endometrium showed acute inflammation. The subject had vaginal candidiasis, which was diagnosed during pregnancy on January 2008. Subject received treatment with Miconazole ovules for 5 days and the infection was resolved on the same month, exact day unknown. The subject also received Indomethacin during pregnancy, start date on January, but the exact date unknown.

Subject # 012035 was a 16-year-old female, randomized to Group III, who received Boostrix (Tdap) on 28JUL2007, MenACWY on 01SEP2007 and GARDASIL (HPV) on 23SEP2007, on 02DEC2007 and on 03APR2008. On 10MAY2008 the subject went to visit according to protocol and her mother informed that the subject was pregnant and had had a spontaneous abortion on 23APR2008. The subject had a positive pregnancy test on 15APR2008 performed in a private laboratory. The subject was in good clinical condition and completely recovered.

7.6 Safety Conclusions

The clinical safety data indicate that MenACWY has a similar safety profile to the U.S. licensed vaccine Menactra with regards to local and systemic reactogenicity. Unsolicited AEs and SAE reports were also similar between MenACWY and Menactra. Review of SAE reports did not raise concerns for causality. In general, MenACWY was well tolerated.

8 Overview of Immunogenicity (Effectiveness) Across Trials

The immunogenicity profiles of the final MenACWY formulation are based on four studies, all conducted under United States (US) Investigational New Drug Application (IND) in (i) adolescents aged 11 to 18 years or (ii) adolescents and adults aged 11 to 55 years.
Two pivotal studies were:

- V59P13, a phase 3 lot comparison study using a US-licensed control, Menactra, conducted in the US in 3539 adolescents aged 11 to 18 years and adults aged 19 to 55 years;
- V59P18, a phase 3 noninterference study comparing MenACWY alone with concomitantly administered US-licensed Tdap (Boostrix) and human Papillomavirus (HPV) vaccine, (GARDASIL ™) or sequential Tdap (Boostrix) vaccination, conducted in Costa Rica on 1620 adolescents aged 11 to 18 years.

The two supportive studies were:

- V59P6, a phase 2 noninferiority study comparing MenACWY (with or without adjuvant) with the US-licensed comparator Menomune conducted in the US in 524 adolescents aged 11 to 17 years;
- V59P11, a phase 3 noninterference study including a comparison of MenACWY administered alone and concomitantly with Tdap (EU-licensed Boostrix) conducted in Italy in a total of 1072 subjects aged 11 to 25 years.

8.1 Methods

Immunogenicity was determined using human complement serum bactericidal activity assays (hSBA). The assay SOP and validation have been submitted and reviewed and are considered adequately validated for the purpose of this application.

8.2 General Discussion of Efficacy Endpoints

Lot consistency and non-inferiority to Menactra was evaluated in study V59P13. Interference with co-administration with routine vaccines was assessed in study V59P18. Supportive immunogenicity was provided for studies V59P6 and V59P8. These studies are not described in detail, but immunogenicity was consistent with the findings of study V59P13.

8.3 Study Design

In all studies, sera was obtained pre and at 28 or 30 days post immunization. All hSBA assays were performed in the Novartis Vaccines and Diagnostics

---b(4)--- --- Immunogenicity end-points were also similar in each study.

8.4 Immunogenicity Findings

See individual study immunogenicity results for V59P13 and V59P18.

Similar percentages of hSBA seroresponders were observed in all MenACWY alone groups across the four studies for serogroup A and serogroup C (range, 75% to 82% for serogroup A; range 75% to 84% for serogroup C). For serogroup W, the percentages of seroresponders observed in studies V59P6, V59P13 and V59P18 (84%, 75% and 81%, respectively) were higher than in study V59P11 (59%). This is consistent with the observation that the seroresponse endpoint is most sensitive to the percentage of subjects who are seropositive at baseline (55% of adolescents in study V59P11 had hSBA ≥ 1:8 for serogroup W at baseline). For serogroup Y, the percentages of seroresponders observed in studies V59P6 and V59P18 (86% and 82%, respectively) were higher than those in studies V59P11 and V59P13 (71% and 68%, respectively).

For serogroup A, 1% to 5% had prevaccination hSBA titers ≥ 1:8 among the four studies which increased to 75% to 82% postvaccination. For serogroup C, 17% to 24% of pre-vaccination and 83% to 90% of post immunization sera had an hSBA titer ≥ 1:8. For serogroup W, similar percentages of subjects had prevaccination hSBA titer ≥ 1:8 for studies V59P13 and V59P18 (40% and 43%, respectively), reaching 55% in study V59P11; the lowest percentage (13%) was observed in V59P6. Postvaccination, 90% to 99% had hSBA titers ≥ 1:8. Serogroup Y prevaccination hSBA titers ≥ 1:8 occurred in 36% and 34% in studies V59P11 and V59P13 respectively and in 23% and 20% in studies V59P6 and V59P18 respectively. Post vaccination hSBA titers ≥ 1:8 against serogroup Y were similar among the four studies (range, 88% to 95%).

8.5 Immunogenicity Conclusions

The immunogenicity data submitted indicate that MenACWY induces functional bactericidal antibody responses that are non-inferior to the licensed meningococcal conjugate vaccine Menactra. IN addition, although the concomitant administration study was not blinded and sera

were assayed based on study visit, the immune responses to MenACWY when administered concomitantly with Tdap (Boostrix) are non-inferior to those achieved when MenACWY was administered alone.

9 Special Populations

9.1 Pediatric populations

A partial waiver (0 to 2 months of age), a deferral (2 months to 10 years of age) and approval for the pediatric age group 11 to 16 years of age are supported by the current clinical development plan and the submitted clinical data.

9.1.1 Partial Waiver (0 to 2 months of age)

The clinical development plan has not included newborn infants because ,with the exception of Hepatitis B vaccine, the infant immunization program in the U.S is routinely initiated at 2 months of age. Studies in this age group would not be feasible, and this vaccine is unlikely to provide a meaningful therapeutic benefit in this age group. In general, neonatal immunization has been limited by characteristics of the neonatal immune response i.e. short-lived antibody responses and interference by maternal antibodies.

9.1.2 Deferral

A deferral is requested for the ages 2 months to 10 years of age because the studies in this age group are ongoing while studies have been completed for adolescents and adults.

10 Conclusions – Overall

11 Recommendations

11.1 Approval, Non-approval, Conditions

The safety and immunogenicity data provided in this application support a recommendation for approval of MenACWY for use in individuals 11 to 55 years of age for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y.

11.2 Recommendation on Postmarketing Actions

The safety database for MenACWY in 11 to 55 year old individuals suggests a similar safety profile to the currently licensed meningococcal conjugate vaccine Menactra. No safety signals were noted that should be specifically examined in post marketing studies. The database size is too small to detect rare adverse events. A postmarketing safety surveillance study, as recommended by CBER's Office of Biostatistics and Epidemiology (OBE), is warranted. In addition a well-designed pregnancy registry is needed given that the vaccine is likely to be used in women of child-bearing age.

Reduced immune response to acellular pertussis antigens filamentous hemagglutinin (FHA) and pertactin were observed when MENVEO was administered concomitantly with Boostrix and GARDSIL. Data are not adequate to evaluate the effect of MENVEO (versus GARDASIL, versus the combination) on the immune responses to pertussis antigens. A post marketing commitment to conduct a randomized, comparative trial, designed primarily to evaluate the potential for immune interference of concomitant use of MENVEO with U.S. licensed human papillomavirus vaccine and tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine as currently recommended by the U.S. vaccine schedule for immunization of adolescents is recommended.

OBE Recommendations to the BLA Chair and Review Committee:

1. Recommended the following post-marketing study be required and reported in accordance with 21 CFR 601.70:
   An open label, descriptive, epidemiological, safety surveillance study that enrolls 50,000 subjects or enrolls for 1 year, whichever results in the larger enrollment. The study protocol should be submitted by [4 months after approval date]. The study should be initiated by [6 months after approval date]. The final study report should be submitted within 1 year after the last subject has completed the study and by [3 years after study start date].

2. Recommended the following adverse events be reported in addition to 21 CFR 600.80 requirements. The expanded adverse experience reporting should be provided to the Vaccine Adverse Event Reporting System for one year following product licensure as follows:
   a. 15 day reports: All serious adverse events whether expected/labeled or unexpected/unlabeled, including but not limited to vaccine failure, seizures, shock, respiratory distress or difficulty breathing, angioedema, inspiratory stridor, and bilateral wheezing.
   b. 30 day (monthly) reports if not already submitted as 15 day reports: all allergic events, including anaphylaxis; neurological events including Bell's palsy, Guillain-Barré Syndrome, encephalitis, encephalopathy, brachial neuritis, optic neuritis, other neuropathy, myelitis including transverse myelitis, ptosis, ataxia, multiple sclerosis, acute disseminated encephalomyelitis, cerebrovascular accidents, and transient ischemic attacks; idiopathic thrombocytopenic purpura; Kawasaki disease; myasthenia gravis; other new onset autoimmune disease; and all cases of non-intentional injury.

3. Noted that the sponsor is planning to establish a pregnancy registry to prospectively collect safety data on spontaneously-reported exposures to MenACWY during pregnancy and lactation, including courses and outcomes of such pregnancies. It is recommended that the sponsor submit a protocol for a U.S. pregnancy registry by [18 months after approval]. This protocol should address elements found in FDA's Guidance for Industry on Establishing Pregnancy Exposure Registries (http://www.fda.gov/cber/gdlns/pregexp.htm). Furthermore, the sponsor should notify CBER of significant deviations from this guidance and/or specify the deviations in the protocol. Patient accrual/data collection should begin at the time of CBER's approval of the protocol and end no sooner than five years later. The sponsor should

submit annual reports and a final summary report of the U.S. pregnancy registry's findings five years after initiation of patient accrual/data collection. The U.S. pregnancy database may be considered completed one month after discontinuation of patient accrual for the purpose of preparing a five-year final summary report. The five-year final summary report should be submitted to CBER five years and six months after initiation of patient accrual/data collection. After reviewing the five-year data, the sponsor should discuss with CBER the need to continue further data collection in the U.S. pregnancy registry. CBER should have final approval regarding any decision to discontinue the U.S. pregnancy registry.

4. Recommended distribution reports should be submitted to CBER in accordance with 21 CFR 600.81.

5. No Risk Evaluation and Mitigation Strategy (REMS) was recommended at this time.

11.3 Labeling

The Package Insert submitted is in the format required by FDA's Final Rule titled "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" published in January 2006. Specific comments on the labeling (not included in this review) are being conveyed to the applicant.

12 Comments and Questions for the Applicant

The following comments were conveyed to the applicant in a Complete Response Letter (June 25, 2009). Responses were received and have been commented on in the relevant sections of the review of clinical studies.

1. *The seroresponse rates for initially seronegative subjects were greater than for seropositive subjects. However, the definition of seroresponse differs for those who were seronegative pre-immunization vs. those who were seropositive. For each immunogenicity study, please provide an analysis of 4-fold rise using the lower limit of detection titer of 1:4 (rather than half the LOD) for those with baseline titers <1:4 (i.e., post immunization titers of 1:16 or greater) and compare to the rate of 4-fold rise for initially seropositive individuals.*

2. *There appears to be inconsistency in the determination of severity and relatedness for treatment emergent adverse events, both within and across studies. For example a) in Study V59P17 [table 14.3.1.1.12 Spontaneous abortion] two abortions are listed as severe, while two are listed as moderate; b) in Table 14.3.1.1.16.[(page 9/12) p351 spontaneous and threatened abortion] some events are designated as unrelated while possibly related would be appropriate unless the subjects were not vaccinated, or the abortion was elective; c) severe arthralgia occurring within 30 days of vaccination is designated possibly related in some cases and unrelated in other cases. Inconsistency in the assessment of adverse event severity affects the ability to accurately evaluate and*

describe the safety profile for this vaccine. Regarding the accuracy of adverse event severity and relatedness, please:

a. *Describe the medical monitoring and quality control of adverse event reporting by study personnel including medical monitors and data safety monitoring committees.*
b. *Assess the accuracy and consistency of adverse event severity and relatedness reported for each study and all studies combined.*

3. *Across all studies, the safety follow-up from day 30 to day 180 includes all medically significant adverse events defined as AEs requiring a physician visit, Emergency Department visit, or leading to subject's withdrawal with the exclusion of pre-planned visits, medical office visits, or Emergency Room visits for routine medical care and common acute conditions such as: upper respiratory tract infections, otitis media, pharyngitis, urinary tract infections, gastroenteritis, superficial skin infections, and contact dermatitis. Please note that this approach may result in under-reporting due to the subjective categorization of routine or common acute conditions, and could result in lower reporting rates for some events. Please comment.*

Regarding study V59P13 entitled A Phase 3, Randomized, Observer-blind, Controlled, Multi-Center Study to Evaluate the Lot to Lot Consistency of Novartis Meningococcal ACWY Conjugate Vaccine when One Dose is Administered to Healthy Adolescents 11-18 Years of Age and to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 11-55 Years of Age

4. *The plan for serologic subsets is provided in Table 3.1.1.2. The plan as described could have resulted in unblinding of some sera in the serologic assays. In the 11 to 18 year old group, the subset scheme planned for MenACWY differed from the subsets planned for Menactra. The plan called for 1050 MenACWY (350 x three lots) and 300 Menactra sera to be tested for all 4 serogroups, 450 MenACWY (150 x 3 lots) and 150 Menactra to be tested for serogroup C only, and 50 Menactra sera to be tested for groups A and C. Based on the subset plan, no MenACWY samples would be tested for serogroups A and C in the 11 to 18 year old age group. Therefore, approximately 50 sera could have been unblinded. In the planned subset testing for the 19 to 55 year old subjects, 500 MenACWY and 300 Menactra recipients were to be tested for all 4 serogroups, 500 MenACWY and 33 Menactra recipients were to be tested for groups A and C. Based on this plan, the majority of sera from the 19 to 55 year old age group that were to be tested for serogroups A and C were from MenACWY recipients. Please provide the following information and analyses:*

a. *Clarify if the participant age group was known for sera.*

b. *Provide an analysis of the immunogenicity data for each serogroup by vaccine and by allocation group (i.e., sera selected for all four serogroups, sera selected for A and C, and sera selected for serogroup C only) for each of the age groups.*
c. *Explain the discrepancies between the serologic subsets planned in Table 3.1.1.2 and the reported available serologic data described in Table 3.1.2.2. In your response please include, by immunization group and by serogroup, a description of:*
    i. *the selection of subsets,*
    ii. *serum aliquot designation (i.e., were separate aliquots used for each serogroup assay, or were specific samples designated for 1 to 4 different assays depending on the subset allocation),*
    iii. *criteria for repeat analysis and number of sera that met these criteria,*
    iv. *sera that were repeated,*
    v. *results obtained by repeat analysis,*
    vi. *sera originally selected for initial or repeat assay that were not run,*
    vii. *sera intended for serologic evaluation for which hSBA data were not available. Please include the criteria used to exclude sera or to designate samples as "no valid result."*

5. *In Study V59P13, subjects were enrolled at 44 sites.*
    a. *Please provide solicited systemic and local adverse events, summary safety and immunogenicity analyses by study site.*
    b. *There were three centers which enrolled less than 10 subjects. Please explain the reasons for such small enrollments in these centers.*

6. *The evaluating investigators/study staff of two study sites were prematurely unblinded with respect to vaccine group assignment. Please evaluate whether these incidents may have had an impact on the study safety results. Also, please submit to CBER a SAS program which would be used for such an analysis.*

7. *For the sake of the exploratory analysis, please assess the statistical significance of differences in rates of solicited, unsolicited days 1-29, unsolicited days 30-180, and severe local and severe systemic solicited reactions between study groups (on V59P13 Complete Study Report pages page 93, 97, and 100 of 712).*

8. *In the MenACWY group, 5 subjects reported 8 suicide attempts. Please compare the rate of suicide attempts in this group with the rate for attempted suicide for the general US population. Please comment on the findings.*

9. *You stated that 18 pregnancies were reported in study V59P13, 15 in the MenACWY group, and 3 in the Menactra group. Of the 15 pregnancies in the MenACWY group, one resulted in miscarriage (08/1006) and four in therapeutic abortion (09/1078, 10/1009, 48/1011, and 54/1003). Of the 3 pregnancies in the Menactra group, one resulted in therapeutic abortion (45/1029) and one in delivery of an infant with hydrocephalus. In the SAE summary, you supplied a clinical summary on the therapeutic abortion only for*

subject 48/1011 (she was admitted to the hospital for a therapeutic abortion after the demise of the fetus). Please submit the available clinical information on all therapeutic abortions. Please note that some of these adverse events likely should be classified as SAEs. Please comment.

10. *In the Clinical Study Report, page 65, you state "None of the subjects withdrew due to an AE." However, according to the SAE Summary, the father of subject 13/1014 withdrew the subject from the study because she required special care after suicide attempt. Please comment. Additionally, please submit safety profiles of subjects who were vaccinated and prematurely withdrew from the study (82 subjects).*

Regarding Study V59P17 entitled A Phase 3, Randomized, Observer-blind, Controlled, Multicenter Study to Compare the Safety and Immunogenicity of Novartis Meningococcal ACWY Conjugate Vaccine with that of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) when One Dose is Administered to Healthy Subjects 19-55 Years of Age and with that of Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune™) when One Dose is Administered to Healthy Subjects 56-65 Years of Age

11. *According to Table 14.1.1.2.1., more study participants were lost to follow-up in the 19-34 year old MenACWY group (12/849) than in the Menactra group (1/470). Please comment.*

12. *According to Table 14.1.1.4.3, receipt of a DT containing vaccine in the previous 5 years was equally distributed between the vaccine groups. Please assess the effect on safety and immunogenicity associated with having had a DT containing vaccine in the previous 5 years.*

Regarding Study V59P18 entitled Phase 3, Single Center, Open-label, Controlled, Randomized Study to Evaluate the Safety and Immunogenicity of Novartis MenACWY vaccine administered either alone or concomitantly with a Combined Tetanus, Reduced Diphtheria Toxoid, Acellular Pertussis Vaccine (Tdap, Boostrix®) and Quadrivalent Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine (GARDASIL®) in Healthy Adolescents

13. *Please provide a subset analysis and summary of immunogenicity and safety outcomes by sex.*

14. *On page 99 of 839 of the P18 Clinical Study Report [Table 12.2.1-1.], it is noted that rates of local, systemic, and other reactions post second dose are all lower than post first dose regardless of study vaccine received. Please comment.*

15. *Regarding Table 12.2.3-7, over the entire study period, all groups have received the same vaccines. In addition to the summary of all AEs for the entire study period, please evaluate for all study groups the occurrence of "all and possibly related adverse events" by study group by the intervals from first vaccination to the time point of group 2 and 3*

second immunization, and from that time-point until the time of 3rd immunization and for 30 days following the group 2 and 3 third immunization.

The applicant provided responses in **125300/0.15 (8/21/2009)**: **1.11.3** Efficacy Information Amendment "Response to Clinical and Statistical Questions" and the information has been incorporated into this review. There are no outstanding questions.