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

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Food and Drug Administration (FDA)

To: BLA STN# 125300/95

Subject: Clinical Review of Biologics License Application for Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate

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1 General Information

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

Paulina E. Mariki, M.D. and Margaret C. Bash, M.D., M.P.H.

1.1.1 BLA #: 125300/95

1.1.2 Related IND #(s): IND (b)(4)
Meningococcal (Groups A, C, Y and W-135) Oligosaccharide Diphtheria CRM_{197} Conjugate Vaccine for persons aged 11 through 55 years

1.1.3 Reviewer Name, Division and Mail Code (HFM Number):
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1.1.4 Submission Received by FDA: April 1st 2010

1.1.5 Review Completed: January 28th 2011

1.2 Product

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

1.2.2 Proposed Trade Name: MENVEO

1.2.3 Product Formulation: Administered as a single 0.5 mL intramuscular injection after reconstitution of 10µg of lyophilized MenA oligosaccharide with liquid MenCWY (MENVEO).

Composition	Amount per 0.5 mL dose after reconstitution
MenA -CRM_{197} conjugate	10 µg MenA, ---(b)(4)----- CRM_{197}
MenC-CRM_{197} conjugate	5 µg MenC, ---(b)(4)----- CRM_{197}
MenW-CRM_{197} conjugate	5 µg MenW, ---(b)(4)----- CRM_{197}
MenY-CRM_{197} conjugate	5 µg MenY, ---(b)(4)----- CRM_{197}
-------(b)(4)---------	(b)(4)
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1.3 **Applicant:** Novartis Vaccines and Diagnostics, Inc

1.4 **Pharmacologic Class or Category:** Vaccine

1.5 **Proposed Indication:** MENVEO is a vaccine indicated for active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135. MENVEO is currently approved for use in persons 11 through 55 years of age. This application is to extend approval for use to children 2 years through 10 years of age.

1.6 **Proposed Population(s):** 2 year old through 10 year old children.

1.7 **Dosage Form and Route of Administration:** Administered as a single 0.5 mL intramuscular injection after reconstitution.

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3 Executive Summary

Background

BLA supplement 125300/95.0 contains safety and immunogenicity data intended to support an extension of the age indication for MENVEO from the current 11 through 55 years of age to include use of a single dose of MENVEO in children 2 through 10 years of age. Current U.S.-licensed meningococcal vaccines for the prevention of disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 in children 2 through 10 years of age are Menomune® and Menactra®. Menomune (Sanofi Pasteur Inc.) is a quadrivalent polysaccharide vaccine indicated in persons 2 years of age and older, and Menactra (Sanofi Pasteur Inc,) is a polysaccharide-diphtheria toxoid conjugate vaccine indicated in persons 2 through 55 years of age. Novartis created MENVEO by conjugation of meningococcal polysaccharides from serogroups A, C, W-135, and Y to a nontoxic mutated form of diphtheria toxin (CRM197).

N. meningitidis is a leading cause of bacterial meningitis and sepsis worldwide. Invasive meningococcal disease has occurred in the U.S at a rate of 0.9 to 1.5/100,000 persons over the past 4 decades. 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. Licensure of serogroup A and serogroup C meningococcal polysaccharide vaccine 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 serum bactericidal activity (SBA), in an assay using exogenous rabbit complement (rSBA). Menactra was licensed in 2005 on the basis of immunologic (SBA) non-inferiority to Menomune using an exogenous complement source that was either human (hSBA) or, when correlated to hSBA, baby rabbit complement.

The safety and effectiveness of MENVEO in children 2 through 10 years of age were evaluated in comparison to currently licensed vaccines, Menactra or Menomune. Vaccine effectiveness was assessed by comparing the hSBA responses after immunization with MENVEO to those following immunization with licensed meningococcal vaccines. 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 that invasive disease did not occur in individuals whose sera (tested at a dilution of 1:4) killed the circulating strain.

Table 1: Description of Clinical Studies

Study Number	Geographic Location	Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (*N*)	Subjects	MENVEO Injections
V59P7	Finland, Poland	Safety and Immune Response of Menveo ----------(b)(4)---------- vs Mencevax	Observer-Blind, Randomized, Active Controlled Phase 2 Multi-Center Study	– Menveo 10-5-5-5µg (b)(4) IM (*N=205*) – Menveo 10-5-5-5µg (b)(4) IM (*N=224 safety data*) – Mencevax™ IM followed by Menveo 10-5-5-5µg (b)(4) IM (*N=81*)	Toddlers 12-35 m Children 36-59 m	Two
V59P8	US	Safety and Immune Response of Menveo vs Menomune	Single-Blind, Randomized, Active Controlled Phase 2 Single-Center Study	– Menveo 10-5-5-5µg (b)(4) IM (*N=308 safety data*) – Menomune™ SC (*N=310*)	Children 2-10 y	One
V59P10	Argentina	Safety and Immune Response Menveo vs Menomune	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– Menveo 10-5-5-5µg (b)(4) IM (*N=949 safety data*) – Menomune™ SC (*N=551*)	Children 2-10 y	One
V59P20	US, Canada	Safety and Immune response to Menveo vs Menactra	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– Menveo 10-5-5-5µg (b)(4) IM (*N=1626 safety data*) – Menveo x 2 doses *(N=351)* – Menactra (*N=1255 safety data*)	Children 2-10 y	One or Two

Safety

The total safety database for MENVEO in children 2 through 10 years of age consists of 3107 children from 1 pivotal study (V59P20) and 3 supportive (V59P7, P8 and P10) studies in which children were exposed to at least one dose of MENVEO. The comparator safety populations in the 2 through 10 year age group were 1255 and 861 enrolled subjects who received Menactra and Menomune, respectively. In supportive study V59P7, the comparator vaccine Mencevax is not licensed in the U.S., hence the safety and immunogenicity data from this study were not considered comparative for this clinical review. However, recipients of MENVEO in this study contributed to the overall safety database.

In the safety evaluation of MENVEO in the pivotal trial (V59P20), the following were observed:

- Demographics and other baseline characteristics were similar across the vaccine groups.

- No major differences were observed in the percentages of subjects who withdrew prematurely, or withdrew consent. The most common reason for withdrawal was lost to follow up.
- No major differences in the percentages of subjects reporting any solicited local or systemic reactions after MENVEO vs Menactra were observed.

Solicited adverse events in the pivotal U.S. safety study:
Adverse events were recorded on study specific diary cards daily for 7 days post-vaccination by subject's parents/legal guardians. The percentages of subjects reporting any solicited AE in the MENVEO group and in the Menactra group were similar at 55% vs 56%, respectively; 49% reported local reactions for both vaccines and 17% vs 16% reported systemic adverse reactions, respectively. The solicited events "use of analgesic/antipyretic medication" and "stayed at home due to vaccination" occurred in 12% of both vaccine groups.

Injection site pain was the most frequently reported local solicited AE (33% in MENVEO recipients vs 35% in Menactra recipients). While local AEs were reported in slightly fewer MENVEO than Menactra recipients, rates of severe local reactions were similar in both vaccine groups (overall, <1% to 1% vs 0% to 2%, respectively). For both vaccine groups, almost all solicited local AEs were experienced during the first three days immediately following vaccination. The most commonly reported systemic solicited AEs in the 2 through 5 year age group for MENVEO and Menactra were irritability (21% vs 22%, respectively) and sleepiness (16% and 18%, respectively). In the 6 through 10 year age group the most common solicted AEs for MENVEO and Menactra were headache (18% vs 13%, respectively), malaise (14% vs 11%, respectively) and myalgia (10% in both vaccine groups). Rates of severe systemic reactions were also similar: in the 2 through 5 year age group, severe irritability or severe sleepiness occurred in 1% of participants in both vaccine groups and in the 6 through 10 year age group, severe headache, myalgia and malaise, each were reported by 1% of study participants in both vaccine groups.

Serious adverse events in the pivotal US safety study:
Serious adverse events (SAE) were reported by 8/1626 subjects (0.5%) in the MENVEO 1 dose group, 2/351 subjects (0.6%) in the MENVEO 2 dose group and 7/1255 subjects (0.6%) in the Menactra group. None of the SAEs were assessed as related to the vaccine administered. No deaths occurred and no AE led to subject withdrawal. Most of the SAEs started > 6 weeks post vaccination with the exception of 4 SAEs in MENVEO recipients: streptococcal infection, bronchopneumonia, dehydration and a case of worsening of an inguinal hernia. The majority of SAEs lasted for six days or less and resolved completely.

Adverse events in the 2 dose group:
When a two-dose regimen was explored in the 2 through 5 years age stratum, the percentage of subjects reporting solicited local reactions after any vaccination were more in the MENVEO 2-dose group vs. MENVEO single dose group (43% and 33%, respectively). However the percentages of subjects reporting solicited local reactions after 1st vaccination and 2nd vaccination in the MENVEO 2 dose group were similar (32% and 28%, respectively). Overall there was a general tendency towards decreased reports of local reactions following the second vaccination. This tendency was more evident for erythema and induration than for injection site pain. Additionally, the percentages of subjects reporting SAEs were similar (≤1%) regardless of whether one or two doses of MENVEO were administered.

Solicited and Serious Adverse Events in the Supportive Studies V59P7, V59P8, and V59P10:
Across all three studies, the most commonly reported local reaction following vaccination with MENVEO was injection site pain (any: 18% to 33%, severe: 0 to 1%). The most commonly reported systemic reaction in 2 through 5 year old children was irritability (11% to 22%), followed by sleepiness (9% to 18%) and change in eating habits (9% to 11%), and in children 6 through 10 years old, the most frequently reported systemic reaction was headache (11% to 19%), followed by malaise (6% to 14%) and myalgia (3% to 10%). Within each comparative study, rates of adverse events were similar between vaccine groups. Overall, reports of severe local or systemic reactions were low and similar across the vaccine groups at ≤1%.The exception was the higher percentages of unsolicited SAEs observed in study V59P7 (8%) which was attributed to a high incidence of varicella infection in this unvaccinated population. In this study all varicella cases, regardless of severity and hospitalization status, were categorized by the investigator as SAEs. Although the comparator vaccine, Mencevax, is not a U.S. licensed vaccine, it is of note that there were no observed differences in varicella severity by vaccine group.

Summary of Safety Results:
Overall the safety profiles of MENVEO and U.S-licensed comparator vaccines had similar rates of solicited and unsolicited local and systemic events Additionally, the reports of severe local or systemic reactions were low and similar across the vaccine groups at ≤1% except in supportive study V59P7 where 8% SAEs were reported (primarily due to an outbreak of varicella). No AEs were reported to have led to subject withdrawal in any of the four studies within the 2 through 10 years age group. No death occurred in any of the four studies used to support this application.

Immunogenicity

The immunogenicity data presented in this sBLA are intended to provide evidence of vaccine effectiveness by establishing the immunologic non-inferiority of MENVEO compared to currently licensed vaccines. An hSBA seroresponse (Table 2), was used

as the primary immunogenicity outcome. Other outcomes of interest are also shown.

Table 2 : Definitions of Endpoints

Endpoint	Endpoint Definitions
Seroresponse	For subjects with prevaccination hSBA <1:4 (seronegatives), seroresponse was defined as postvaccination titer ≥1:8. For subjects with prevaccination hSBA ≥1:4 (seropositives), seroresponse was defined as postvaccination titer ≥4 times the prevaccination titer.
hSBA ≥1:4	Percentage of subjects achieving an hSBA titer ≥1:4
hSBA ≥1:8	Percentage of subjects achieving an hSBA titer ≥1:8
GMT	Geometric mean hSBA titer

Immunogenicity in the Pivotal Study, V59P20:

Primary Objective:

- To demonstrate that the hSBA seroresponses to MENVEO were non-inferior to the hSBA seroresponses to Menactra. Non-inferiority was demonstrated if for all four serogroups the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse (MENVEO minus Menactra) was greater than -10%, i.e., if the CI for the difference is entirely to the right of -10%, then non-inferiority was declared.

Secondary Objectives:

- To evaluate the difference of the percentage of subjects with hSBA ≥ 1:8, hSBA ≥1:4 (MENVEO minus Menactra) and differences in hSBA GMTs (MENVEO/Menactra) for each serogroup in children 2 through 5 years and 6 through 10 years of age.
- To evaluate the difference of the percentage of subjects with seroresponse, hSBA titer ≥1:8, hSBA titer ≥1:4 or hSBA GMT, for each serogroup in children 2 through 10 years of age after administration of MENVEO compared to Menactra, in the 2 through 10 year age group.
- To evaluate hSBA seroresponse, proportion with hSBA titer ≥1:8 (or hSBA titer ≥1:4) or hSBA GMT for each serogroup after administration of 2 doses of MENVEO given 2 months apart compared to 1 dose of MENVEO in the 2 through 5 years group.

The success criteria for the pivotal study V59P20 was based upon only the primary objective for the per protocol population. This study is considered a success if, for both age strata, all four serogroup analyses met the non-inferiority criteria identified for the primary endpoint noted above.

Immunogenicity Results, pivotal study V59P20:

Primary and secondary immunogenicity endpoints evaluated in pivotal study are shown in Table 3 below.

Table 3: Comparison of bactericidal antibody responses to MENVEO and Menactra 28 days after vaccination of subjects aged 2 through 5 and 6 through 10 years

	2 through 5 years			6 through 10 years		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95%CI)**	**% difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**	**MENVEO (95%CI)**	**Menactra (95%CI)**	**% difference (MENVEO - Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**
A	**N=606**	**N=611**		**N=551**	**N=541**	
% Seroresponse[α]	72 (68, 75)	77 (73, 80)	-5 (-10, -0)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
% ≥ 1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
GMT	26 (22, 30)	25 (21, 29)	1.04 (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01 (0.83, 1.24)
C	**N=607**	**N=615**		**N=554**	**N=539**	
% Seroresponse[α]	60 (56, 64)	56 (52, 60)	4[μ] (-2, 9)	63 (59, 67)	57 (53, 62)	6[μ] (0, 11)
% ≥ 1:8	68 (64, 72)	64 (60, 68)	4 (-1, 10)	77 (73, 80)	74 (70, 77)	3 (-2, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33 (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36 (1.06, 1.73)
W-135	**N=593**	**N=605**		**N=542**	**N=533**	
% Seroresponse[α]	72 (68, 75)	58 (54, 62)	14[μ] (9, 19)	57 (53, 61)	44 (40, 49)	13[μ] (7, 18)
% ≥ 1:8	90 (87, 92)	75 (71, 78)	15 (11, 19)	91 (88, 93)	84 (81, 87)	7 (3, 11)
GMT	43 (38, 50)	21 (19, 25)	2.02 (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72 (1.44, 2.06)
Y	**N=593**	**N=600**		**N=545**	**N=539**	
% Seroresponse[α]	66 (62, 70)	45 (41, 49)	21[μ] (16, 27)	58 (54, 62)	39 (35, 44)	19[μ] (13, 24)
% ≥ 1:8	76 (72, 79)	57 (53, 61)	19 (14, 24)	79 (76, 83)	63 (59, 67)	16 (11, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36 (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41 (1.95, 2.97)

Source: Table 11.4.1.1-1 V59P20 report

δ Serum bacterial assay with exogenous human complement source (hSBA)

α Seroresponse was defined as: subjects with a pre-vaccination hSBA titer of <1:4, a post-vaccination titer of ≥ 1:8 and among subjects with a pre-vaccination hSBA titer of ≥1:4, a post-vaccination titer at least 4-fold higher than baseline.

μ Non-inferiority criterion for the primary endpoint met (the lower limit of the two sided 95%CI > -10% for vaccine group differences [MENVEO minus Menactra])

In Study V59P20, non-inferiority was demonstrated in both age strata for serogroups C, W-135 and Y. The non-inferiority end-point was narrowly missed for serogroup A in each age strata. The observed differences in seroresponse rates between the two vaccines were considered unlikely to represent clinically meaningful differences. In addition, non-inferiority was demonstrated for the secondary analysis of the combined age group (i.e., subjects 2 through 10 years of age) for all 4 serogroups. Statistically

higher seroresponse rates were observed for serogroups W-135 and Y for each age strata.

Immunogenicity Results, two dose schedule:

The data presented in this application were intended to support a single dose schedule; however, as a secondary objective, the hSBA responses to a second dose were analyzed in study V59P20 and were also examined in the earlier supportive study V59P7. In the pivotal study, V59P20, children 2 through 5 years of age were randomized to receive a second dose 2 months following the first dose. Significantly higher seroresponse rates, proportions with titers ≥ 1:8 and GMTs were observed for each serogroup at 28 days following the second dose compared to the group who received a single dose (Table 4). In supportive study V59P7, the percentages of seroresponders were also notably higher in the MENVEO 2-dose group than in the MENVEO single dose group for all four serogroups (A 91% vs. 72%, C: 98% vs. 60%, W: 89% vs. 72%, and Y: 95% vs. 66%), and higher when the doses were spaced 12 months apart compared to a 6 month interval.

Table 4: Immunogenicity of 2 doses vs 1 dose: % of Subjects with hSBA titer ≥1:8, seroresponse and GMTs of Subjects at Day 1 and at One Month Post-Vaccination, in 2 through 5 year old children, PP population study V59P20

Serogroup	hSBA Titer ≥1:8		Seroresponse		GMTs	
Day 1	**MENVEO 2 Doses**	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**
A[a]	1% (0-3)	1% (1-3)	NA	NA	2.1 (2.02-2.18)	2.1 (2.04-2.16)
C[b]	9% (6-13)	10% (8-13)	NA	NA	2.92 (2.65-3.23)	3.05 (2.83-3.29)
W[c]	21% (17-26)	24% (21-28)	NA	NA	4.07 (3.42-4.84)	4.38 (3.84-5.01)
Y[d]	9% (6-13)	14% (11-17)	NA	NA	2.75 (2.44-3.09)	3 (2.74-3.28)
Day 29						
A[a]	91% (88-94)	72% (68-75)	91% (87-94)	72% (68-75)	64 (51-81)	27 (23-32)
C[b]	99% (97-100)	68% (64-72)	98% (95-99)	60% (56-64)	144 (118-177)	18 (15-21)
W[c]	99% (98-100)	90% (87-92)	89% (85-92)	72% (68-75)	132 (111-157)	41 (36-47)
Y[d]	98% (95-99)	76% (72-79)	95% (91-97)	66% (62-70)	102 (82-126)	23 (20-27)

Source: section 5.3.5.1.1. Study V59P20 Table 11.4.1.2-6
a serogroup A: MENVEO 2 Doses N=291, MENVEO 1 Dose N=606
b serogroup C: MENVEO 2 Doses N=293, MENVEO 1 Dose N=607
c serogroup W: MENVEO 2 Doses N=288, MENVEO 1 Dose N=594
d serogroup Y: MENVEO 2 Doses N=286, MENVEO 1 Dose N=593

Immunogenicity Results, persistence:
Additionally, persistence of serum bactericidal activity over a period of up to 12 months post- vaccination was investigated within the 2 through 10 years of age group in supportive studies V59P7, V59P8, and V59P10. The hSBA responses were assessed at 6 or 12 months post-vaccination in children 2 through 5 years of age in V59P7, 12 months after vaccination in children 2 through 10 years of age in V59P8, and 6 months after vaccination in children 2 through 10 years of age in study V59P10. In study V59P8 the percentage of subjects with hSBA ≥ 1:8 at 12 months compared to 1 month post-vaccination remained close for serogroup W (92% and 90% at 1 month and 12 months, respectively) and Y (88% and 77%,). However the percent of subjects with hSBA ≥1:8 at 12 months compared to 1 month post-vaccination was significantly lower for serogroup A (80% and 23% at 1 month and 12 months, respectively) and C (73% and 53%). In study V59P10 the percentage of subjects with hSBA ≥ 1:8 at 6 months compared to 1 month post-vaccination decreased for all serogroups except for serogroup Y in the MENVEO group. In study V59P7 the percentage of subjects with hSBA ≥ 1:8 at 6 or 12 months compared to 1 month post-vaccination decreased by ~ 50 % for serogroup A with only 7-17% decrease for serogroup C, W-135 and Y.

Summary of Immunogenicity Results:
Overall, the immunogenicity data from the pivotal and supportive studies indicate that MENVEO is immunogenic and stimulates functional antibody responses in children 2 through 10 years of age. The immunogenicity of MENVEO is similar to that of the currently licensed quadrivalent vaccine Menactra although in the pivotal study lower responses were observed for serogroup A and higher responses were observed for serogroups Y and W-135. The comparator vaccine is indicated for use in the 2 through 10 year age group as a single dose vaccine. This supplement contained immunogenicity data that showed an immunologic benefit to receipt of a second dose in the 2 through 5 year old age group. Although the indication sought was for a single dose in children 2 though 10 years of age, the two dose data were considered clinically relevant. Therefore, the safety and immunogenicity of two doses administered to children 2 through 5 years of age was included in the package insert with permissive use of a second dose stated in the dosage and administration section.

Pediatric Review Committee (PeRC)

The MENVEO (Meningococcal [Groups A, C, Y, and W 135] Oligosaccharide Diphtheria CRM197 Conjugate Vaccine) pediatric assessment was reviewed by the PeRC PREA Subcommittee on November 03, 2010. The Division presented an assessment for patients 2 years through 10 years of age. The PeRC PMR for the 2 through 10 years of age group has been fulfilled for this product.

Recommendations

- The clinical data provided in this supplement demonstrate that MENVEO has a similar safety profile and similar immunogenicity to the licensed meningococcal conjugate vaccine Menactra in children 2 through 10 years of age. The data support a recommendation for approval of this vaccine administered as a single dose to individuals 2 through 10 years of age for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135.
- The hSBA responses following a two dose regimen in children 2 through 5 years of age are substantially higher for each serologic end-point: proportion above the threshold of 1:8 hSBA, seroresponse and GMT, for all 4 serogroups. The difference in immunogenicity between a single dose regimen and a two dose regimen is considered clinically relevant. Although the two dose regimen was evaluated in an unblinded manner in the clinic, it was a randomized group and the comparison was a pre-defined secondary objective of the pivotal study. The safety data and the immunogenicity data should be presented in the label with permissive language for administration of a second dose 2 months after the first dose in children 2 through 5 years of age who are at continued high risk of meningococcal disease.
- Further evaluation of a 2 dose regimen of MENVEO is needed. The available data do not address: 1) whether older children (6 through 10 years of age) can benefit from a 2-dose regimen; 2) the need for revaccination (antibody persistence) of children 2 through 10 years of age; 3) safety of two dose regimens in the pediatric population. To address these limitations of the available data, a post marketing study is recommended.
- No safety signals were identified that should be specifically examined in post marketing studies. However, because the total safety experience in the 2 through 10 year age group is insufficient to detect and characterize uncommon and rare adverse events of medical significance, a post marketing study to extend the safety experience is recommended.

4 Clinical and Regulatory Background

4.1 Disease 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 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.

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.

N. meningitidis serogroup B 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 serogroup B polysaccharide capsule is poorly immunogenic, even when conjugated to a protein. *N. meningitidis* serogroup B is not included in the currently licensed U.S. quadrivalent meningococcal vaccines.

4.2 Previous Human Experience with the Product

The data submitted in BLA 125300/0 describes the first human experience with MENVEO. MENVEO was licensed for use in adolescents and adults age 11 through 55 years on February 19th, 2010. This sBLA describes the first use of MENVEO in children age 2 years through 10 years of age.

4.3 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 to Menactra), evaluation of dose and schedule, and ----------(b)(4)----------. In September 2003 clinical investigations of Novartis' quadrivalent meningococcal polysaccharide conjugate vaccine MENVEO 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)---------- Novartis is filing this application with an indication for use in persons aged 2 years through 10 years of age.

5 Clinical Data Sources and Review Strategy

5.1 Material Reviewed

125300/95:
2.2 Introduction;
2.5 Clinical Overview;
2.7 Clinical Summary;
5.2 Tabular Listing of all Clinical Studies;
5.3.5.1 Active-Control-Without-Placebo (V59P7, V59P8, V59P10, V59P20);
5.3.5.3 Integrated Summary of Efficacy and Integrated Summary of Safety

5.2 Review Strategy

The clinical study reports provided safety and immunogenicity data to evaluate the reactogenicity, safety and immunogenicity of MENVEO in comparison to U.S.-licensed quadrivalent meningococcal vaccines, Menactra and Menomune.

Pivotal study V59P20 provided safety and immunogenicity data for MENVEO in comparison to Menactra in 2 through 10 year old children. Safety and immunogenicity data were also provided for a subset of 2 through 5 year old children comparing 2 doses with 1 dose of MENVEO.

Supportive study V59P8 and V59P10 provided safety and immunogenicity data for MENVEO in comparison to Menomune in 2 through 10 year old children.

Supportive study V59P7 was a phase 2 study comparing safety and immunogenicity of MENVEO with a non-US licensed vaccine Mencevax in 2 through 5 year old children. Hence only the reactogenicity and immunogenicity data in the MENVEO recipients were used in this clinical review.

5.3 Clinical Studies

See Table 1 in the Executive Summary

5.4 Good Clinical Practices (GCP) and Data Integrity

5.4.1 BIMO Inspection Summary

Background

----------Information withheld per Privacy Act----------
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Summary

---------- Information withheld per Privacy Act ----------
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6 Clinical Studies

6.1 Indication #1

Active immunization of individuals 2 through 10 years of age to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W-135 and Y.

6.1.1 Trial #1

6.1.1.1 Protocol # and Title

Protocol V59P20:
A Phase 3, Randomized, Observer-blind, Multi-Center Study to Compare the Safety and Immunogenicity of One Dose of Novartis Meningococcal ACWY Conjugate Vaccine (MENVEO) with One Dose of Licensed Meningococcal ACWY Conjugate Vaccine (Menactra™) Administered to Healthy Children 2 through10 years of age

6.1.1.1.1 Objective/Rationale

Study V59P20 was undertaken as a pivotal study to compare the safety and immunogenicity of MENVEO to the currently licensed meningococcal conjugate vaccine, Menactra. Study V59P20 also compared the immunogenicity of a single dose of MENVEO to the immunogenicity of two doses of MENVEO administered 2 months apart (Subjects in Group I).

Immunogenicity

Primary Objective:

- To compare the immunogenicity of a single dose of MENVEO with the immunogenicity of a single dose of Menactra, defined as percentage of subjects with an hSBA seroresponse directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy children 2 through 5 years of age or 6 through 10 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:

- To assess the immunogenicity of two doses of MENVEO administered 2 months apart (Subjects in Group I), and compare it to the immunogenicity of a single dose of MENVEO, defined as percentage of subjects with seroresponse (as defined above), hSBA titers ≥1:4, ≥1:8 and hSBA GMT directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination when administered to healthy children 2 through 5 years of age.
- To compare the immunogenicity of a single dose of MENVEO with the immunogenicity of a single dose of Menactra, defined as the percentage of subjects with seroresponse, hSBA titers ≥1:4 or ≥1:8 and hSBA GMT directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 2 through 10 years of age.
- To compare the immunogenicity of a single dose of MENVEO with the immunogenicity of a single dose of Menactra, defined as the percentage of subjects with hSBA titers ≥1:4 or ≥1:8 and hSBA GMT directed against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy subjects 2 through 5 years of age or 6 through 10 years of age.

Safety

To describe the safety profile of MENVEO and to compare the percentages of subjects the MENVEO and Menactra vaccine groups when administered to healthy children 2 through 10 years of age in terms of:

- Immediate hypersensitivity reactions (within 30 minutes) following vaccination
- Local and systemic reactions during days 1 through 7 after vaccination

- Adverse events (AEs) during the time periods
- Medically significant AEs for the duration of the study
- Serious adverse events (SAEs) for the duration of the study

6.1.1.1.2 Design Overview

Study V59P20 was a randomized, controlled, observer-blind multicenter study conducted in the U.S. and Canada. Subjects were administered either MENVEO or Menactra intramuscularly (IM) by an unblinded study vaccine administrator. With the exception of the 2 dose MENVEO group, all subjects were blinded to the study vaccine given. Blood was drawn before vaccination at day 1 and after vaccination at day 29 (window:+ 14 days) and before vaccination at day 1 and after vaccination at day 89 (window + 14 days) for the 2 dose MENVEO group. The end of study, for subjects who completed all study visits, was study day 180 for subjects in the single dose MENVEO group and study day 240 for subjects in the 2 dose MENVEO group.

6.1.1.1.3 Population

Study Period

The study period was from March 13th, 2008 to October 14th, 2009

Study Sites and Recruitment

Study participants were recruited at 62 centers in the U.S. and Canada. A total of 2907 healthy children 2 through 10 years of age were randomly assigned to either MENVEO or Menactra. The randomization was stratified by age with the following targets per age strata: children 2 through 5 years of age (n = 1751), and children 6 through 10 years of age (n = 1156). In the 2 through 5 years of age group, subjects were to be randomized in a 1:2:2 ratio to receive either two doses of MENVEO, one dose of MENVEO, or one dose of Menactra (Group I, II, III). The subjects 6 through 10 years of age were to be randomized in a 1:1 ratio to receive a single dose of either MENVEO or Menactra (Group IV and V).

The following table summarizes the number of subjects enrolled; planned and analyzed verses actual.

Table 5: Enrolled and Actual Population

Vaccine Group	Subjects enrolled (planned) and actual	Subjects enrolled (planned) and actual 2-5 yo	6-10 yo
MENVEO 2-Doses	(340) 359	(340) 359	N/A
MENVEO	(1240) 1278	(680) 696	(560) 582
Menactra	(1240) 1270	(680) 696	(560) 574

*Source: 5.3.5.1 CSR V59P20 Study Synopsis Table 9.1-1 (CSR) and Table 11.1-1 (CSR)

Inclusion Criteria:

- Healthy male and female children 2 through 10 years of age
- Written assent and/or informed consent by parent or legal guardian provided
- Available for all visits and telephone calls scheduled for the study
- In good health as determined by medical history, physical assessment, and clinical judgment of the investigator
- Up to date with age appropriate routine childhood vaccination

Exclusion Criteria:

- Unwilling or unable to give written informed assent or consent
- 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);
- 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.
- 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.

Reason for delay of blood draws or subsequent vaccinations:

- Significant acute or chronic infections required systemic antibiotic treatment or antiviral therapy commenced within the past 7 days;
- Oral temperature of ≥ 38.0°C or presence of an acute systemic illness on the day of immunization;
- Use of systemic corticosteroids (oral, intramuscular or intravenous) administered for more than 5 days or in a daily dose >1 mg/kg/day prednisone or equivalent for ≤ 5 days delayed immunization for 15 days;
- Use of systemic corticosteroids (oral, intramuscular or intravenous) administered during the study in a daily dose <1 mg/kg/day prednisone or equivalent for ≤ 5 days delayed immunization for 7 days

Concomitant Vaccines or Therapy:

- No concomitant vaccines were to be administered during Visit 1 and Group 1 was not to receive other vaccinations between Visit 1 and Visit 3.
- Normal routine or catch-up licensed vaccines appropriate for age group could be administered up to 30 days prior to study immunization and no less than 30 days after the study immunization. Exception Inactivated influenza vaccine were:
    - permitted up to 15 days prior to or after study vaccination. Cold-adapted
    - influenza vaccine could be administered up to 30 days prior to or after study vaccination)
- Analgesics or antipyretics were not routinely administered, but their use within the first 7 days following immunization was recorded on the subjects case report forms.
- All over the counter or prescription medications were recorded on the case report forms

6.1.1.1.4 Products mandated by the protocol

The investigational Novartis MENVEO vaccine was obtained by mixing of the lyophilized Men A component with the liquid MenCYW-135 component just before injection. After reconstitution, the MENVEO vaccine had the following composition per 0.5 mL of injectable solution (Table 6):

Table 6: MENVEO Composition

Composition	Quantity per 0.5 mL dose
CRM_{197}-MenA conjugate	10 µg MenA ---(b)(4)-------- CRM_{197}
CRM_{197}-MenC conjugate	5 µg MenC ---(b)(4)------ -- CRM_{197}
CRM_{197}-MenW conjugate	5 µg MenW ---(b)(4)--------- CRM_{197}
CRM_{197}-MenY conjugate	5 µg MenY ---(b)(4)---------- CRM_{197}
-----(b)(4)---------	(b)(4)
--(b)(4)--	(b)(4)
-------(b)(4)----------	(b)(4)
-------(b)(4)----------	(b)(4)
(b)(4)	---(b)(4)------

Menactra

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

6.1.1.1.5 Study Endpoints

Safety Endpoints

Descriptive analysis of the proportion of study participants 2 through 10 years of age experiencing solicited or unsolicitied local and systemic adverse reactions (mild, moderate, severe or all), serious adverse events and/or all adverse events up to 7 days after each vaccination and/or adverse events requiring a medical office or ER visit and/or resulting in premature withdrawal from the study, per vaccination group were reported.

Immunogenicity Endpoints

Immune response to MENVEO and Menactra was measured in terms of bactericidal antibody as assessed by human complement mediated serum bactericidal activity (hSBA).

Primary:
hSBA antibody responses to MENVEO were considered non-inferior to hSBA antibody responses to Menactra if the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MENVEO minus Menactra) was greater than -10%. Novartis also evaluated hSBA responses for superiority for each individual serotype, but on careful review FDA did not find these

analyses to be contributory to the evaluation of effectiveness of MENVEO in this age group.

The success criteria for this study was based upon only this primary objective for the per protocol population. As pre-specified in the clinical protocol, this study was considered a success if, for both age strata, all four serogroup analyses met the non-inferiority criteria identified for the endpoint noted above.

Secondary:
hSBA antibody responses to MENVEO were considered non-inferior to hSBA antibody responses to Menactra, if the lower limit of the two-sided 95% CI around the difference of the percentage of subjects with hSBA ≥ 1:8 (or hSBA ≥ 1:4) for that serogroup (MENVEO minus Menactra) was greater than -10%.

hSBA GMT responses to MENVEO were considered non-inferior to hSBA GMT responses to Menactra, in the 2 through 10 years of age group or each age stratum separately, if the lower limit of the two-sided 95% confidence interval (CI) around the ratio of hSBA GMTs between MENVEO and Menactra, 1 month after vaccination, was greater than 0.5.

6.1.1.1.6 Surveillance/Monitoring

Blinded study personnel observed subjects for 30 minutes post-vaccination. Subjects' parents or legal guardians were given a diary card and instructed on reporting AEs for Visit 1 through Visit 2 except for Group 1 who completed their diary cards for Visit 1 through Visit 3. Subjects were contacted by phone on study day 3. During Visit 2 (study day 29), subjects of Groups II through V (single dose MENVEO group) had blood drawn for immunoassays and diary cards were collected and reviewed and subsequently a worksheet was provided for study day 30 to 180.

During Visit 3 (study day 61) only Group I subjects (2 dose MENVEO group) completed this visit. Their diary cards were collected and reviewed and subsequently another diary card was given for Visit 3 through 4. A physical assessment was performed, a single dose of MENVEO was given and subjects were monitored for 30 minutes post-vaccination. Group I subjects were contacted by phone on study day 63. During Visit 4 subjects of Group I had blood drawn for immunoassays and diary cards were collected and reviewed and subsequently a worksheet was provided for study day 90 to 240. At 6 months follow up (study day 179 +/- 28 days), study personnel contacted parents or legal guardians by phone to review and record any safety information on the worksheets.

Local and systemic solicited and unsolicited adverse events were recorded on a diary card by parents or legal guardians for study days 1 to 7. Solicited local reactions were local pain, erythema, induration and temperature. Solicited systemic adverse events for

participants 2 through 5 years of age were: change in eating habits, sleepiness, irritability, vomiting, diarrhea, arthlagia, headache and rash. Solicited systemic adverse events for participants 6 through 10 years of age were: chills, nausea, malaise, myalgia, arthlagia, headache and rash.

All adverse events necessitating a physician's visit +/or resulting in premature study withdrawal were monitored from study day 1 through 28 days after last vaccination.

Medically significant AEs that required a physician visit, Emergency Department visit or leading to a subject's withdrawal were monitored from study day 29 after last vaccination through study day 180 or study day 240 for subjects in the 2 dose MENVEO group (excluding pre-planned 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 during the entire duration of the study through study termination or early termination, i.e. from study day 1 to 180 (or 240) until resolution +/or the cause is identified.

An independent, external Data Monitoring Committee was established to monitor safety by performing scheduled analyses.

6.1.1.1.7 Statistical considerations including plan for analysis

See study safety and immunogenicity endpoints above in section 6.1.1.1.5. Safety analyses were based on the safety population (defined below). Descriptive statistics were calculated for the baseline characteristics by vaccine group and for each age group.

Primary immunogenicity analyses were based on the per protocol immunogenicity population, (see definition below). The primary analysis of immunogenicity was a non-inferiority comparison of the percentage of subjects with seroresponse to *N. meningitidis* serogroups A, C, W and Y at 1 month after vaccination with MENVEO and Menactra.

In the protocol and statistical analysis plan, the non-inferiority hypothesis was stated as below:

H_0: ($P_{MenACWY} - P_{Menactra}$) ≤ -10% for serogroups A, C, W, or Y
H_A: ($P_{MenACWY} - P_{Menactra}$) > -10% for serogroups A, C, W, and Y

The success criterion for meeting the non-inferiority primary objective was: for all four serogroups, the lower limit of the two-sided 95% CI for the difference in the percentages of subjects with seroresponse should be greater than -10%.

Definition of population to be analyzed:

Randomized Population:
Contained all subjects enrolled and randomized in the study. This population was used for analysis of demographics and all subject listings.

Exposed population:
Subjects who actually received a study vaccination were included in the exposed population. 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.

Modified Intention-to-treat (MITT) population, Immunogenicity:
All subjects in the ITT who actually received a study vaccination and provided an evaluable serum sample both before and after vaccination. Subjects were included in the vaccine group they were assigned during randomization. The size of the ITT 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 and secondary immunogenicity objectives. Major deviations were 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).

6.1.1.2 Results

6.1.1.2.1 Populations enrolled/analyzed

A total of 2907 subjects were enrolled and randomized to receive either 2 doses of MENVEO, a single dose of MENVEO, or a single dose of Menactra. This resulted in 2898 healthy 2 to 10 years old children who were exposed to the vaccine. 356 subjects were administered 2 doses of MENVEO, 1279 received a single dose of MENVEO, and 1263 received a single dose of Menactra. Overall, 9 subjects were not vaccinated (7 due to withdrawal of consent, 1 due to inappropriate enrollment, and 1 unable to classify). These subjects were excluded from the safety analysis. In the 2 to 5 years of

age group, subjects were to be randomized in a 1:2:2 ratio to receive either two doses of MENVEO, one dose of MENVEO, or one dose of Menactra. The subjects 6 to 10 years of age were to be randomized in a 1:1 ratio to receive a single dose of either MENVEO or Menactra. Review of demographic information suggests that adequate randomization occurred. A total of 105 subjects withdrew prematurely from the study, 279 had major protocol deviation and excluded from the immunogenicity analysis but analyzed for safety, hence the per protocol population consisted of 2698 subjects while 2802 completed the protocol.

Protocol deviations were similar between the MENVEO and Menactra group but major protocol deviations were higher in the 2 dose MENVEO group than the single dose MENVEO group. Two through 5 year olds also reported more major protocol deviations than 6 to 10 year olds. Most common deviation among the major protocol deviations were: 136 subjects had no post-vaccination blood draw, 60 subjects had no pre-vaccination blood draw and 37 subjects had post-vaccination blood draw that was out of the per-protocol window. Other protocol deviations included 20 subjects were enrolled and did not satisfy the entry criteria, 20 received the wrong vaccine or an incorrect dose, 12 received an exclusionary concomitant treatment or vaccine and 28 were categorized as miscellaneous. One subject was not vaccinated because of an entry criteria violation and 1 developed withdrawal criteria (received meningococcal C vaccine prior to study) without being withdrawn from the study.

Table 7: Summary of Major Protocol Deviations

Major Protocol Deviations	MENVEOx2	MENVEO 2-5 yo	Menactra 2-5 yo	MENVEO 6-10 yo	Menactra 6-10 yo	MENVEO 2-10 yo	Menactra 2-10 yo
Selected	359	696	696	582	574	1278	1270
No pre-vaccination blood draw	6	27	23	2	2	29	25
No post-vaccination blood draw	39	35	35	9	13	44	49
Post-vaccination blood draw out of the window	7	9	11	4	6	13	17
Did not meet entry criteria	3	3	5	5	4	8	9
Incorrect vaccine or wrong dose given	5	6	7	0	2	4	9
Received excluded concomitant vaccine	5	2	4	1	0	3	4
Miscellaneous	4	7	3	7	7	14	10

Source: 5.3.5.1 CSR V59P20 Table 14.1.1.8

6.1.1.2.2 Safety outcomes

The primary safety objective was to provide a descriptive analysis of the proportion of study participants 2 through 10 years of age, in the MENVEO and Menactra vaccine groups experiencing solicited or unsolicitied local and systemic adverse reactions (mild, moderate, severe or all), serious adverse events and/or all adverse events up to 7 days after each vaccination and/or adverse events requiring a medical office or ER visit and/or resulting in premature withdrawal from the study, per vaccination group.

Immediate Reactions

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

Solicited Local and Systemic Reactions

The percentages of subjects reporting solicited AEs (local and/or systemic reactions during first 7 days post-vaccination) were similar in the MENVEO and Menactra groups (55% vs. 56%, respectively) There was no difference in the percentages reporting any local reactions (49% in both vaccine groups). Additionally there were no differences in the percentages reporting use of analgesics/antipyretic medication and staying at home due to vaccination (12% in both vaccine groups).

Local AEs in participants 2 through 5 years of age:
No significant difference was observed between the vaccine groups for the number that had pain, erythema or induration. However, 5 subjects in the MENVEO group reported erythema >100mm vs 1 subject in the Menactra group. Severe local reactions were also similar in the MENVEO group compared with the Menactra group. For both vaccines, almost all solicited local AEs were experienced during the first 3 days immediately post-vaccination and were self-limiting. During days 1-3, no statistically significant difference was observed between the two vaccine groups for pain, erythema or induration. During days 4-7, no significant difference between the two vaccine groups was observed for pain, erythema and induration (pain: 3% vs. 4%; erythema: 8% vs. 6%, induration: 5% vs. 5%.

Local AEs in participants 6 through 10 years of age:
In the 6 to 10 year age group population, significantly fewer subjects reported pain in the MENVEO group compared with Menactra (39% vs. 45%). More erythema was reported in the MENVEO group compared with Menactra group (28% vs. 22%). No significant difference was observed between the MENVEO group compared with the Menactra group for induration (17% vs. 13%) Severe local reactions were similar in the MENVEO group compared with Menactra, pain (1% vs. 2%), erythema (1% vs. <1%) and induration (<1% vs. 0).

During days 1-3, lower percentages of pain were reported in the MENVEO group than in the Menactra group (38% vs. 44%), however higher percentage of MENVEO subjects reported erythema than Menactra subjects (27% vs 22%). There was no significant difference between the two vaccine groups for induration. During days 4 to 7, no significant difference between the two vaccine groups was observed for pain and induration (pain: 5% vs.5%; induration: 5% vs. 4%. Erythema during days 4 to 7 remained significantly higher in the MENVEO group as compared to Menactra (9% vs. 4%).

Local AEs after 2 doses vs 1 dose of MENVEO in participants 2 through 5 years of age:
The percentage of subjects reporting local reactions after any vaccination were more in the MENVEO 2-dose group vs. MENVEO single dose group (43% and 33%, respectively). However the percentages of subjects reporting local reactions after 1st vaccination and 2nd vaccination in the MENVEO 2 dose group were similar (32% and 28%, respectively). Severe local reactions were similar in both groups.

Systemic AEs in participants 2 through 5 years of age:
The percentages of subjects reporting solicited systemic AEs were similar in the MENVEO and Menactra groups. The most commonly reported selected systemic reactions in both the MENVEO and Menactra groups were irritability (21% and 22%, respectively) and sleepiness (16% and 18%, respectively). The percentages of subjects reporting any severe systemic reactions were similar between the two vaccine groups. Severe irritability and sleepiness were reported by 1% in both the groups. The majority of cases of irritability lasted four days or less; three subjects in the MENVEO group (35/0007, 37/0002, and 39/0012) and four subjects in the Menactra group (29/0032, 30/0014, 32/0007, and 37/0019) reported irritability which lasted from 5 to 7 days. The majority of cases of sleepiness lasted five days or less; three subjects in the MENVEO group (32/0055, 39/0012, and 39/0048) and three subjects in the Menactra group (37/0019, 39/0015, and 46/0001) reported sleepiness which lasted from six to seven days. The percentages of subjects reporting any other reaction (analgesic/antipyretic medication used and stayed at home due to vaccination) were similar between the two vaccine groups.

Systemic AEs in participants 6 through 10 years of age:
The percentages of subjects reporting solicited systemic AEs were similar in the MENVEO and Menactra groups. The most commonly reported solicited systemic reaction, headache, was more frequently reported in the MENVEO group than the Menactra group (18% vs 13%). Other common systemic reactions were malaise (14% and 11%, respectively), and myalgia (10% in both vaccine groups) The percentages of subjects reporting any severe systemic reaction were similar between the two vaccine groups. Severe headache, severe myalgia and severe malaise, all were reported by 1% in both vaccine groups. All cases of severe headache lasted three days or less. The majority of cases of severe myalgia lasted three days or less; two subjects in the MENVEO group (01/3025 and 09/3001) and three subjects in the Menactra group

(32/3028, 33/3057, and 37/3005) reported severe myalgia which lasted from four to seven days. The majority of cases of severe malaise lasted four days or less; one subject in the MENVEO group (01/3025) and one subject in the Menactra group (07/3046) reported severe malaise which lasted six and five days, respectively. The percentages of subjects reporting any other reaction (analgesic/antipyretic medication used and stayed at home due to vaccination) were similar between the two vaccine groups.

In both vaccine groups, most solicited systemic reactions were reported in the 3 days immediately following vaccination. Both in the MENVEO and Menactra groups, the most commonly reported systemic reactions across the three time periods (days 1 to 3, 4 to 7, and 1 to 7) were headache, malaise, and myalgia. The percentages of subjects reporting each of the selected systemic reactions, as well as the percentages of subjects reporting other indicators of reactogenicity, were statistically similar among all three time periods when compared between the two vaccine groups, except for headache and malaise, which was slightly more frequent in the MENVEO group during days 1 to 3 (15% vs. 11% and 11% vs. 8%, respectively) and days 1 to 7 (18% vs. 13% and 14% vs. 11%, respectively).

Solicited systemic reactions in the 2 dose vs 1 dose MENVEO groups:
In both vaccine groups, most solicited systemic reactions were reported in the 3 days immediately following vaccination. In both the groups, the most commonly reported solicited systemic reactions across the three time periods (study day 1-3, 4-7 and 1-7) were irritability, sleepiness and change in eating habits. The percentages of subjects reporting each of the selected systemic reactions, as well as the percentages of subjects reporting other indicators of reactogenicity, were higher among all three time periods in the MENVEO 2-dose group. However, the percentages of subjects reporting each of the selected systemic reactions, as well other indicators of reactogenicity were similar when compared after the first dose and second dose in the MENVEO 2-dose group and, when compared after dose 1 for the 1-dose and 2-dose groups. Seventeen subjects in the 2 dose MENVEO group did not have safety reported for the second dose. The observations of similar or less reactogenicity following the second dose were also seen when only those participants that received both doses were compared.

Unsolicited Adverse Events, Including Serious Adverse Events

The percentage of subjects experiencing any unsolicited AE between day 1 and day 29 were similar between the MENVEO and Menactra groups [19%(248/1275) and 18%(226/1255)], respectively). The percentages of subjects reporting unsolicited AEs designated by study investigators as at least possibly related were identical in the two vaccine groups (5% of each group; i.e 60 and 62 for MENVEO and Menactra, respectively). All possibly or probably related unsolicited AEs were reported within 29 days of vaccination except for 2 subjects in infections and infestations (one in each

group) and one in nervous system disorders (Menactra group). Review of all unsolicited AEs did not identify any concerns for causality.

The most commonly experienced possibly or probably related unsolicited AEs were injection site erythema (reported by 5 MENVEO and 7 Menactra subjects) and injection site hematoma (6 and 3 subjects, respectively) The other most commonly reported possibly or probably related unsolicited AEs reported were injection site pruritus (3 and 7 subjects, respectively), cough (2 and 6 subjects, respectively), and headache, reported by 5 subjects in the MENVEO group and 1 subject in the Menactra group.

No deaths or AEs leading to withdrawal occurred during this study. A total of 17 subjects reported 26 SAEs. Two SAEs were reported (27/0006, 44/0011) in the MENVEO 2-dose group, eight subjects (22/0003, 25/0030, 26/3072, 29/3028, 30/3006, 33/0029, 33/0041, and 33/0073) in the MENVEO one dose group, and seven subjects (20/0002, 25/3035, 26/0085, 34/0009, 34/0035, 34/3005, and 56/0013) in the Menactra group. None of the SAEs were designated by study investigators as related, and review of the narrative descriptions for these SAEs did not raise concerns for causality. Most of the serious adverse events started later than 6 weeks after the vaccination with the exception of 4 cases, streptococcal infection, bronchopneumonia, dehydration and a case of worsening of the inguinal hernia. The majority of SAEs lasted for six days or less and resolved completely. Exceptions where the duration of SAEs exceeded six days were as follows: one subject with pneumonia in the 2 through 5 year old Menactra group whose SAE lasted 23 days; one subject with shigella infection in the 6-10 year old MENVEO group whose condition lasted 25 days; one subject with pneumonia in the 2 through 5 year old MENVEO group whose condition lasted 8 days; one subject in the 2 through 5 year old MENVEO 2-dose group whose condition lasted 9 days; and one subject with bacterial arthritis in the 2 through 5 year old Menactra group whose condition lasted 23 days. Two events (parvovirus infection in a MENVEO 2 dose-subject and psychiatric symptoms in a 6-10 year old Menactra subject) were still persisting at the end of the trial.

Table 8: Listing of subjects with SAEs by treatment group

Subject No.	Age	Preferred Term	Onset (Study Day)	Duration (days)	Outcome	Hospital-ization	Relatedness
MenACWY 2-doses							
27/0006	5	Parvovirus Infection	176	-	AE Persist	Yes	None
		Intestinal Obstruction	200	6	Recovered	Yes	None
46/0011	4	Bronchopneumonia	80 (16 post inj #2)	9	Recovered	Yes	None
MenACWY							
22/0003	4	Bronchial hyperreactivity	61	3	Recovered	Yes	None
25/0030	2	Pneumonia	159	3	Recovered	Yes	None
26/3072	7	Adrenal Haematoma	87	4	Recovered	Yes	None
		Loss Of Consciousness	87	<1	Recovered	Yes	None
		Pneumothorax	87	4	Recovered	Yes	None
		Rib Fracture	87	4	Recovered	Yes	None
		Skin Laceration	87	4	Recovered	Yes	None
		Traumatic Liver Injury	87	4	Recovered	Yes	None
		Traumatic Lung Injury	87	4	Recovered	Yes	None
29/3028	10	Shigella Infection	63	25	Recovered	Yes	None
30/3006	6	Staphylococcal Infection	22	5	Recovered	Yes	None
33/0029	2	Peritonsillar Abscess	53	2	Recovered	Yes	None
33/0041	4	Dehydration	94	2	Recovered	Yes	None
		Pneumonia	94	8	Recovered	Yes	None
33/0073	3	Dehydration	7	1	Recovered	Yes	None
Menactra							
20/0002	5	Pneumonia	101	23	Recovered	Yes	None
25/3035	9	Mouth Cyst	177	<1	Recovered	Yes	None
26/0085	5	Excoriation	167	4	Recovered	Yes	None
34/0009	3	Arthritis Bacterial	105	23	Recovered	Yes	None
		Pyrexia	126	2	Recovered	Yes	None
34/0035	3	Inguinal Hernia	20	4	Recovered	Yes	None
34/3005	9	Psychiatric Symptom	156	-	AE Persist	Yes	None
56/0013	2	Viral Infection	55	4	Recovered	Yes	None

Source: Table 12.3.1.2-1 V59P20-report

Unsolicited AEs by System Organ Class (MENVEO 2-dose group vs. MENVEO single-dose group):
The percentage of subjects experiencing any unsolicited AE was higher in the MENVEO 2-dose group (43%(151/351)) than in the MENVEO single dose group (30%(210/693)).The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was “infections and infestations” (22% and 13% MENVEO 2-dose group and MENVEO single dose group, respectively).Similar number of subjects reported possibly or probably related unsolicited AEs considered possibly or probably related by the study investigator (6% and 5% in MENVEO 2-dose group and MENVEO single dose group, respectively). All possibly or probably related unsolicited AEs were reported within 29 days of vaccination.

6.1.1.2.3 Effectiveness outcomes

A total of 2907 subjects were enrolled and randomized while 2898 subjects were vaccinated to receive MENVEO 2-dose (356), Menactra (1263) or MENVEO (1279). The overall PP populations consisted of 2628 subjects (297 in the MENVEO 2-dose group, 1170 in the MENVEO 1-dose group and 1161 in the Menactra group). Demographic and other baseline characteristics of the overall randomized population (2 to10 years of age) were similar in the MENVEO 2-dose, and the MENVEO and Menactra one-dose groups. Twenty-one subjects received the wrong vaccine and were excluded from the immunogenicity analyses.

Primary Objective:
The primary objective of this study was to demonstrate that the hSBA seroresponses to MENVEO were non-inferior to the hSBA seroresponses to Menactra.when administered to healthy children 2 through 5 years of age and 6 through 10 years of age. Non-inferiority was demonstrated if, for all four serogroups, the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MENVEO minus Menactra) was greater than -10%, i.e., if the CI for the difference is entirely to the right of -10%.

In the 2 through 5 years of age group, the noninferiority criterion was met for serogroups C, W-135 and Y, but not for serogroup A. The percentages of seroresponders at 1 month postvaccination were numerically higher in the MENVEO group than in the Menactra group for serogroups C (60% vs. 56% for MENVEO and Menactra, respectively), W-135 (72% vs. 58%), and Y (66% vs. 45%), but lower for serogroup A (72% vs. 77%). See Table 9 below.

In the 6 through 10 years of age group, the non-inferiority criterion was met for serogroups C, W and Y, but not for serogroup A. The percentages of seroresponders were numerically higher in the MENVEO group than in the Menactra group for serogroups C (63% vs. 57%), W-135 (57% vs. 44%), and Y (58% vs. 39%), but lower for serogroup A (77% vs. 83%). See Table 9 below:

Table 9. hSBA response at 1 month postvaccination by age group and by vaccine, PP population

	2 through 5 years			6 through 10 years		
Endpoint by Serogroup	**MENVEO (95% CI)**	**Menactra (95%CI)**	**% difference (MENVEO – Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**	**MENVEO (95%CI)**	**Menactra (95%CI)**	**% difference (MENVEO - Menactra) or GMT ratio (MENVEO/ Menactra) (95%CI)**
A	**N=606**	**N=611**		**N=551**	**N=541**	
% Seroresponse[α]	72 (68, 75)	77 (73, 80)	-5 (-10, -0)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
% ≥ 1:8	72 (68, 75)	78 (74, 81)	-6 (-11, -1)	77 (74, 81)	83 (80, 86)	-6 (-11, -1)
GMT	26 (22, 30)	25 (21, 29)	1.04 (0.86, 1.27)	35 (29, 42)	35 (29, 41)	1.01 (0.83, 1.24)
C	**N=607**	**N=615**		**N=554**	**N=539**	
% Seroresponse[α]	60 (56, 64)	56 (52, 60)	4[μ] (-2, 9)	63 (59, 67)	57 (53, 62)	6[μ] (0, 11)
% ≥ 1:8	68 (64, 72)	64 (60, 68)	4 (-1, 10)	77 (73, 80)	74 (70, 77)	3 (-2, 8)
GMT	18 (15, 20)	13 (11, 15)	1.33 (1.11, 1.6)	36 (29, 45)	27 (21, 33)	1.36 (1.06, 1.73)
W-135	**N=593**	**N=605**		**N=542**	**N=533**	
% Seroresponse[α]	72 (68, 75)	58 (54, 62)	14[μ] (9, 19)	57 (53, 61)	44 (40, 49)	13[μ] (7, 18)
% ≥ 1:8	90 (87, 92)	75 (71, 78)	15 (11, 19)	91 (88, 93)	84 (81, 87)	7 (3, 11)
GMT	43 (38, 50)	21 (19, 25)	2.02 (1.71, 2.39)	61 (52, 72)	35 (30, 42)	1.72 (1.44, 2.06)
Y	**N=593**	**N=600**		**N=545**	**N=539**	
% Seroresponse[α]	66 (62, 70)	45 (41, 49)	21[μ] (16, 27)	58 (54, 62)	39 (35, 44)	19[μ] (13, 24)
% ≥ 1:8	76 (72, 79)	57 (53, 61)	19 (14, 24)	79 (76, 83)	63 (59, 67)	16 (11, 21)
GMT	24 (20, 28)	10 (8.68, 12)	2.36 (1.95, 2.85)	34 (28, 41)	14 (12, 17)	2.41 (1.95, 2.97)

Source: Table 11.4.1.1-1 V59P20 report

δ Serum bacterial assay with exogenous human complement source (hSBA)

α Seroresponse defined as: in subjects with pre-vaccination hSBA titer <1:4, a post-vaccination titer of ≥ 1:8; in subjects with pre-vaccination hSBA titer ≥ 1:4, a post-vaccination titer at least 4-fold higher than baseline.

μ Non-inferiority criterion for the primary endpoint met (the lower limit of the two sided 95%CI > -10% for vaccine group differences [MENVEO minus Menactra])

Secondary Objectives:

1. To assess the immunogenicity of two doses of MenACWY, administered 2 months apart, and compare it to the immunogenicity of a single dose of MenACWY, defined as percentage of subjects with seroresponse, hSBA ≥ 1:4, hSBA ≥ 1:8 and hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 5 years of age.

2. 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, hSBA ≥ 1:8 and hSBA GMTs directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 2 to 10 years of age
3. 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 hSBA ≥ 1:4, hSBA ≥ 1:8, and hSBA GMT response directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 2 to 5 years of age or 6 to 10 years of age

Two doses v/s single dose:

In the 2 through 5 year age group, the percentages of seroresponders were higher in the MENVEO 2-dose group (43%) than in the MENVEO single dose group (30%) for all four serogroups. The percentages of subjects with baseline hSBA ≥ 1:8 at day 1 were similar between the two vaccine groups. At one month post-vaccination, the percentages of subjects with hSBA ≥ 1:8 showed a large increase for all four serogroups in both vaccine groups but were higher in the MENVEO 2-dose group. Similar results were observed for the percentage of subjects with hSBA ≥ 1:4. Baseline GMTs at day 1 were similar between the two vaccine groups. At day 29 post 1 or 2 doses, the GMTs showed a large increase for all four serogroups in both vaccine groups but were higher in the MENVEO 2-dose group (Table 10).

Table 10: V59P20 Immunogenicity of 2 doses vs 1 dose: Day 1 and at One Month Post-Vaccination in participants 2 through 5 years of age, PP population

	hSBA Titer ≥ 1:8		Seroresponse		GMTs	
Day 1	**MENVEO 2 Doses**	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**	**MENVEO 2 Doses**	**MENVEO 1 Dose**
A[a]	1% (0, 3)	1% (1, 3)	NA	NA	2.1 (2.02, 2.18)	2.1 (2.04, 2.16)
C[b]	9% (6, 13)	10% (8, 13)	NA	NA	2.92 (2.65, 3.23)	3.05 (2.83, 3.29)
W[c]	21% (17, 26)	24% (21, 28)	NA	NA	4.07 (3.42, 4.84)	4.38 (3.84, 5.01)
Y[d]	9% (6, 13)	14% (11, 17)	NA	NA	2.75 (2.44, 3.09)	3 (2.74 3.28)
Day 29						
A[a]	91% (88, 94)	72% (68, 75)	91% (87, 94)	72% (68, 75)	64 (51, 81)	27 (23, 32)
C[b]	99% (97, 100)	68% (64, 72)	98% (95, 99)	60% (56, 64)	144 (118, 177)	18 (15, 21)
W[c]	99% (98, 100)	90% (87, 92)	89% (85, 92)	72% (68, 75)	132 (111, 157)	41 (36, 47)
Y[d]	98% (95, 99)	76% (72, 79)	95% (91, 97)	66% (62, 70)	102 (82, 126)	23 (20, 27)

Source: section 5.3.5.1.1. Study V59P20 Table 11.4.1.2-6

Immunogenicity of a single dose of MENVEO vs Menactra in 2 through 10 years of age:
MENVEO met non-inferiority criteria in comparisons to Menactra for all four serogroups. See Table 11 below.

Table 11: Percentage of subjects with hSBA seroresponse at 1 month following a single vaccination (95% CI) in subjects 2 through 10 years of age, PP population

		Seroresponse		
		MENVEO (1170)	**Menactra (1161)**	**MenACWY - Menactra**
Serogroup A	Baseline hSBA < 4	835 (74%) (71, 77) N=1126	899 (80%) (78, 82) N=1122	-6% (-9, -3)
	Baseline hSBA ≥ 4	21 (68%) (49, 83) N=31	17 (57%) (37, 75) N=30	11% (-13, 34)
	Overall	856 (74%) (71, 76) **N=1157**	916 (80%) (77, 82) **N=1152**	-6% (-9, -2)
Serogroup C	Baseline hSBA < 4	537 (64%) (61, 67) N=838	503 (60%) (57, 63) N=837	4% (-1, 9)
	Baseline hSBA ≥ 4	175 (54%) (49, 60) N=323	152 (48%) (42, 54) N=317	6% (-2, 14)
	Overall	712 (61%) (58, 64) **N=1161**	655 (57%) (54, 60) **N=1154**	5% (1, 9)
Serogroup W-135	Baseline hSBA < 4	622 (86%) (83, 88) N=727	531 (70%) (66, 73) N=763	16% (12, 20)
	Baseline hSBA ≥ 4	112 (27%) (23, 32) N=409	54 (14%) (11, 18) N=375	13% (7, 19)
	Overall	734 (65%) (62, 67) **N=1136**	585 (51%) (48, 54) **N=1138**	13% (9, 17)
Serogroup Y	Baseline hSBA < 4	593 (71%) (68, 74) N=836	415 (49%) (46, 53) N=843	22% (17, 26)
	Baseline hSBA ≥ 4	117 (39%) (33, 44) N=302	68 (23%) (18, 28) N=296	16% (9, 23)
	Overall	710 (62%) (60, 65) **N=1138**	483 (42%) (40, 45) **N=1139**	20% (16, 24)

Source: adapted from table 11.4.1.1-1 p. 63 V59P20 report

hSBA ≥ 1:8 Results:
The percentages of subjects in the 2 through 10 age group with a baseline hSBA ≥1:8 at day 1 were similar between the two vaccine groups, however lower for serogroup A (2%) compared to other serogroups (16-35%). At day 29, the percentages of subjects with hSBA ≥1:8 increased for all four serogroups for both MENVEO and Menactra, respectively; (A: 75%(72-77) vs. 80%(78-83), C: 72%(70-75) vs. 68%(66-71), W-135: 90%(88-72) vs. 79%(77-81), and Y: 77%(75-80) vs. 60%(57-63). The lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse (MENVEO minus Menactra) for all 4 serogroups was greater than -10% (-6 to 18%).

hSBA GMTs Results:
For subjects 2 through 10 years of age, pre-vaccination GMTs were similar between the two vaccine arms (2.1 to 5.2). At day 29, the GMTs (95% CI) increased for all four serogroups for both MENVEO and Menactra vaccine groups, respectively; (A: 30(27, 34) vs. 29(26, 33); C: 23(21, 27) vs. 17(15, 20); W-135: 49(44, 59) vs. 26(23, 29); Y: 29(25, 32) vs. 12(11, 14). The two-sided 95% CI around the ratio of hSBA GMTs between MENVEO and Menactra 1 month after vaccination was greater than 0.5 (0.89 to 2.73).

6.1.1.3 Comments & Conclusions

Study Design and Population

Study V59P20 was a randomized, controlled, observer blind multicenter study conducted in the U.S. and Canada. All subjects were blinded to the study vaccine given except for the 2-dose MENVEO group. It is unlikely that unblinding of subjects in the 2-dose group affected the overall study conclusions because study personnel involved in assessing safety were blinded to the study group for the MENVEO and Menactra single dose groups. The solicited local and systemic reactions observed following the second dose do not suggest increased reactogenicity compared to the first dose.

Safety Conclusions

Rates of solicited and unsolicited adverse events were similar between MENVEO and Menactra recipients within each age strata and for both age groups combined. In 2 through 5 year old subjects there were no significant differences in solicited local reactions for pain, erythema and induration. However in 6 through 10 year old subjects MENVEO subjects had significantly less pain but more erythema than the Menactra subjects. Additionally percentages of subjects with solicited systemic reactions were similar for both vaccine groups. In the 2 through 5 year old subjects the most common solicited systemic reaction was irritability, followed by sleepiness and change in eating habits. In 6 through 10 year old subjects, headaches and malaise occurred more frequently in the MENVEO group than the Menactra group.

Unsolicited adverse events were similar for both vaccine groups with the most common SOC being infection and infestations. Of 125 unsolicited AEs were reported as possibly or probably related, all but 2 occurred within 29 days with the most common AEs being injection site erythema observed in 7 Menactra subjects.

There were seventeen total SAEs but the rate of reported SAEs were low and review of all SAEs did not raise concerns for causality. No deaths occurred. Overall, MENVEO appeared to have a similar safety profile to Menactra in children 2 through 10 years of age. There was no clinically meaningful negative impact observed in the short-term

safety profile when a second dose of MENVEO was administered to children 2 through 5 years of age two months after the first dose.

Effectiveness Conclusions

1. The seroresponse to MENVEO was shown to be non-inferior to that of Menactra for C,W-135 and Y serogroups both in the 2 through 5 year and the 6 through 10 year age stratifications [i.e., the lower limit of the two-sided 95% CI around the difference in the percentages of seroresponders (MENVEO minus Menactra) was greater than -10%].
2. MENVEO did not meet the non-inferiority criterion for the comparison with Menactra for serogroup A for either the 2 through 5 year or the 6 through10 year age groups.

The primary endpoint of noninferiority for seroresponse was therefore not met.

Among the secondary endpoints;

1. In the comparison of one dose of MENVEO vs. one dose of Menactra in 2 through 10 year old subjects, the proportion of subjects with seroresponse and with a post vaccination hSBA ≥ 1:8 was non-inferior for all four serogroups.
2. For subjects 2 through 10 years, the GMTs following one dose of MENVEO were non-inferior to Menactra for all four serogroups.
3. In the 2 through 5 year and in the 6 through 10 year age groups, the percentage of subjects with an hSBA ≥ 1:8 was non inferior for serogroups C, W-135 and Y.
4. In both the 2 through 5 year and 6 through 10 year age groups, the GMTs following one dose of MENVEO were non-inferior to those following one dose of Menactra for all four serogroups.
5. Among subjects 2 through 5 years of age, for all endpoints tested (percentage of subjects with seroresponse, hSBA ≥ 1:8, and hSBA GMTs), subjects who received two doses of MENVEO had significantly higher immune response than subjects who received one dose of MENVEO.

Overall, the immunogenicity data from the pivotal study indicate that MENVEO is immunogenic and stimulates functional antibody responses in children 2 through 10 years of age. The non-inferiority end-point was narrowly missed for serogroup A in each age strata. The seroresponse rates for serogroup A are statistically lower (CI did not include 0) for each age group, but the observed differences in seroresponse rates between the two vaccines is considered unlikely to represent a clinically meaningful difference. In addition, non-inferiority was demonstrated for the secondary analysis of the combined age group (i.e., subjects 2 through 10 years of age) for all 4 serogroups. Statistically higher seroresponse rates were observed for serogroups W-135 and Y for each age strata. The immune responses, taken as a whole, support that the immunogenicity of MENVEO is similar to that of the currently licensed quadrivalent

vaccine Menactra. The comparator vaccine is indicated for use in the 2 through 10 year age group as a single dose vaccine. This study contained immunogenicity data that showed an immunologic benefit to receipt of a second dose in the 2 through 5 year old age group.

6.2 Indication #1

6.2.1 Trial #2

6.2.1.1 Protocol # and Title:

Study V59P8:
A phase 2, randomized, single-blind, controlled, single-center study to compare the safety and immunogenicity of one dose of Novartis Meningococcal ACWY Conjugate Vaccine (MENVEO conjugate vaccine) with one dose of already licensed Meningococcal ACWY polysaccharide vaccine (Menomune) administered to healthy children 2 through10 years of age and an open-label study to assess the safety and immunogenicity of one dose of MENVEO conjugate vaccine administered to healthy toddlers 12 through 23 months of age.

6.2.1.1.1 Objective/Rationale:

To compare the safety and immunogenicity of one dose of MENVEO with one dose of Menomune in healthy 2 through 10 year old children and healthy 12 through 23 months old toddlers.

Immunogenicity Objective

Primary Objective:

- To demonstrate that the hSBA seroresponses (i.e. ≧ 1:4) to a single dose of MENVEO were non-inferior to the hSBA seroresponses to a single dose of Menomune when administered to healthy children 2 through 10 years of age. Non-inferiority was demonstrated if, for all four serogroups, the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MENVEO minus Menactra) was greater than -10%, i.e., if the CI for the difference is entirely to the right of -10%, then non-inferiority was declared for that serogroup.

Secondary Objective:

1. To evaluate the hSBA geometric mean titer (GMT) antibody response after a single dose of MENVEO compared to after a single dose of Menomune when administered to healthy children 2 through 10 years of age.
2. To evaluate the difference of the percentage of subjects with hSBA ≥ 1:4 or hSBA GMT antibody response after a single dose of MENVEO compared to

Menomune when administered to healthy children 2 through 5 years of age and 6 through 10 years of age.
3. To evaluate the difference of the percentage of subjects with hSBA ≥ 1:4 or hSBA GMT antibody response after a single dose of MENVEO compared to after a single dose of Menomune at 1 month and at 12 months after vaccination, when administered to healthy toddlers 12 through 23 months of age (who received MENVEO) and healthy children 3 through 5 years of age (who received Menomune).
4. To evaluate the difference of the percentage of subjects with hSBA ≥ 1:4 or hSBA GMT antibody response after a single dose of MENVEO compared to after a single dose of Menomune at 12 months after vaccination, when administered to healthy children 2 through 10 years of age, overall and within 2 through 5 years of age and 6 through 10 years of age.

Safety Objectives

1. To assess the safety and tolerability of a single dose of MENVEO vaccine compared to the safety and tolerability of a single dose of Menomune when administered to healthy children 2 through 10 years of age.
2. To assess the safety and tolerability of a single dose of MENVEO vaccine when administered alone or concomitant with PnC to healthy toddlers 12 through 15 months of age and when administered alone or concomitant with DTaP to healthy toddlers 16 through 23 months of age.

Reviewers note: The age group 12 through 23 months was not within the indicated age group (2 through 10 years old), hence their data will not be considered in this clinical review.

6.2.1.1.2 Design/Overview:

Phase 2, single-center study divided in two parts:

1. Randomized, single-blind, and controlled to evaluate the safety and immune response at 1 and 12 months following vaccination with one dose of either MENVEO or Menomune in healthy children 2 through 10 years of age
2. Open label with and without concomitant Pneumococcal conjugate (PnC) vaccine (for toddlers12 through 15 months of age), or with and without concomitant DTaP (for toddlers 16 through 23 months of age) to evaluate the safety and immune response at 1 and 12 months following vaccination with one dose of MENVEO in healthy toddlers 12 through 23 months of age.

Table 12: Planned Enrollment Part 1:

Vaccine Age	MENVEO (n=350)	Menomune (n=350)
2 through 5 years of age	175	175
6 through 10 years of age	175	175

Part 2:
Included 12 through 23 months old infants, hence not reviewed here.

6.2.1.1.3 Population

Planned enrollment was for 700 healthy children 2 through 10 years of age. Of the 619 children randomized, 618 subjects were treated.

Study Period

14 April 2005 to 03 November 2006

Study Site

Kaiser Permanente Vaccine Study Center, Oakland, CA 94612

Inclusion Criteria (healthy children 2 through 10 years):
Individuals eligible for enrollment in this study were male and female children, who were:

1. 2 through 10 years of age inclusive (and who gave written assent, if applicable) whose parent or legal guardian gave written informed consent at the time of enrollment;
2. Available for all visits and telephone calls scheduled for the study;
3. In good health as determined by:
   - medical history;
   - physical assessment;
   - clinical judgment of the investigator.

Exclusion Criteria (healthy children 2 through 10 years):
Criteria for individuals not eligible to be enrolled in the study were similar as stated above in the pivotal study V59P20 in section 6.1.1.1.3 Population.

6.2.1.1.4 Products Mandated by the Protocol

The investigational Novartis MENVEO vaccine was obtained by mixing of the lyophilized Men A component with the liquid MenCYW-135 component just before injection. The vaccine was to be prepared just prior to administration to the study subject as a single dose injection, IM (left deltoid).

Menomune was supplied as a single dose (one vial of vaccine and one vial of diluent) and administered SQ. The vaccine consists of four meningococcal capsular polysaccharide serogroups (A, C, W-135, and Y).

6.2.1.1.5 Study Endpoints

Safety Endpoints

Descriptive analysis of reactogenicity, and adverse events reported throughout the study period including local, systemic, or other reactions and all other adverse events collected during the first 7 days after the injection, including the day of vaccination, and serious adverse events (SAE) and/or adverse events necessitating a physician's visit and/or resulting in subject's premature withdrawal from the study were collected throughout the study.

Immunogenicity Endpoints

The primary immunogenicity objective was to demonstrate that the hSBA seroresponses to MENVEO were non-inferior to the hSBA seroresponses to Menomune based on the proportion of participants with hSBA titers ≥ 1:4) in children 2 through 10 years of age at 1 month after immunization with MENVEO versus Menomune against each of the four serogroup components. Other comparisons of interest included comparing percentage of seroresponders in the subgroups of children aged 2 through 5 and 6 through 10 years. These comparisons were also performed using the seroresponse criterion of proportion with hSBA titers ≥ 1:8 and hSBA GMTs.

6.2.1.1.6 Surveillance/Monitoring

Safety Monitoring

Following vaccination, subjects were monitored in the clinic for 30 minutes to be evaluated for anaphylaxis and local injection site and systemic reactions. 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 28 to 35 after visit 1), all subjects completed a medical office visit including measurement of 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 29 to 360. On day 360 (days 344 to 374), the subjects and their parents/legal guardians returned to the clinic for study termination visit. A physical assessment was done including an examination of the study injection site. The worksheet was collected at this visit and reviewed with the subject's parents/legal guardians by the investigator (or designated study nurse).

Immunogenicity

For the immunogenicity subset, a blood sample (10 mL) was obtained at visit 1 (day 1), prior to administration of study vaccine, at visit 2 (day 29) and visit 3 (day 360) for assessment of bactericidal antibody titers against each serogroup (hSBA).

6.2.1.1.7 Statistical Considerations

Statistical Methods

Immunogenicity

See section 6.1.2.2

Safety

All AEs were coded using the Medical Dictionary for Regulatory Affairs (MedDRA), version 9.1, and grouped by MedDRA preferred terms into frequency tables according to MedDRA system-organ-class categories.

6.2.1.2 Results

6.2.1.2.1 Population Enrolled/Analyzed

In part 1 of the study, 619 children 2 through 10 years of age were enrolled and randomly assigned by age group (2 through 5 year old and 6 through 10 year old subjects) to MENVEO or the reference vaccine Menomune. Of the 305 children 2 through 5 years of age, 152 subjects were randomized to receive MENVEO, and 153 were randomized to receive Menomune. Of the 314 children 6 through 10 years of age, 157 subjects were randomized to each vaccine group (MENVEO or Menomune). Demographic characteristics were similar among the randomized groups. Six hundred eighteen (618) children were vaccinated. Five hundred twenty-five (525) subjects completed the protocol, including 84%, 82%, 87%, and 85% of the MENVEO 2 through 5 years of age, Menomune 2 through 5 years of age, MENVEO 6 through 10 years of age, and Menomune 6 through 10 years of age, respectively. Among the 94 subjects who did not complete the study, none of the subjects withdrew due to local or systemic reactions or due to AEs. Twenty subjects withdrew consent, 24 subjects were lost to follow-up, 46 subjects were withdrawn due to administrative reasons, 1 subject was withdrawn due to a protocol deviation, and 3 subjects were withdrawn for a reason that could not be classified according to the study protocol (not able to keep the appointment).

6.2.1.2.2 Safety Outcomes

Children Aged 2 through 10 Years

Immediate Reactions

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

Solicited Local and Systemic Adverse Events

Local AEs:
In children 2 through 5 years of age, 56% of the children in the MENVEO group and 44% in the Menomune group experienced at least one local, systemic, or other reaction during the 7-day reactogenicity monitoring period. In children 6 through 10 years of age, the respective percentages were 55% in the MENVEO group and 43% in the Menomune group. Injection site reactions were observed in 37% of the 2 through 5 year old children in the MENVEO group and in 24% of the children in the Menomune group. In children 6 to 10 years of age injection site reactions were observed in 45% of the children after vaccination with MENVEO and in 32% of the children after Menomune.

Systemic AEs:
In children 2 through 5 years of age, 36% of the children in the MENVEO group and 29% of the children in the Menomune group experienced systemic reactions. Change in eating habits, sleepiness, and irritability were the most frequently reported systemic reactions. In children 6 through 10 years of age the respective systemic reaction percentages were 25% in the MENVEO group and 18% in the Menomune group. The incidence of chills, myalgia (both reported by 8% of the subjects after MENVEO and 3% after Menomune), and headache was slightly higher in the MENVEO group than in the Menomune group. The frequency of use of analgesic/antipyretic medication was higher overall and between days 1-3 and 4-7 in the MENVEO group than in the Menomune group (48% vs 33%, respectively). There were no apparent differences between the vaccination groups in the percentage of subjects who stayed at home due to reactions (8% vs 5%) or the percentage of subjects with oral temperature ≥ 38°C (7% vs 7%).

Overall, the percentage of subjects with local, systemic, or other reactions was higher in the MENVEO groups than in the Menomune groups; particularly, local reactions were observed more often after vaccination with MENVEO than after Menomune. Most reactions were mild and of limited duration with no more than 2% of subjects in either group reporting severe reactions. The differences between the vaccine groups were most pronounced for erythema (15-17% vs 6-7%) and induration (11-17% vs. 3-4%) for MENVEO and Menomune, respectively. Local reactions of erythema and/or induration ≥ 100 mm were observed in three subjects in the MENVEO 6 through 10 year old age

group. The erythema in all three subjects resolved within 3 days and none had associated systemic reactions except for mild nausea in one subject.

Unsolicited Adverse Events, Including Serious Adverse Events

There were no deaths reported during or after the study. Three children 2 through 10 years of age (two children in the MENVEO 2 through 5 year age group (appendicitis and complicated pneumonia) and one child in the Menomune 2 through 5 year age group (perforated appendicitis)) experienced SAEs during the study. All occurred > 30days post-vaccination and all recovered. None of the SAEs were considered by study investigators to be related to the study vaccine and review suggested no associated causality. Six of 151 (4%) and 15 of 157 (10%) of children in the MENVEO 2 through 5 year and MENVEO 6 through 10 year age groups, respectively, and 7 of 153 (5%) and 9 of 157 (6%) children in the Menomune 2 through 5 year and Menomune MENVEO 6 through 10 year age groups, experienced AEs that were considered by the investigator to be possibly or probably related to study vaccines. Irritability, dizziness, headache, and pruritus were the only vaccine-related AEs reported for more than one subject within a vaccine group. Except for viral infection (MENVEO 2 through 5) and alopecia areata (Menomune 2 through 5), all these events occurred within the first 7 days after vaccination.

Immunogenicity Outcomes

Primary Objective:
In the 2 through 10 year age group, the noninferiority criterion was met for all four serogroups. The percentages of subjects with hSBA titers ≥ 1:4 at 1 month post-vaccination was higher in the MENVEO group than in the Menomune group for all four serogroups: A 81% (76-86) vs 44% (39-51), C 83% (78-87) vs 64% (58-70), W-135 94% (91-97) vs 72% (66-77) and Y 91% (87-94) vs. 59%(53-65) for MENVEO and Menomune, respectively.

Table 13: Percentages of subjects with hSBA ≥ 1:4 at 1 month postvaccination in 2 through 10 year old children, per protocol population

Serogroup	Day	hSBA	MENVEO	Menomune	Difference (MENVEO minus Menomune) 95% CI (%)
A	1	n(%) ≥ 1:4 95%CI (%) N	6 (2) 1-5 280	1(0) 0.009-2 281	2 0-4
	29	n(%)≥ 1:4 95%CI (%) N	228 (81) 76-86 280	125(44) 39-51 281	37 29-44
C	1	n(%)≥ 1:4 95%CI (%) N	80(28) 23-34 281	81(29) 23-34 283	0 -8-7
	29	n(%)≥ 1:4 95%CI (%) N	232(83) 78-87 281	181(64) 58-70 283	19 12-26
W-135	1	n(%)≥ 1:4 95%CI (%) N	111(40) 34-46 279	108(38) 33-44 282	1 -7-10
	29	n(%)≥ 1:4 95%CI (%) N	263(94) 91-97 279	202(72) 66-77 282	23 17-29
Y	1	n(%)≥ 1:4 95%CI (%) N	61(22) 17-27 280	68(24) 19-30 282	-2 -9-5
	29	n(%)≥ 1:4 95%CI (%) N	254(91) 87-94 280	167(59) 53-65 282	31 25-38

Source: CSR Section 5.3.5.1.1 Study V59P8 Table 2-3

Secondary Objectives:

1. In children 2 through 10 years of age, hSBA antibody GMTs after MENVEO compared to Menomune were statistically higher for all four serogroups. MENVEO showed 8.6- to 18-fold increases from baseline in 1-month GMTs, whereas Menomune exhibited 2.5- to 4.6-fold increases.
2. For children 2 through 5 years and 6 through 10 years of age, higher percentage of participants with hSBA ≥ 1:4 and higher GMTs of hSBA titer were observed at 1 month following immunization with MENVEO compared to Menomune for both age subgroups and for all serogroups except serogroup C in 6-10 year olds. For the children 2 through 5 years of age, GMTs at 1 month postvaccination ranged from 14 to 43 (Geometric mean ratios (GMRs) 5.01 to 14) after MENVEO and from 5.8 to 7.84 (GMRs 2.15 to 2.91) after Menomune. For the children 6 through 10 years of age the corresponding GMTs were 45 to 80 (GMRs 12 to 22) for MENVEO and 6.84 to 33 (GMRs 2.84 to 7.21) for Menomune.
3. For children 2 through 10 years of age, the percentage of participants with hSBA titer ≥ 1:4 and the hSBA GMT antibody response at 12 months after vaccination decreased compared to 1 month post vaccinaiton in both vaccine groups for all

four serogroups. The percentage of participants with hSBA titer ≥ 1:4 was higher in the MENVEO group than in the Menomune group. The decrease was most pronounced for serogroup A (from 82%(77-87) to 28%(23-34) at 1 and 12 months after MENVEO, and from 45%(39-52) to 18%(14-24) after vaccination with Menomune). Similar percentages of participants with hSBA titer ≥ 1:4 were observed for serogroups W-135 and Y at 1 and 12 months after MENVEO vaccination (95%(91-97) to 94%(90-97) and 91%(87-94) to 86%(81-90), respectively), but not after Menomune vaccination (for serogroup W-135, the percentage of participants with hSBA titer ≥ 1:4 decreased from 71%(65-77) to 50%(44-57) and for serogroup Y from 61%(55-67) to 38%(31-44).

4. The hSBA GMT antibody response decreased from 1 month to 12 months postvaccination after both MENVEO and Menomune vaccinations for all four serogroups. GMTs at 12 months postvaccination were higher after MENVEO (GMT range = 3.88 to 42) than after Menomune (GMT range = 3 to 9.02) for serogroups A, W-135, and Y, but not for serogroup C. The percentage of participants with hSBA titer ≥ 1:4 at 12 months after vaccination were mostly higher in the group of children 6 through 10 years of age than in children aged 2 through 5 years of age.

6.2.1.3 Comments and Conclusions

Study Design and Population

This study was conducted in Oakland, California. The population of 12 through 23 month old participants does not contribute to the indication sought in this application.

Safety Conclusions

Overall, rates of solicited and unsolicited adverse events were higher in the MENVEO groups than in the Menomune groups; particularly, local reactions were observed more often after vaccination with MENVEO than after Menomune. This was consistent with observations of increased reactogenicity following MENVEO compared to Menomune in older age groups. Severe reactions were rare in either group at ≤ 2%. Overall, MENVEO appeared to be associated with a modest increase in local and systemic adverse reactions compared to Menomune in children 2 through 10 years of age.

Immunogenicity Conclusions

The proportion of study participants with hSBA titers ≥ 1:4 at 1 month after vaccination with MENVEO were non-inferior to those at 1 month after vaccination with Menomune for each of the 4 serogroups across the 2 through 10 year old age group, based on the pre-specified criteria. Thus, the primary immunogenicity objective was demonstrated. In the 2 through 5 year and 6 through 10 year age groups analyzed separately, seroresponder rates (hSBA ≥ 1:4) were also equivalent or greater for MENVEO

compared to Menomune for all 4 serogroups. The hSBA GMTs for MENVEO met non-inferiority criteria in comparisons to Menomune for all 4 serogroups in the 2-10 year age group overall, and for the two age strata separately. Twelve months after vaccination, the proportion of study participants with hSBA titers ≥ 1:4 decreased compared to 1 month data in both vaccine groups for all serogroups. Numerically higher proportions of study participants with hSBA titers ≥ 1:4 and hSBA GMTs at 1 and 12 months post vaccination were observed for MENVEO compared to Menomune in children 2 through 10 years of age.

6.3 Indication #1

6.3.1 Trial #3

6.3.1.1 Protocol # and Title

Study V59P10:
A Phase 3, randomized, observer-blind, controlled, multi-center study to compare the safety of one dose of Novartis Meningococcal ACWY Conjugate Vaccine (MENVEO) with that of a Licensed Meningococcal ACWY Polysaccharide Vaccine (Menomune), administered to healthy children 2 through 10 years of age.

6.3.1.1.1 Rationale/Objectives

Study V59P10 was conducted to evaluate the safety and immunogenicity of MENVEO when administered as a single dose to healthy children 2 through 10 years of age.

Immunogenicity Objectives

Primary Objective:
To compare the immunogenicity of a single injection of MENVEO with the immunogenicity of a single injection of PS vaccine (Menomune), defined as the percentage of subjects with seroresponse in hSBA against *N. meningitidis* serogroups A, C, W-135, and Y at 1 month after vaccination, when administered to healthy children 2 through 10 years of age.

Seroresponse was defined as:
For a subject with hSBA < 1:4 at baseline, seroresponse was defined as a post-vaccination hSBA titer ≥ 1:8; for a subject with ≥ 1:4 at baseline, seroresponse was defined as hSBA titer of at least four times the baseline.

Secondary Objective:

1. To compare the immunogenicity of a single injection of MENVEO and the immunogenicity of a single injection of Menomune, defined as: (a) percentage of subjects with hSBA ≥ 1:4, (b) percentage of subjects with hSBA ≥ 1:8, and (c)

hSBA geometric mean titers (GMTs) against *N. meningitidis* serogroups A, C, W135, and Y at 1 month after vaccination, when administered to healthy children 2 to 10 years of age.

2. To compare the immunogenicity of a single injection of MENVEO and a single injection of Menomune, defined as: (a) percentage of subjects with hSBA ≥ 1:8, (b) percentage of subjects with hSBA ≥ 1:4, and (c) hSBA GMTs against *N meningitides* serogroups A, C, W135, and Y at day 181 after vaccination, when administered to healthy children 2 through 10 years of age.

Safety Objective

Primary Objective:
To compare the percentage of subjects presenting at least one severe solicited systemic reaction to MENVEO with the percentage presenting at least one severe solicited systemic reaction to Menomune during the first 7 days (day 1 to 7) following a single injection administered to healthy children 2 through 10 years of age.

Secondary Objective:
To provide a descriptive analysis of the proportion of subjects experiencing immediate hypersensitivity reactions; solicited local and systemic adverse events (AEs), axillary temperature, unsolicited AEs, and serious AEs.

6.3.1.1.2 Design Overview

1500 healthy children 2 through 10 years of age were randomly assigned to one of the two vaccine groups (MENVEO or Menomune) at a 2:1 ratio. The randomization was stratified by age: 750 children 2-5 years of age and 750 children 6-10 years of age. Blood samples were to be obtained from a subset of 75 subjects in each group and age stratum.

6.3.1.1.3 Population

Table 14: Study population V59P10

Planned and Actual Enrollment		
Vaccine Group N planned (actual)	**Age Group N planned (actual)**	**Subjects for Immunogenicity N planned (actual)**
MenACWY 1000 (950)	2 to 5 years 500 (452)	75 (74)
	6 to 10 years 500 (498)	75 (76)
Menomune 500 (550)	2 to 5 years 250 (264)	75 (75)
	6 to 10 years 250 (286)	75 (75)

Source: Clinical study report, Section 5.3.5.1.1, Study V59P8

Study Period

May 24, 2006 through March 21, 2007

Study Sites and Recruitment

1. Centro de Desarrollo de Proyectos Avanzados CEDEPAP, Roma 1464, B Pueyrredon (X5000BJH), Cordoba, Argentina;
2. FUNCEI – Fundacion Centro de Estudios Infectologicos, French 3085 (C1425AWK), Ciudad Autonoma de Buenos Aires, Argentina;
3. Hospital de Pediatria “Sor Maria Ludovica”, Calle 14 N 1631, (1900) La Plata, Argentina.

Inclusion Criteria:

1. 2 to 10 years of age inclusive whose parents or legal guardians gave written informed consent at the time of enrollment;
2. Available for all visits and telephone calls (parents or legal guardians) scheduled for the study;
3. In good health as determined by:
    - medical history;
    - physical assessment;
    - clinical judgment of the investigator;
4. Up to date with primary course and booster vaccines (BCG and four doses of diphtheria-tetanus-pertussis vaccine [DTP], oral polio vaccine [OPV] or inactivated polio vaccine [IPV], *H influenzae* type b vaccine [Hib], measles-mumps-rubella vaccine [MMR], and hepatitis A or B, according to the vaccine calendar and subject age for Argentina).

Exclusion Criteria and Concomitant Vaccines and Medications:
Criteria for individuals not eligible to be enrolled in the study were similar as stated above in the pivotal study V59P20 in section 6.1.1.1.3 Population.

6.3.1.1.4 Products Mandated by the Protocol

The investigational MENVEO vaccine was obtained by resuspending the lyophilized MenA component with the liquid MenCWY component just before injection. After reconstitution, the MENVEO vaccine had the following antigen composition per 0.5 mL of intramuscular injectable solution:

Table 15: Investigational vaccine MENVEO composition

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

Licensed meningococcal ACWY PS vaccine: Menomune. The vaccine consisted of four meningococcal capsular polysaccharide serogroups (A, C, W135, and Y and was administered by subcutaneous (SC) injection in the deltoid area of the arm.

6.3.1.1.5 Study Endpoints

Safety Endpoints

Immediate hypersensitivity reactions; solicited local and systemic adverse events (AEs), axillary temperature, unsolicited AEs, and serious AEs were collected for all vaccinated study participants.

Immunogenicity Endpoints

Primary:
The immunogenicity of MENVEO vaccine was considered non-inferior to the immunogenicity of Menomune, 1 month post-vaccination for any of the four serogroups if the lower limit of the two-sided 95% confidence interval around the difference of the percentage of subjects with hSBA seroresponse for that serogroup (MENVEO vaccine group minus Menomune vaccine group) was greater than -10% in 2 through 10 year old children.

Seroresponse was defined as:
For a subject with hSBA < 1:4 at baseline, seroresponse was defined as a post-vaccination hSBA titer ≥ 1:8; for a subject with hSBA ≥ 1:4 at baseline, seroresponse was defined as an hSBA titer of at least four times the baseline.

Secondary:
The immunogenicity of MENVEO vaccine was considered non-inferior to the immunogenicity of Menomune for any of the four serogroups if the lower limit of the two-

sided 95% confidence interval around the difference of the percentage of subjects achieving an hSBA titer ≥ 1:8, and an hSBA titer ≥ 1:4, 1 month or 181 days following the vaccination was greater than -10% in 2 through 10 year old children. The hSBA GMTs at baseline (day 1), 1 month after the vaccination (day 29) and on study day 181 in response to *N. meningitidis* serogroup A, C, W, and Y were also calculated.

6.3.1.1.6 Surveillance Monitoring

Safety and Immunogenicity Monitoring

Table 16: Study design: monitoring

Study Day (window in days)	Screening (-14)	Day 1	Day 3 (+3)	Day 8 (+3)	Day 29 (+14)a	Day 181 (±15)a
Visit number		1			2	3
Procedures						
Obtain informed consent	X					
Inclusion/exclusion criteria	X					
Medical history and prior medications [b]	X					
Physical assessment	X	X			X [c]	X [c]
Obtain blood sample		X [c]			X [c]	X [c]
Administer study vaccine [d]		X				
Injection-site examination		X			X [c]	
Assess local and systemic reactions and body temperature [e]		X	X	X		
Concomitant medications		X	X	X	X	X
Adverse events [f]		X	X	X	X	X
Collect diary cards					X	
Collect worksheets						X
Study termination						X

Note: Day 1 is defined as the day of study vaccination

[a]For subjects not included in the immunogenicity analysis, a phone call could replace the medical office visit.

b Includes vaccination history.

c Applicable to subjects included in the immunogenicity analysis.

d Vaccine administered after blood sample is obtained.

e Includes assessment of immediate hypersensitivity.

f From day 1 to 7, record and collect information regarding all AEs. From day 8 to 181, record and collect SAEs and information regarding any event requiring a physician visit/emergency room visit, and any event resulting in a subject's early termination from the study. From day 1 to 29, common childhood exanthematous diseases were also recorded.

6.3.1.1.7 Statistical Considerations

Safety of MENVEO conjugate vaccine was considered non-inferior to safety of PS vaccine if the upper limit of the two-sided 95% CI of the ratio (MenACWY conjugate vaccine group divided by PS vaccine group) of the proportion of subjects experiencing at least one severe systemic reaction during the first 7 days (day 1 to day 7) after vaccination was less than 3. The other safety data were analyzed descriptively comparing the proportion of study participants in each vaccine group that experienced immediate, solicited, unsolicited and SAEs. All safety analyses were carried out using the safety population.

The percentage of subjects achieving an hSBA titer ≥ 1:8, an hSBA titer ≥ 1:4, and a seroresponse in hSBA 1 month following the vaccination (day 29) and associated two sided 95% CIs were computed for each vaccine group and for each age group within each serogroup. Similarly, CIs were computed for percentage of subjects achieving an hSBA titer ≥ 1:8 and hSBA titer ≥ 1:4 on study day 181. Differences between proportions with two sided 95% CIs were determined for each serogroup within each age groups and at each time point. If for all four serogroups, the CI was entirely to the right of (i.e., greater than) -10%, then non-inferiority was declared. The hSBA GMTs at baseline (day 1), 1 month after the vaccination (day 29) and on study day 181 in response to *N. meningitidis* serogroup A, C, W, and Y was also calculated. The primary dataset for the immunogenicity analyses was the PP population.

6.3.1.2 Results

6.3.1.2.1 Population Enrolled/Analyzed

A total of 1500 subject were enrolled, randomized, and vaccinated. Ten subjects withdrew prematurely from the study while 1490 subjects completed the protocol. All premature withdrawals (11/009, 11/013, 11/014, 11/047, 11/058, 11/139, 11/140, 11/520, 11/570, and 20/613) were due to withdrawal of consent for personal reasons. Nine of the 10 subjects withdrawn were in the immunogenicity subset. None of the subjects was withdrawn due to an adverse event.

Table 17: Summary of Study Terminations- Randomized Population

	Number (%) of Subjects					
	2-5 Years		6-10 Years		2-10 Years	
Vaccine Group	**MenACWY**	**Menomune**	**MenACWY**	**Menomune**	**MenACWY**	**Menomune**
Enrolled	452	264	498	286	950	550
Completed study	448	261	496	285	944	546
Premature withdrawals	0	0	0	0	0	0
AE or death	0	0	0	0	0	0
Withdrew consent	4	3	2	1	6	4
Lost to follow-up	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0

Source: Clinical Study Report, Section 5.3.5.1.3, Part 1 V59P10

Table 18: Summary of All Protocol Deviations, Number of Subjects (Percentage)

Reason	2 – 5 Years		6 – 10 Years	
	MenACWY	Menomune	MenACWY	Menomune
	N=17	N=19	N=27	N=17
Subject didn't receive 4 doses of DTP	0	2 (11%)	1 (4%)	0
Missing blood draw at visit 2 or visit 3	4 (24%)	3 (16%)	1 (4%)	1 (6%)
Received an excluded concomitant medication	1 (6%)	2 (11%)	0	1 (6%)
Did not meet entry criteria	1 (6%)	1(5%)	2 (7%)	1 (6%)
Wrong vaccine administered	0	1 (5%)	0	0
Protocol procedure not performed as per protocol	3 (18%)	4 (21%)	11 (41%)	6 (35%)
Follow-up contact outside window	8 (47%)	6 (32%)	11 (41%)	9 (53%)
Withdrawals from the study	4 (24%)	3 (16%)	2 (7%)	1 (6%)

Source: Clinical Study Report, Section 5.3.5.1.3, Part 1 V59P10

6.1.3.4 Safety Outcomes

Immediate Reactions

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

Solicited Local and Systemic Reactions

Table 19. Rates of solicited and systemic reactions

Type of Reaction	2-5yo MENVEO N=452	2-5yo Menomune N=264	6-10 MENVEO N=498	6-10 Menomune N=286	2-10 MENVEO N=950	2-10 Menomune N=550
Any	209 (46%)	138 (52%)	235 (47%)	148 (52%)	444 (47%)	286 (52%)
Local	138 (31%)	99 (38%)	189 (38%)	125 (44%)	327 (34%)	224 (41%)
Systemic	130 (29%)	73 (28%)	119 (24%)	69 (24%)	249 (26%)	142 (26%)
Other	69 (15%)	42 (16%)	69 (14%)	47 (16%)	138 (15%)	89 (16%)

Source: Table 12.2.1-1, Clinical Study report, Section 5.3.5.1.3, Part 1 of V59P10

Overall, the percentages of subjects in 2 through 10 year old children, experiencing any solicited reaction were balanced between the two vaccine groups (47% - 52%). More subjects experienced local reactions (34% - 41%) than systemic reactions (26% in both groups). The results were similar in the analysis performed for the overall population and in the analysis stratified by age group, with 46% - 52% of the subjects experiencing any reaction in the 2 to 5 age group and 47% - 52% in the 6 to 10 age group.

Table 20. 95% CI of subjects with severe solicited reactions during days 1 through 7

Systemic Reaction	2-10 yo MENVEO N=950	2-10 yo Menomune N=550	MENVEO/Menomune Ratio (95% CI)	Primary Objective Upper 95%CI limit<3
Severe	11 (1.16%)	1 (0.2%)	6.37 (0.82-49.2)	Not met

Source: CSR section 5.3.5.1.1. Study V59P10 part 1, Table 12.2-1.

Of the 12 subjects experiencing severe solicited systemic reactions, four were in the 6 through 10 year age group, and eight in the 2 through 5 year age group. Eleven of these subjects were exposed to MENVEO and one to Menomune (enrollment ratio was 2:1). All were of limited duration and resolved without sequelae.

Unsolicited Adverse Events, including Serious Adverse Events

Study Day 1 to Day 29:
The percentage of subjects experiencing any unsolicited AE between day 1 and day 29 was 21% for the MENVEO group and 16% for the Menomune group. The percentage of subjects experiencing possibly or probably related AEs was 2% and 1% for MENVEO and Menomune, respectively. The incidence rate for reported SAEs was low (5 subjects overall, < 1%), and all except one SAE were judged as not related to the study vaccine. One SAE, febrile convulsion occurring one day after vaccination, was judged by the investigator as possibly or probably related to the vaccine administered, and occured in the MENVEO 2 through 5 year age group (subject 12/010). Three of the SAEs were reported in the 2 through 5 year age group, while the remaining two were reported in the 6 through 10 age group.There were no deaths and no withdrawals due to AEs during the study. There were higher percentages of subjects experiencing any unsolicited AEs

in the 2 through 5 year than the 6 through 10 year age group (23% - 25% vs. 10% - 16%).

Table 21. Overview of Unsolicited AEs, Day 1 through 29

Type of Reaction	2-5 yo MENVEO N=452	2-5 yo Menomune N=264	6-10 yo MENVEO N=498	6-10 yo Menomune N=286	2-10 yo MENVEO N=950	2-10 yo Menomune N=550
Any AE	115 (25%)	62 (23%)	81 (16%)	28 (10%)	196 (21%)	90 (16%)
Possibly or probably related AE	10 (2%)	4 (2%)	6 (1%)	2 (1%)	16 (2%)	6 (1%)
SAEs[a]	3 subjects (<1%) (12/010, 18/002, 30/074)		2 subjects (<1%) (11/575, 20/568)		5 subjects (< 1%)	
AEs leading to discontinuation	0	0	0	0	0	0
Possibly or probably related SAEs	1 subject (<1%) (12/010)	0	0	0	1 subject (<1%)	0
Death	0	0	0	0	0	0

Source: Table 12.2.1-2, Clinical Study report, Section 5.3.5.1.3, Part 1 V59P10

Study Day 30 to day 181:

The percentage of subjects experiencing unsolicited AEs with onset during days 30 to 181 was balanced between the two vaccine groups (5% - 6%) and was considerably lower than the percentage of subjects with unsolicited AEs with onset during days 1 to 29, probably reflecting the different methods of data collection (i.e., only SAEs and AEs requiring a physician visit/emergency room visit or resulting in early termination were to be reported after day 29). No possibly or probably related AEs, AEs leading to discontinuation, or deaths were reported after day 29. SAEs were reported for five subjects (two cases of pneumonia, one injury, one asthma crisis, and one appendicitis, < 1%), all of which were assessed by the investigator as not related to the study vaccine.

When analyzed by age stratification, the incidence rates of unsolicited AEs were balanced between vaccine groups; however, in the 2 through 5 years age group there was a higher percentage of subjects for whom unsolicited AEs were reported, probably reflecting an increased number of physician visits within this group.

Table 22. Overview of Unsolicited AEs, Days 30 through 181

Type of Reaction	2-5 yo MENVEO N=452	2-5 yo Menomune N=264	6-10 yo MENVEO N=498	6-10 yo Menomune N=286	2-10 yo MENVEO N=950	2-10 yo Menomune N=550
Any AE	29 (6%)	21 (8%)	14 (3%)	10 (3%)	43 (5%)	31 (6%)
Possibly or probably related AE	0	0	0	0	0	0
SAEs	2 subjects (<1%) (11/043, 12/067)		3 subjects (<1%) (11/645, 20/557, 30/577)		5 subjects (< 1%)	
AEs leading to discontinuation	0	0	0	0	0	0
Possibly or probably related SAEs	0	0	0	0	0	0
Death	0	0	0	0	0	0

Source: Table 12.2.1-3 Clinical Study Report, Section 5.3.5.1.3 Part 1 V59P10

6.3.1.2.2 Immunogenicity Outcomes

Seroresponse

For a subject with hSBA < 1:4 at baseline, seroresponse was defined as a post-vaccination hSBA titer ≥ 1:8; for a subject with ≥ 1:4 at baseline, seroresponse is defined as hSBA titer of at least four times the baseline.

Primary Immunogenicity Objectives

The primary immunogenicity objective of this study, assessed at 1 month after a single injection administered to healthy children aged 2 through 10 years, was to compare the immunogenicity of MENVEO with that of Menomune, measured in terms of the percentages of hSBA seroresponders against each of the four serogroups.

The percentages of seroresponders in the MENVEO and Menomune groups for all four serogroups were as follows: serogroup A: 93% vs. 55%; serogroup C: 82%vs. 52%; serogroup W-135: 74% vs. 46%; serogroup Y: 82% vs. 63%, all respectively. The lower limit of the two-sided 95% CI around the difference in the percentage of overall seroresponders (MENVEO minus Menomune) was greater than -10% (noninferiority criterion) for all four serogroups.

Secondary Immunogenicity Objectives

Study Day 29:
In the overall population (2 through 10 years of age), the percentages of subjects with postvaccination hSBA titer ≥ 1:8 for MENVEO vs. Menomune were as follows: serogroup A: 95% vs. 55%; serogroup C: 88% vs. 70%; serogroup W: 99% vs. 73%;

serogroup Y: 89% vs. 66%, all respectively. The lower limit of the two-sided 95% CI around the difference in the percentage of overall seroresponders (MENVEO minus Menomune) was greater than -10% (noninferiority criterion).

In the by age analysis (2-5 and 6-10 years of age), for all four serogroups, the percentages of subjects with postvaccination hSBA ≥1:8 or hSBA ≥ 1:4 were higher in the MENVEO than in the Menomune group.

In the overall population (2 through 10 years of age), at day 29, the hSBA GMTs for all four serogroups for MENVEO vs.Menomune were: serogroup A: 65 vs. 11; serogroup C: 42 vs 20; serogroup W: 72 vs. 20; serogroup Y: 47 vs. 25, all respectively.

Table 23. hSBA Seroresponse (95% CI) 1 Month Post Vaccination in 2 through 10 Year Old Children, Per Protocol Population

Serogroup	MENVEO	Menomune	Difference 95% CI (MENVEO minus Menomune)
A			
Baseline < 1:4	95% (90-98) n=140	55% (46-63) n=143	40% (32,49)
Baseline ≥1:4	50% (16-84) n=8	60% (15-95) n=5	-10% (-55, 41)
Overall	93% (87-96) n=148	55% (46-63) n=148	38% (29,47)
C			
Baseline < 1:4	85% (77-91) n=109	60% (50-70) n=100	25% (14,37)
Baseline ≥1:4	71% (54-85) n=38	34% (20-50) n=44	37% (16, 55)
Overall	82% (74-88) n=148	52% (44-60) n=144	30% (19,40)
W-135			
Baseline < 1:4	99% (94-100) n=86	57% (46-68) n=89	42% (31,52)
Baseline ≥1:4	37% (24-51) n=57	26% (15-40) n=53	10% (-7,27)
Overall	74% (66-81) n=143	46% (37-54) n=142	28% (17,39)
Y			
Baseline < 1:4	87% (79-92) n=121	62% (53-71) n=124	25% (14,35)
Baseline ≥1:4	56% (35-76) n=25	68% (45-86) n=22	-12% (-38,16)
Overall	82% (74-87) n=146	63% (55-71) n=146	18% (8,28)

Source: CSR section 5.3.5.1.1. Study V59P10 part 2, Table 7.4.1.1-1.

Study Day 181:
In the overall population (2 through 10 years of age), the percentages of subjects with hSBA titer ≥ 1:8 at day 181 decreased compared with those observed at day 29 for all serogroups in both vaccine groups except serogroup Y in the MENVEO group. In comparing the persistence of immunity between the two vaccines, for serogroups C, W-135, and Y, the percentages of subjects with hSBA titer ≥1:8 at day 181 were numerically higher in the MENVEO than in the Menomune group (serogroup C: 81% vs. 55%; serogroup W: 96% vs. 66%; serogroup Y: 89% vs. 59%). The percentages observed for serogroup A were lower in the MENVEO than Menomune group (35% vs. 38%).

The results observed when a less conservative threshold, i.e., hSBA titer ≥ 1:4, was used, were generally similar to those observed in the analysis of the percentages of subjects with hSBA titer ≥1:8.

6.3.1.3 Comments and Conclusions

Study Design and Population

The study was conducted at three centers in Argentina and enrolled 1500 healthy children 2 through 10 years of age who were randomly assigned to one of the two vaccine groups (MENVEO or Menomune) at a 2:1 ratio. The randomization was stratified by age: 750 children 2-5 years of age and 750 children 6-10 years of age. Blood samples were to be obtained from a subset of 75 subjects in each group and age stratum for the immunogenicity subset group.

Safety

The observed percentages of subjects experiencing severe solicited systemic reactions were higher in the MENVEO than the Menomune group, but occurred at a low rate overall (i.e., 1% [11 subjects] in the MENVEO group and <1% [1 subject] in the Menomune group). Additionally all severe solicited systemic reactions were of limited duration (i.e., < 5 days, median of 1 day) and resolved without sequelae. Overall solicited reactions were of short duration, mostly mild or moderate in severity and were reported by similar percentages of subjects in the MENVEO and Menomune groups.

One of the 10 SAEs (febrile convulsion, subject12/010, MENVEO group) was reviewed and assessed as possibly or probably related to MENVEO administration by temporal association. The onset of the SAE was on study day 2, the event was of moderate severity, and it occurred in a subject with 2 prior episodes of febrile seizure. The episode of convulsion lasted less than 10 minutes and the subject was hospitalized for observation and discharged in good condition. The SAE was assessed as possibly related due to the temporal association to the vaccination. The seriousness criterion was hospitalization.

No deaths or AEs leading to discontinuation were reported in this study.

Immunogenicity

The immunogenicity subset, consisting of 300 subjects enrolled at study site 11, was randomized in each of two groups at a 1:1 ratio to receive either one injection of MENVEO or one injection of Menomune at day 1.
The primary immunogenicity objective, measured at 1 month after a single injection of vaccine administered to healthy subjects aged 2 through10 years, was met. MENVEO was noninferior to Menomune for all four serogroups.

Among the secondary immunogenicity objectives:

- MENVEO was noninferior to Menomune using hSBA titer ≥ 1:8 or hSBA titer ≥ 1:4 when measured at 1 month after a single injection of vaccine administered to healthy subjects aged 2 through 10 years.
- MENVEO was noninferior to Menomune using hSBA titer ≥ 1:8 or hSBA titer ≥ 1:4 for serogroup C, W and Y measured 6 months after a single injection of vaccine administered to healthy subjects aged 2 through 10 years; noinferiority of MENVEO to Menomune was not met for serogroup A at 6 months following a single injection.

6.4 Indication #1

6.4.1 Trial #4

6.4.1.1 Protocol # and Title:

Study V59P7:
A Phase 2, randomized, observer blind, multi-center, active controlled study

6.4.1.1.1 Rationale/Objectives

Study V59P7 was conducted to evaluate the safety and immunogenicity of MENVEO in healthy children aged 12 to 59 Months.

Immunogenicity Objectives

Primary Objective:
For subjects aged 36 to less than 60 months

- To compare the functional immune response 28 days after administration of one dose of MENVEO conjugate vaccine ----------(b)(4)---------- with that of a Mencevax polysaccharide (PS) vaccine, as measured by the

percentage of subjects with human complement serum bactericidal activity (hSBA) ≥1:4 against *N. meningitidis* serogroups A, C, W, and Y.

Secondary Objectives:

- To compare the functional immune response 28 days after administration of one dose of MENVEO (b)(4) with that of a Mencevax PS vaccine, as measured by hSBA geometric mean titers (GMTs) and hSBA ≥1:8 against *N. meningitidis* serogroups A, C, W, and Y.

In addition, the following secondary objectives were to be evaluated using hSBA GMTs and percentage of responders with hSBA titers ≥1:4 and ≥1:8:

- The persistence of functional immune response at 6 or 12 months following administration of one dose of either MENVEO (b)(4) or Mencevax PS vaccine.
- The booster effect 21 days after one dose of MENVEO (b)(4) vaccine administered 6 or 12 months after the first dose of either MENVEO (b)(4) or Mencevax PS vaccine.

For subjects aged 12 to < 36 months
The children < 24months or subjects who received the non-formulated MENVEO ---(b)(4)---- vaccine were outside the indicated age use of 2 through 10 years of age for --------(b)(4)----- MENVEO and hence were not further investigated in this clinical review.

Safety Objective

To evaluate the safety and tolerability of MENVEO when administered to healthy children 24 to less than 60 months old.

6.4.1.1.2 Design Overview

Children 36 through 59 months of age received one IM dose of MENVEO (b)(4) or Mencevax PS on day 1; each group was divided in two subsets of 50 subjects each, who received a second dose of MENVEO (b)(4) (both groups) at 6 or 12 months after the first dose, respectively. Blood was collected at visit 1 (day 1, prior to vaccination) and at visit 2 (28 days after visit 1) in all subjects. In addition blood samples were taken prior to and 21 days after the second vaccination. In subjects who received the second vaccination on day 29, an additional blood sample was taken at visit 4 (357 days after visit 1).

The subjects remained in the clinic for 30 minutes after each vaccination to monitor for any hypersensitivity reactions and other adverse events (AEs). A diary card was completed to describe local (i.e., tenderness, erythema, induration) and systemic reactions (i.e., change in eating habits, sleepiness, vomiting, diarrhea, and irritability) for

7 days following each vaccination. During this period, axillary or rectal temperature (based on local routine practice and subject's age) were also recorded daily.

Table 24. Study V59P7: Planned enrollment by vaccine group

Vaccination Group	Treatment and Number of Subjects Planned			
	First Vaccination	Second vaccination		
	Day 1	1 Month	6 Months	12 Months
Toddlers aged 12-35 months*	MENVEO (b)(4) N=200	MENVEO (b)(4) N=66		
			MENVEO (b)(4) N=66	
				MENVEO (b)(4) N=66
Toddlers aged 12-35 months*	MENVEO (b)(4) N=200	MENVEO (b)(4) N=66		
			MENVEO (b)(4) N=66	
				MENVEO (b)(4) N=66
Children aged 36-59 months	MENVEO (b)(4) N=100		MENVEO (b)(4) N=50	
				MENVEO (b)(4) N=50

Source Clinical Study report, Section 5.3.5.1.2 Synopsis
* Groups of toddlers 12 through 35 years of age were divided into two subgroups; toddlers 12 through 24 months and toddlers 25 through 35 months (toddlers < 24 months were outside the age indication and hence not reviewed in this supplement)

6.4.1.1.3 Population

Approximately 600 subjects were planned to be recruited in the study centers in Finland and Poland, 623 were actually enrolled; 617 subjects were exposed to study vaccine and included in the safety analysis, 574 were included in the immunogenicity analysis.

Study Period

14 March 2005 – 16 May 2006

Study Sites and Recruitment

1. University of Tampere Medical School, Tampere, Finland
2. Oddz. Neuroinfekcji, Szpital Jana Pawla II, Kraków, Poland
3. Samodzielny ZOZ, Lubartów, Poland

Inclusion Criteria:
1. Healthy 12 to less than 60-month-old children

2. A parent/legal guardian had given written informed consent after the nature of the study had been explained.
3. Available for all the visits scheduled in the study
4. In good health as determined by: medical history, physical examination, and clinical judgment of the investigator.

Exclusion Criteria:
Criteria for individuals not eligible to be enrolled in the study were similar as stated above in the pivotal study V59P20 in section 6.1.1.1.3 Population.

6.4.1.1.4 Products Mandated by the Protocol

The investigational Novartis MENVEO vaccine was obtained by mixing of the lyophilized Men A component with the liquid MenCYW-135 component just before injection. See section 6.1.1.1.4 for composition of MENVEO.

Mencevax (GlaxoSMithKline) consists of four meningococcal capsular polysaccharide serogroups (A, C, Y and W-135). Each dose of 0.5 mL of vaccine was obtained by mixing just before injection two vials: a vial containing the lyophilized purified polysaccharide of *N. meningitidis* and a vial containing diluent. One 0.5 mL dose of GSK Mencevax was administered IM in the right deltoid. Mencevax is not licensed in the U.S.

6.4.1.1.5 Outcomes

Safety results

Overall local reactogenicity in children 2 through 5 year old following a single dose of MENVEO was reported in 39% (127/319) with tenderness being the most frequently reported local reaction at 32%(102/319).. Additionally the percentage of children 2 through 5 year old reporting systemic AEs following a single dose of MENVEO was 24% (80/319). The most frequently reported systemic AEs were changes in eating habits, sleepiness and irritability. The most frequently reported unsolicited AE was upper respiratory infections at 11% (14/125). Incidence of Varivcella was reported at similar percentage of subjects across all vaccination groups in this study at 3-7% (7 of the 15 varicella episodes were MENVEO recipients in the 2 through 5 year old population) All varicella episodes occurred > 30 days post-vaccination and resolved without sequelae. No deaths occurred in the study.

Efficacy results

The functional immune response, as measured by hSBA, in children 36 through 59 months of age at 28 days after vaccination was higher in subjects who received

MENVEO (b)(4) compared to those who received Mencevax PS for all serogroups. The immune response at 6 and 12 months after vaccination with MENVEO (b)(4) declined for serogroup A but were relatively well-maintained for serogroups C, W-135 and Y. A second vaccination with MENVEO (b)(4) at 6 or 12 months after the first vaccination showed very robust responses (>90% achieving an hSBA titer ≥1:4 for all serogroups), with GMTs higher in subjects who received the second dose at 12 months versus a second dose at 6 months.

Reviewers note: This study only contributes to the MENVEO safety and immunogenicity data after a single or 2 dose vaccination. The comparator vaccine, Mencevax is not licensed in the U.S. and hence will not be investigated further in this clinical review.

7 Overview of Safety Across Trials

7.1 Safety Database

Overview of integrated MENVEO safety data:
A total of 3107 subjects from 1 pivotal study (V59P20) and 3 supportive studies (V59P7, V59P8, V59P10) provided safety data on MENVEO. For comparator vaccines, 1255 subjects provided safety data for Menactra, 816 provided safety data for Menomune.

7.2 Safety Assessment Methods

Safety monitoring, definitions of relatedness as determined by study investigators, severity, and solicited AEs were generally the same for all studies contributing to the safety database for this indication, except arthlagia and headaches were not solicited in supportive study V59P7, and rash was only solicited in pivotal study V59P20.

7.3 Significant or Potentially Significant Events

7.3.1 Deaths

No death occurred in any of the four studies used to support this application.

7.3.2 Other Potentially Significant Events

Overall in the 2 through 10 year old population, across the total MENVEO and comparator Menactra and Menomune groups, the percentage of the subjects reporting any SAEs was < 1%. Additionally, across the four studies, 38 MENVEO subjects reported SAEs, and two of the SAEs reported were reviewed as at least possibly vaccine-related. One was an episode of febrile convulsion, experienced by a MENVEO recipient in the 2 through 5 year old age stratum in study V59P10 (subject number 12/010). The second SAE (study V59P10, subject number 20/568, post-vaccinal tonic convulsion) was also reviewed as possibly or probably vaccine-related. This subject

was noted to have a history of 3 similar episodes in close association with vaccine administration and recovered without sequelae.

Table 25. Percentage of Subjects with SAEs by age group, pooled analysis

2-5 years					
	MENVEO N=1295	**Menactra N=684**	**Menomune N=418**	**MENVEO→MENVEO N=575**	**Following MENVEO in Mencevax→MENVEO N=74**
Any SAE	11 (0.8%)	5 (0.7%)	2 (0.5%)	19 (3.3%)	2 (2.7%)
At least possibly related SAEs	2 (<0.2%)	0	0	0	0
6-10 years					
	MENVEO N=1237		**Menactra N=571**		**Menomune N=443**
Any SAE	8 (0.6%)		2 (0.4%)		0
At least possibly related SAEs	0		0		0
2-10 years					
	Total MENVEO (minus Mencevax recipients) N=3107		**Menactra N=1255**		**Menomune N=861**
Any SAE	40 (1.3%)		7 (0.6%)		2 (0.2%)
At least possibly related SAEs	2 (<0.1%)		0		0

Source: Table 2.1.3-1, Section 2.7.4, Summary of Clinical Safety (2 through 10 years)

In the pooled analysis, reports of SAEs were more frequent when two doses of meningococcal vaccine were administered in the 2 through 5 years age group (3% in the MENVEO →MENVEO group). This was accounted for in part by the fact that the overall reporting period for the subjects receiving two vaccinations was longer compared with the reporting period for the single vaccination groups (8 to 18 months vs. 6 months). When the MENVEO →MENVEO group was analyzed separately for studies V59P7 and V59P20, the percentage of subjects reporting SAEs in study V59P7 (8%) was higher than the respective percentage observed in study V59P20 (1%). The higher percentages reporting SAEs in study V59P7 were accounted for by a comparatively high incidence of varicella infection in this unvaccinated population and the fact that all varicella cases, regardless of severity and hospitalization status, were categorized by the investigator as SAEs. In the large V59P20 study, when a two-dose regimen was explored in the 2 through 5 years age stratum, the percentage of subjects reporting SAEs was the same (1%) regardless of whether one of two doses of MENVEO were administered.

No AEs led to subject withdrawal in any of the four studies within the 2 through 10 year age group.

Table 26. Listing of SAEs by Study, Ages 2-10 years

Subject No.	Vaccine group	Preferred Term	Onset (Study Day)	Duration (days)	Outcome	Hospitali-zation	Related-ness
Study V59P7							
11/112	MENVEO	varicella	290	20	recovered	no	none
13/109	MENVEO	Limb injury	388	24	recovered	no	none
13/119	MENVEO	varicella	292	7	recovered	no	none
13/126	MENVEO	varicella	140	6	recovered	no	none
14/202	MENVEO	varicella	315	6	recovered	no	none
14/204	Mencevax	varicella	335	5	recovered	no	none
14/213	MENVEO	humerus fracture	399	23	recovered	yes	none
14/218	Mencevax	varicella	328	7	recovered	no	none
14/226	MENVEO	varicella	288	5	recovered	no	none
15/202	MENVEO	varicella	134[a]	<1-30	recovered	no	none
15/217	Mencevax	localized infection	399	4	recovered	yes	none
15/219	MENVEO	varicella	50	7	recovered	no	none
15/224	Mencevax	concussion	250	1	recovered	yes	none
15/226	Mencevax	varicella	249	7	recovered	no	none
16/223	Mencevax	varicella	133	<1-17	recovered	no	none
16/228	Mencevax	varicella	105	14-44	recovered	no	none
20/105	MENVEO	varicella	144	20	recovered	no	none
20/119	MENVEO	epiglottitis	223	2	recovered	yes	none
20/204	MENVEO	varicella	342	9	recovered	no	none
20/206	MENVEO	varicella	314	7	recovered	no	none
20/219	MENVEO	Nephrolith-iasis	235	63	recovered	yes	none
Study V59P8							
01/13440	Menomune	abdominal pain	7	2	recovered	yes	none
		appendicitis perforated	134	5	recovered	yes	none
		peritonitis	134	5	recovered	yes	none
01/13444	MENVEO	appendicitis	338	3	recovered	yes	none
01/14462	MENVEO	pneumonia	255	48	recovered	yes	none
		pleural effusion	258	45	recovered	yes	none
		empyema	261	42	recovered	yes	none

StudyV59P10							
11/043	MENVEO	pneumonia	55	10	recovered	yes	none
11/575	MENVEO	appendicitis	7	12	recovered	yes	none
11/645	MENVEO	injury	123	2	recovered	yes	none
12/010	MENVEO	febrile convulsion	2	2	recovered	yes	possibly related
12/067	MENVEO	pneumonia	31	19	recovered	yes	none
18/002	MENVEO	pneumonia	1	18	recovered	yes	none
20/557	MENVEO	asthmatic crisis	98	3	recovered	yes	none
20/568	MENVEO	tonic convulsion	1	1	recovered	yes	none
30/074	Menomune	lobar pneumonia	3	20	recovered	yes	none
30/577	MENVEO	appendicitis	140	3	recovered	yes	none
StudyV59P20							
20/0002	Menactra	pneumonia	101	23	recovered	yes	none
22/0003	MENVEO	bronchial hyperreactivity	61	3	recovered	yes	none
25/0030	MENVEO	pneumonia	159	3	recovered	yes	none
25/3035	Menactra	mouth cyst	177	<1	recovered	yes	none
26/0085	Menactra	excoriation	167	4	recovered	yes	none
26/3072	MENVEO	adrenal haematoma	87	4	recovered	yes	none
		loss of consciousness	87	<1	recovered	yes	none
		pneumothorax	87	4	recovered	yes	none
		rib fracture	87	4	recovered	yes	none
		skin laceration	87	4	recovered	yes	none
		traumatic liver injury	87	4	recovered	yes	none
		traumatic lung injury	87	4	recovered	yes	none
27/0006	MENVEO[b]	parvovirus infection	176	--	AE persist	yes	none
		intestinal obstruction	200	6	recovered	yes	none
29/3028	MENVEO	shigella infection	63	25	recovered	yes	none
30/3006	MENVEO	staphylococcalinfection	22	5	recovered	yes	none
33/0029	MENVEO	peritonsillar abscess	53	2	recovered	yes	none

33/0041	MENVEO	dehydration	94	2	recovered	yes	none
		pneumonia	94	8	recovered	yes	none
33/0073	MENVEO	dehydration	7	1	recovered	yes	none
34/0009	Menactra	arthritis bacterial	105	23	recovered	yes	none
		pyrexia	126	2	recovered	yes	none
34/0035	Menactra	inguinal hernia	20	4	recovered	yes	none
34/3005	Menactra	psychiatric symptom	156	--	AE persist	yes	none
46/0011	MENVEOb	bronchopneumonia	80	9	recovered	yes	none
56/0013	Menactra	viral infection	55	4	recovered	yes	none

Source: Summary of Clinical Safety, Section 2.7.4, Table 2.1.3-2

7.3.3 Dropouts

Table 27. Subject Disposition: Safety Population

StudiesV59P7[a],V59P8, V59P10, V59P20		**Total Enrolled**	**Safety Population**
2-5 years	**Total MENVEO[a]**	1968	1944 (99%)
	Menactra	696	684 (98%)
	Menomune	418	418 (100%)
	Mencevax	82	74 (90%)
6-10 years	**Total MENVEO[a]**	1237	1237 (100%)
	Menactra	574	571 (99%)
	Menomune	443	443 (100%)
2-10 years	**Total MENVEO[a]**	3205	**3181 (99%)**
	Menactra	1270	**1255 (99%)**
	Menomune	861	**861 (100%)**

Source: Summary of Clinical Safety, Section 2.7.4, Table 1.2-2
[a]Subjects who received one or two doses of MENVEO or Mencevax followed by MENVEO

In both age strata, both in the MENVEO and Menactra groups, lost to follow-up was the most common reason for withdrawal (range, <1% to 2%), while in the Menomune group, the most common reason for withdrawal in both age strata was “administrative reason” (3%). No subject in any vaccine or age group withdrew prematurely due to an AE within the 2 through 10 year old population.

7.3.4 Drug Interactions

For children 2 through 10 years of age, no data are available for evaluating safety and immunogenicity of other childhood vaccines when administered concomitantly with MENVEO.

7.4 Other Safety Findings

7.4.1 Local and Systemic Events

There were no episodes of anaphylaxis or immediate hypersensitivity reactions within 30 minutes following vaccination in any of the studies.

Table 28. Percentages of children 2 through 5 years reporting any (severe) local reactions after first/single meningococcal vaccination by study

	V59P7		V59P8		V59P10		V59P20	
	MENVEO	Mencevax	MENVEO	Menomune	MENVEO	Menomune	MENVEO	Menactra
Reaction	**1-3 and 1-7d N=224**	**1-3 and 1-7d N=74**	**1-3 and 1-7d N=151**	**1-3 and 1-7d N=153**	**1-3 and 1-7d N=451**	**1-3 and 1-7d N=265**	**1-3 and 1-7d N=1044**	**1-3 and 1-7d N=684**
Pain	33% (1, <1%)	45% (4%)	28% (1%)	20%* (0)	20%* (0)	26%* (0)	32% (1%)	35% (3,<1%)
Erythema >50mm	21% (1%)	16% (0)	15% (3%)	7% (0)	17%* (1%)	13% (0)	28% (7%)	25% (4%)
Induration >50mm	13% (1,<1%)	14% (0)	11% (2%)	3% (0)	13%* (0)	9% (0)	18% (2%)	18% (2%)

*Difference in percentage from 1-3 to 1-7d is 1-2%

Source: Summary of Clinical Safety, Section 2.7.4, Table 2.1.1.1-3

Across the four studies, the percentages reporting severe pain after MENVEO ranged between 0 and 1%. Across all studies and vaccine groups, in the majority of subjects aged 2 through 5 years, pain occurred within the first 3 days postvaccination: the percentages of subjects reporting severe pain were the same for days 1 to 7 vs. days 1 to 3. The percentages reporting severe erythema after MENVEO was higher than those observed for Menactra in study V59P20 (7% and 4%, respectively).

Table 29. Percentages of Children 2 through 5 years of age reporting any(severe) local reactions after 2nd Vaccination with MENVEO vs First Meningococcal Vaccination, studies V59P7 and V59P20

	V59P7			V59P20	
Vaccination	**1st**	**2nd**		**1st**	**2nd**
	MENVEO	**MENVEOx2**	**Mencevax/MENVEO**	**MENVEO**	**MENVEO**
Reaction	**1-3 and 1-7d N=217**	**1-3 and 1-7d N=217**	**1-3 and 1-7d N=74**	**1-3 and 1-7d N=333**	**1-73 and 1-7d N=333**
Pain	33% (1, <1%)	30% (0)	31% (0)	32% (1%)	28% (1%)
Erythema >50mm	22% (1%)	19% (1,<1%)	7% (0)	32% (8%)	22% (6%)
Induration >50mm	14% (1,<1%)	11% (1,<1%)	8% (0)	19% (2%)	13% (2%)

Source: Summary of Clinical Safety, Section 2.7.4, Table 2.1.1.1-4

Across the studies, vaccine groups, and injections, the most commonly reported local reaction was pain (range, any: 28% to 33%, severe: 0 to 1%). A general tendency towards decreased reports of local reactions was observed with the second vaccination.

This tendency was more evident for erythema and induration than for pain. With the exception of severe erythema (>50 mm) in study V59P20, (reported by 8% and 6%) of the MENVEO recipients after the first and second injection, respectively, reports of severe local reactions were infrequent across the studies, vaccine groups, and injections (range 0 to 2%). Across the studies, vaccine groups, and injections, in the majority of subjects, each of the three selected local reactions (any and severe) occurred within the first 3 days postvaccination: the difference in the percentages reporting local reactions of any severity on days 1 to 7 vs. days 1 to 3 ranged between 0 and 2%, while the respective percentages for severe local reactions were the same.

Table 30. Percentages of children 6 through 10 years reporting any (severe) local reactions after first/single meningococcal vaccination by study

	V59P8		V59P10		V59P20	
	MENVEO	**Menomune**	**MENVEO**	**Menomune**	**MENVEO**	**Menactra**
Reaction	**1-3 and 1-7d N=157**	**1-3 and 1-7d N=157**	**1-3 and 1-7d N=498**	**1-3 and 1-7d N=286**	**1-73 and 1-7d N=582**	**1-73 and 1-7d N=571**
Pain	34% (1%)	27%* (0)	27%* (0)	35% (1,<1%)	39%* (1%)	45%* (2%)
Erythema >50mm	17% (4%)	6%* (0)	18% (1%)	13% (0)	28%* (7%)	22% (2%)
Induration >50mm	17% (4%)	4%* (0)	17%* (2,<1%)	13%* (0)	17%* (2%)	13%* (2%)

*Difference in percentage from 1-3 to 1-7d is 1-2%

Source: Summary of Clinical Safety, Section 2.7.4, Table 2.1.1.1-5

Across the three studies, the percentages of 6 through 10 year olds reporting severe erythema during the 7 days following MENVEO ranged between 1% and 7%. In the majority of 6 through 10 year old subjects, severe erythema did not persist past study day 3. The percentages of subjects 6 to 10 years old reporting severe induration after MENVEO ranged between <1% and 4% and the highest percentage was observed after MENVEO in study V59P8 (4%), while they were lowest after Menomune (0%) in both study V59P8 and V59P10. Except for two subjects in study V59P20 (one in the MENVEO and one in the Menactra group), in all cases, severe induration occurred within the first 3 days postvaccination. There was no evidence of late onset or “second peak” of reactogenicity.

Systemic Reactions

During the 7-day reporting period following the first/single meningococcal vaccination, in the overall 2 through 10 years age population, across all vaccine groups, the most commonly reported systemic reaction was irritability, (range 11% to 22%), followed by sleepiness (9% to 18%), change in eating habits (10% in all three vaccine groups), malaise (8% to 12%), and headache (9% to 11%). The reporting rates for irritability and sleepiness following administration of MENVEO (18% and 14%, respectively) were

lower than those observed for Menactra but still higher than those observed for Menomune.

Overall, reports of severe systemic reactions were low and similar across the vaccine groups, No severe systemic reaction was reported by more than 1% of the subjects in any vaccine group. Across the vaccine groups, in the majority of subjects, systemic reactions (any and severe) occurred within the first 3 days postvaccination.

Fever:
No major difference in the percentages reporting fever was observed across the three vaccine groups. Reports of severe fever (i.e., temperature ≥39°C) were low and similar across the vaccine groups (<1% to 1%). A total of 4% of the MENVEO recipients reported fever, while 1% reported severe fever. In the majority of MENVEO subjects, fever (any and severe) occurred within first 3 days postvaccination.

Analgesic/Antipyretics:
No major difference in the percentages reporting use of analgesic/antipyretic medication was observed across the three vaccine groups. A total of 13% of the MENVEO recipients reported use of analgesic/antipyretic medication during the 7-day postvaccination. The majority of MENVEO subjects who used analgesic/antipyretic medication did so within the first 3 days postvaccination.

Stayed at home:
The percentages of subjects reporting having stayed at home due to a reaction were similar across the three vaccine groups. A total of 3% of the MENVEO recipients reported having stayed at home due to a reaction during the 7-day postvaccination period. The majority of MENVEO subjects who stayed at home due to a reaction did so within the first 3 days postvaccination.

Overall, the majority of systemic reactions reported following the first/single vaccination with MENVEO in the 2 through 10 years population were mild to moderate in severity and transient induration.

Overall, reports of severe systemic reactions were low and similar across the vaccine groups. No severe systemic reaction was reported by more than 1% of the subjects in any vaccine group. Severe fever was reported by no more than 2% of the subjects in any study or vaccine group. The percentages of MENVEO recipients reporting use of analgesic/antipyretic medication during the 7-day postvaccination period ranged between 10% and 25%. Having stayed at home due to a reaction was only solicited and reported in studies V59P8 and V59P20. The percentages of 2 through 5 year olds reporting having stayed at home due to a reaction on days 1 to 7 were low and similar across the two studies and vaccine groups (range, 2% to 4%). The majority of MENVEO 2 through 5 yo subjects reported their systemic reaction within the first 3 days postvaccination.

A second dose of meningococcal vaccine was administered in the 2 through 5 years age group in studies V59P7 and V59P20. Across the studies and vaccine groups, the systemic reactions most commonly reported during the 7 days postvaccination were irritability, sleepiness and change in eating habits. The percentages reporting each of the selected systemic reactions after the second dose of vaccines were either similar or lower compared with those observed after the first dose. No increase in the percentages reporting fever was observed when a second dose of meningococcal vaccine was administered in the 2 through 5 years age group. Overall there was a tendency towards a decrease in the percentages reporting use of analgesic/antipyretic medication was observed after the second injection. Having stayed at home due to a reaction was not solicited in study V59P7. In study V59P20, similar percentages of subjects reported having stayed at home due to a reaction during the 7-day period following the first and second MENVEO injections (3% and 2%, respectively).

The most frequently reported systemic reaction during the 7 days following a single meningococcal vaccine administered in the 6 to 10 year age group overall was headache (range, 11% to 19%), followed by malaise (range, 6% to 14%) and myalgia (range, 3% to 10%). Severe headache was reported infrequently, and wast reported most frequently in MENVEO recipients in study V59P8 (2%). Across the studies and vaccine groups, severe fever was infrequent (range, 0 to 1%). The majority of subjects reporting fever did so within the first 3 days postvaccination. During the 7 days following a single meningococcal vaccination administered to 6 to 10 year old in studies V59P10 and V59P20, the percentages reporting use of analgesic/antipyretic medication were similar between MENVEO and comparator vaccines.

Having stayed at home due to a reaction was solicited and reported in studies V59P8 and V59P20 only. The percentages of children aged 6 through 10 years reporting having stayed at home due to a reaction on days 1 to 7 were low and similar across the two studies and vaccine groups (range, 2% to 4%). In all three studies contributing data for the 6 through 10 age group, the majority of systemic reactions reported after a single dose of MENVEO were mild to moderate in severity and transient in duration.

Unsolicited Events

Overall, the reporting rates observed in the 6 through 10 years age group for unsolicited AEs irrespective of relatedness were lower than those observed in the younger, 2 through 5 years age group, while the rates observed for possibly or probably vaccine-related unsolicited AEs were similar in the two age strata.

Table 31. Percentages of subjects reporting unsolicited AEs within 1 Month of meningococcal vaccination by age group, pooled analysis

	2-5 years					
	1 Month after1stVaccination				1 Month after2nd Vaccination	
	MENVEO N=1870	Menactra N=684	Menomune N=418	Mencevax N=74	MENVEO/ MENVEO N=550	Mencevax/ MENVEO [b] N=74
AnyAE	24%	20%	22%	N/A	19%	19%
At least possibly related AEs	4%	5%	3%	N/A	2%	1%
	6-10 years (1 Month after Single Vaccination)					
	MENVEO N=1237		Menactra N=571		Menomune N=443	
Any AE	16%		14%		13%	
At least possibly related AEs	4%		5%		2%	
	2-10 years (1 Month after First or Single Vaccination)					
	MENVEO N=3107		Menactra N=1255		Menomune N=861	
Any AE	21%		18%		18%	
At least possibly related AEs	4%		5%		3%	

Source: Summary of Clinical Safety, Section 2.7.4, Table 2.1.1.2-1

Severe AEs assessed as possibly vaccine-related were reported only for one subject after the first dose of MENVEO (nausea and mood swings) and for one subject after the second dose of MENVEO (injection site erythema).

7.5 Safety Conclusion

In the clinical trials in children 2 through 10 years of age, the safety profile of MENVEO was similar to that of the licensed comparator vaccine, Menactra. No major safety issues were identified. Careful review of SAEs revealed two probably or possibly related SAEs in MENVEO recipients in study V59P10. Both were seizure episodes that occurred in close association with vaccine administration and resolved without sequelae. Review of the remaining SAEs did not raise concerns of causality.

Overall the safety profiles of MENVEO and the U.S-licensed comparator conjugate vaccine Menactra, had similar rates of solicited and unsolicited local and systemic events A moderate increase in local and systemic reactogenicity was observed in comparison to the licensed polysaccharide vaccine Menomune, but most reactions were mild and resolved within less than 3 days. Additionally, the reports of severe local or systemic reactions were low and similar across the vaccine groups at $\leq$1% except in supportive study V59P7 where 8% SAEs were reported (primarily due to an outbreak of varicella). No AEs were reported to have led to subject withdrawal in any of the four

studies within the 2 through 10 years age group. No death occurred in any of the four studies used to support this application.

8 Overview of Immunogenicity Across Trials

The immunogenicity profiles of the final MENVEO formulation are based on four studies; 1 pivotal study and 3 supportive studies:

- V59P20, a phase 3, randomized, observer-blind, controlled, multi-center pivotal study conducted in the US and Canada in children ages 2 through 10 years, using a US-licensed control vaccine, Menactra.
- V59P7, phase 2, randomized, observer-blind, multi-center, active controlled supportive study conducted in Finland and Poland in children ages 1 through 5 years of age, using the control vaccine Mencevax which is not licensed in the U.S., and a study arm using a non-final formulation ----(b)(4)------ MENVEO which is not further discussed in this clinical review.
- V59P8, is a phase 2, randomized, single-blind, controlled, single-center study conducted in the US in children ages 2 through 10 years of age, using a US-licensed control vaccine, Menomune.
- V59P10, a phase 3, randomized, observer-blind, controlled, multi-center study conducted in Argentina in children ages 2 through 10 years, using a US-licensed control vaccine, Menomune.

8.1 Methods

The study designs, methodologies, and study populations were basically the same among the studies. 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. Exceptions are listed below:

- Data from toddlers in studies V59P7 and V59P8 are not included in this clinical review as these children are outside the 2 through 10 years age range.
- In supportive study V59P7, Mencevax is not licensed in the U.S., hence the safety and immunogenicity data from this study were not considered comparative for this clinical review.
- Additionally, study V59P7 included study arms containing non-final formulation ----(b)(4)------ of MENVEO which are not further discussed in this clinical review.
- The ethnic origins of subjects varied in the studies.

8.2 General Discussion of Efficacy Endpoints

Three studies investigated safety and immunogenicity of MENVEO compared with a US-licensed control meningococcal conjugate vaccine Menactra or Menomune. The immunogenicity data were assessed for all vaccinated subjects with a prevaccination and post-vaccination blood draw and without any major protocol deviation, as defined before unblinding.

Table 32. Definitions of Endpoints

Endpoint	Endpoint Definitions
Seroresponse	For subjects with prevaccination hSBA <1:4 (seronegatives), seroresponse was defined as postvaccination titer ≥1:8. For subjects with prevaccination hSBA ≥1:4 (seropositives), seroresponse was defined as postvaccination titer ≥4 times the prevaccination titer.
hSBA ≥1:4	Percentage of subjects achieving an hSBA titer ≥1:4
hSBA ≥1:8	Percentage of subjects achieving an hSBA titer ≥1:8
GMT	Geometric mean hSBA titer

Source: Summary of Clinical Efficacy, Section 2.7.3, Table 1-2

8.3 Study Design

In all four studies, sera were obtained on study day1 and day 29 post immunization. In supportive studies V59P10 and V59P8, sera were collected at 6 months and 12 months post vaccination, respectively. In pivotal study V59P20 sera were also collected on study day 89 in the group of subjects who received 2 doses of MENVEO. All serum samples were sent to the centralized Novartis laboratory ----------(b)(4)---------- to assess the immune response against the meningococcal vaccines using a validated human serum bactericidal assay (hSBA).

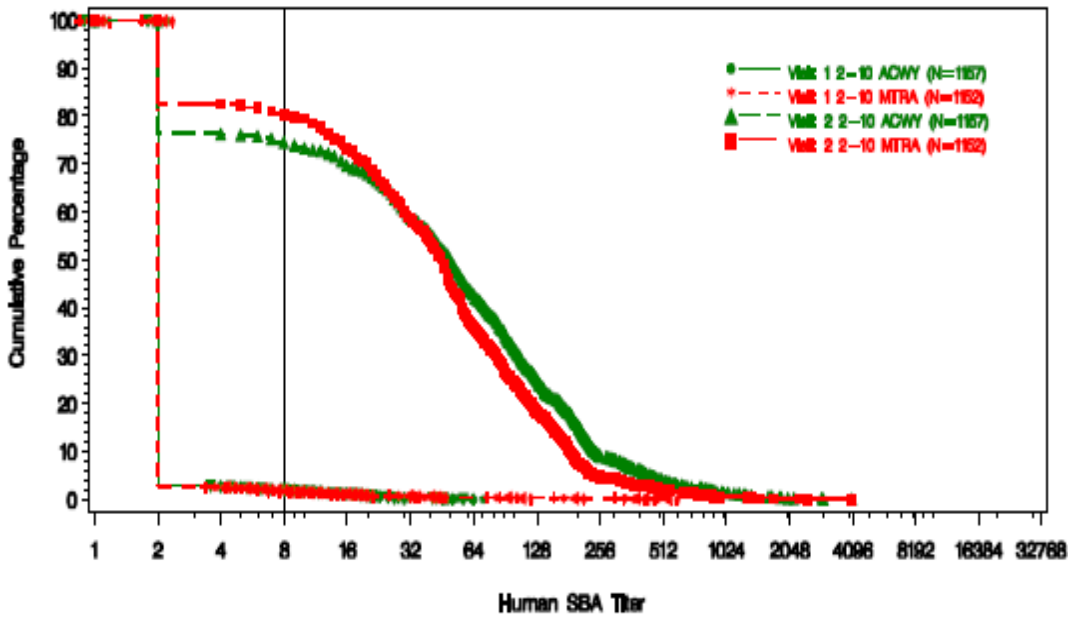
8.4 Immunogenicity Findings

Across the four studies, a total of 1801 subjects aged 2 through10 years in the per protocol population, provided immunogenicity data on MENVEO for analysis from 1 pivotal study (V59P20) and 3 supportive studies (V59P7, V59P8, V59P10). In the 2 through 5 years age group, 1023 received MENVEO and 778 children aged 6 through10 years received MENVEO. For comparator vaccines, 1161 subjects provided immunogenicity data for Menactra, and 433 provided immunogenicity data for Menomune. Although four studies evaluated the immunogenicity of MENVEO, the pivotal study V59P20 is the one considered most critical to establish vaccine immunogenicity in children 2 through10 years old.

The four studies reviewed were conducted in different countries and in one study (V59P7) the subjects who participated were 2 through 5 years old. Overall, a pre-immunization hSBA of ≥1:4 was observed most frequently for serogroup W and least often for serogroup A. This is consistent with results from the studies with older populations (11-55 years of age) reviewed in the BLA.

In general, the results post-vaccination across the four studies met non-inferiority criteria and showed a higher immune response demonstrated by more than a single endpoint (i.e. seroresponse, hSBA ≥ 1:8, GMTs), for subjects vaccinated with MENVEO than with the US-licensed comparators used in these studies (Menomune, Menactra) across all four serogroups (A, C, W, and Y) The notable exception to this pattern was for serogroup A in the pivotal study (V59P20). In that study non-inferiority was achieved in the combined age group analysis (i.e., subjects 2-10 years of age), but narrowly missed non-inferiority in the separate age groups (2-5 and 6-10 years of age). In this study, the hSBA GMTs and the reverse cumulative distribution curves for the two vaccines were similar.

Figure 1. Reverse Cumulative Distribution Curve of hSBA for Serogroup A, Study V59P20, 2 through 10 Years of Age, PP Population



Source: CSR Section 5.3.5.1.1. study V59P20 Figure 14.2.2-3

For subjects 2 through 5 years of age, the percentages of hSBA seroresponders across studies mirrored the results for all subjects 2 through 10 years of age. Subjects that received MENVEO had non-inferior hSBA responses in comparison to comparator vaccines in all four studies for serogroups C, W, and Y, and in three of the four studies for serogroup A (not observed in study V59P20).

Overall, for all subjects 6-10 years of age, the percentages of hSBA seroresponders mirrored the results for all subjects 2 through 10 years of age and the 2 through 5 years of age subgroup. Subjects that received MENVEO had non-inferior hSBA responses in comparison to the comparator vaccines in all four studies for serogroups C, W, and Y, and in three of the four studies for serogroup A (not observed in studyV59P20).

2 doses vs 1 dose:
The data presented in this application indicate that a single dose of MENVEO provides a similar immune response to the currently licensed meningococcal conjugate vaccine currently licensed for a single dose administration in children 2 through 10 years of age. However, as a secondary end-point, the immune response to a second dose was analyzed in studies V59P7 and V59P20. As expected, 2 doses elicited a stronger immune response than 1 dose in both studies across all 4 serogroups. In study V59P20, the percentages of subjects with seroresponse were statistically significantly higher one month after receiving a second vaccination than they were 1 month after vaccination in the single dose group for all four serogroups (A: 91% vs 72%; C: 98% vs 60%; W: 89% vs 72%; Y: 95% vs 66%). Similar results were obtained when the immune response was measured by the percentages of subjects with hSBA ≥ 1:8 and hSBA GMTs. These differences were highly statistically significant for each serogroup. In study V59P7, 199 subjects aged 2 to 5 years received a first vaccination with MENVEO and then received a second vaccination with MENVEO either 6 or 12 months later. Overall, immune responses to a second vaccination were higher than to a first vaccination for all serogroups, and higher the further the first and second doses were spaced apart.

Persistence of Immunogenicity:
Within the 2-10 years of age range, persistence of serum bactericidal activity was investigated in studies V59P7, V59P8, and V59P10. Immune responses were assessed at 6 or 12 months post-vaccination in children 2-5 years of age in V59P7, 12 months after vaccination in children 2-10 years of age in V59P8, and 6 months after vaccination in children 2 through10 years of age in study V59P10.

In study V59P7, the persistence of hSBA titers at 6 months postvaccination following a single dose of MENVEO in 2 through 5 year old participants dropped by 7%, 10% and 10% for serogroup C, W and Y, respectively, but decreased significantly for serogroup A by 59%. In study V59P8, the 12 month hSBA antibody persistence after a single vaccination with MENVEO or Menomune remained relatively close to the values at 1 month post-vaccination for serogroups W (92% vs 90% at 1 month and 12 months, respectively) and Y (88% vs 77%) and decreased for A and C. In study V59P10, the persistence of a single vaccination with MENVEO at 6 months vs 1 month post-vaccination in children 2 through 10 years of age decreased slightly for serogroups C, W and Y (by 7%, 3% and 0%, respectively) whereas the percentage of subjects with detectable hSBA titers dropped significantly for serogroup A from 95% to 35%.

8.1 Immunogenicity Conclusion

Overall, the immunogenicity data from the pivotal and supportive studies indicate that MENVEO is immunogenic and stimulates functional antibody responses in children 2 through 10 years of age. The immunogenicity of MENVEO is similar to that of the currently licensed quadrivalent vaccine Menactra, although in the pivotal study lower responses were observed for serogroup A and higher responses were observed for serogroups Y and W-135. The comparator vaccine in the pivotal study is indicated for use in the 2 through 10 year age group as a single dose vaccine. This supplement contained immunogenicity data that showed an immunologic benefit to receipt of a second dose in the 2 through 5 year old age group. Although the indication sought was for a single dose in children 2 though 10 years of age, the two dose data were considered clinically relevant. Therefore, the safety and immunogenicity of two doses administered to children 2 through 5 years of age was included in the package insert with permissive use of a second dose for children at continued high risk of meningococcal disease stated in the dosage and administration section.

9 Conclusions – Overall

The clinical data provided in this supplement demonstrate that MENVEO has a similar safety profile and similar immunogenicity to the licensed meningococcal conjugate vaccine Menactra in children 2 through 10 years of age.

10 Recommendations

10.1 Approval, Non-approval, Conditions

- The safety and immunogenicity data provided in this application support a recommendation for approval of MENVEO for use in individuals 2 through 10 years of age for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W-135 and Y.

- The hSBA responses following a two dose regimen in children 2 through 5 years of age are substantially higher for each serologic end-point: proportion above the threshold of 1:8 hSBA, seroresponse and GMT, for all 4 serogroups. The difference in immunogenicity between a single dose regimen and a two dose regimen is considered clinically relevant. Although the two dose regimen was evaluated in an unblinded manner in the clinic, it was a randomized group and the comparison was a pre-defined secondary objective of the pivotal study. The safety data and the immunogenicity data should be presented in the label with permissive

language for administration of a second dose 2 months after the first dose in children 2 through 5 years of age who are at continued high risk of meningococcal disease.

- Statements regarding statistically higher immune responses, currently in the label for adolescent and adult immunogenicity, should be removed. Statistical and clinical rationale for removal was conveyed to the sponsor.

10.2 Recommendations on Postmarketing Actions

- Further evaluation of a 2 dose regimen of MENVEO is needed. The available data do not address: 1) whether older children (6 through 10 years of age) can benefit from a 2-dose regimen; 2) the need for revaccination (antibody persistence) of children 2 through 10 years of age; 3) safety of two dose regimens in the pediatric population. To address these limitations of the available data, a post marketing study is recommended.

- No safety signals were identified that should be specifically examined in post marketing studies. However, because the total safety experience in the 2 through 10 year age group is insufficient to detect and characterize uncommon and rare adverse events of medical significance, a post marketing study to extend the safety experience is recommended.

10.3 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) have been conveyed to the applicant.