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

Statistical Review and Evaluation
BLA STN 125300/95

BLA/Supplement Number:	BLA STN 125300/95
Product Name:	MENVEO (or MenACWY referred in the submission)
Indication(s):	Active immunization to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135.
Applicant:	Novartis Vaccines & Diagnostics, Inc.
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1. EXECUTIVE SUMMARY

Menveo®(also referred to as MenACWY), by Novartis Vaccines and Diagnostics Inc., is a meningococcal (Groups A, C, W-135, and Y) CRM_{197} oligosaccharide conjugate vaccine for prevention of invasive meningococcal disease caused by *Neisseria meningitides*, serogroups A, C, W-135, and Y bacteria. The vaccine was approved for license for use in subjects 11-55 years of age in the U. S. by FDA on February 19, 2010. Following the initial approval of Menveo®, Novartis submitted a supplement Biologics License Application (sBLA) STN 125300 Amendment 95 on March 31, 2010 to seek an extension of the use of Menveo® vaccine in children 2 through 10 years of age.

1.1 Brief Overview of Clinical Studies

The applicant submitted safety and immunogenicity data in four clinical trials in children aged 2 through 10 years to support this proposed expansion of licensure of Menveo®. The four clinical trials include one pivotal clinical study (V59P20) conducted in the US and Canada and three supportive studies conducted in various countries (V59P7, V59P8, and V59P10). The description of the studies is listed in Table 1.

Table 1: Description of Clinical Studies

Study	Location	Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration (*N*)	Health Subjects (N)	Number of MenACWY Injections
V59P7	Finland, Poland	Safety and Immune Response of MenACWY ---------(b)(4)---------- vs Mencevax™	Observer-Blind, Randomized, Active Controlled Phase 2 Multi-Center Study	– MenACWY 10-5-5-5µg (b)(4) IM (*N=205*) – MenACWY 10-5-5-5µg (b)(4) IM (*N=331*) – Mencevax™ IM followed by MenACWY 10-5-5-5µg (b)(4) IM (*N=81*)	Toddlers 12-35 m Childern 36-59 m	Two
V59P8	US	Safety and Immune Response of MenACWY vs Menomune™	Single-Blind, Randomized, Active Controlled Open-Label in Toddlers Phase 2 Single-Center Study	– MenACWY 10-5-5-5µg (b)(4) IM (*N=453*) – MenACWY 10-5-5-5µg (b)(4) (+ PnC) IM (*N=71*) – MenACWY 10-5-5-5µg (b)(4) (+ DTaP) IM (*N=73*) – Menomune™ SC (*N=310*)	Children 2-10 y Toddlers 12-23 m	One
V59P10	Argentina	Safety and Immune Response MenACWY vs Menomune	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– MenACWY 10-5-5-5µg (b)(4) IM (*N=949*) – Menomune™ SC (*N=551*)	Children 2-10 y	One
V59P20	US, Canada	Safety and Immune response to MenACWY vs Menactra®	Observer-Blind, Randomized, Active Controlled Phase 3 Multi-Center Study	– MenACWY 10-5-5-5µg (b)(4) IM (*N=1635*) – Menactra® (*N=1263*)	Children 2-10 y	One or Two

1.2 Conclusions, Major Statistical Issues and Recommendations

The objective of this application is to provide evidence of the non-inferiority of immunogenicity and safety of MenACWY compared to the US-licensed meningococcal ACWY conjugate vaccine Menactra® when administered to healthy children 2 through 10 years of age.

The pivotal study (Study V59P20) conducted in U.S. and Canada was designed to evaluate and ideally demonstrate the non-inferiority of Menveo® to Menactra®, an approved comparator in both the 2-5 years and 6-10 years age groups for serogroups A, C, W-135, and Y. The study results indicated that non-inferiority was demonstrated for the primary immunogenicity endpoint, seroresponse at one month after a single vaccination, for serogroups C, W-135, and Y. However, for serogroup A, the non-inferiority criterion was narrowly missed, i.e., the lower bounds of the 95% confidence interval for the difference in seroresponse for Serogroup A between the Menveo and the Menactra® groups (Menveo-Menactra) were slightly below the pre-specified non-inferiority margin of -10% for both of the age groups (-10.1% and -10.8% for the 2-5 years and 6-10 years age groups, respectively. See Table 6).

Three secondary objectives concerning various endpoints were examined in Study V59P20. When the endpoints were proportions of subjects achieving a post-vaccination titer of ≥1:4 or ≥1:8 in age groups 2-5 years and 6-10 years, the conclusions were similar to those based on the seroresponses (primary objective) described above, i.e. non-inferiority was not strictly met. However, the secondary objective of non-inferiority measured by geometric mean titers (GMTs) was met in both age groups for all the serogroups. In addition, two other secondary objectives were met. Specifically, when the seroresponse data were compared among children 2 through 10 years of age, i.e., the 2-5 years and 6-10 years were combined, the non-inferiority criteria measured by seroresponse were met. The combination of both age groups likely met the non-inferiority criterion because of the larger sample size which narrowed the confidence interval. Finally, another secondary objective in which the seroresponse rates were compared between the two-dose and one-dose Menveo® groups (see Table 8), the seroresponse rates were notably higher after two doses of Menveo® (91%-98%) than those after a single dose of Menveo® (60%-72%). The secondary objective of establishing the non-inferiority of the two-dose group to the single dose group was met.

The safety profile of Menveo® was evaluated in all four studies. A total of 3,181 children aged 2-10 years were exposed to Menveo®. The overall serious adverse event rates (see Table 21) were around 0.6% (excluding the events related to the varicella among the unvaccinated subjects in Study V59P7). Only one of the SAEs (a subject in Study V59P10 experienced febrile convulsion two days after vaccination) was considered to be possibly related to vaccine. All other SAEs were considered not related to vaccine. For local and systemic reactogenicity, pain was the most reported local reaction (20% to 45%). The event rates for Menveo® varied by study but the majority of them were comparable with the reference groups (the rate differences were within 3%). In Study V59P20, it appears that there was an increase in event rates for erythema (>50mm) and headache in the children 6-10 years of age in the Menveo® group when compared to the Menactra™ group. Please refer to the clinical review for more safety details and assessment of clinical significance of some of the observed differences.

RECOMMENDATIONS:

A regulatory decision based on this submission depends on evaluation of the clinical significance of these findings. It is important to note that the non-inferiority margin of -10% for seroresponse was nearly met when examining the 2-5 and 6-10 year old individuals, with observed lower confidence limits of -10.1% and -10.8%, respectively.

An observed trend that may deserve future consideration is that within a small subset of the subjects in the pivotal study, a second dose of Menveo® administered two months after the first vaccine provided a noticeable increase in seroresponse when compared to the one dose group. Additional studies on dosing interval, persistence of antibody response, and further safety monitoring might be desirable if an indication for two doses may be requested in the future.

2. INTRODUCTION

2.1 Overview

Menveo® is a sterile liquid vaccine, administered by intramuscular injection, that contains N. meningitidis serogroups A, C, W-135, and Y oligosaccharides conjugated individually to C. diphtheriae CRM_{197} protein carrier. The vaccine is intended for prevention of invasive meningococcal disease caused by Neisseria meningitides, serogroups A, C, W-135, and Y bacteria. The vaccine was approved for use in individuals 11-55 years of age in the U. S. by the FDA on February 19, 2010. Following the approval, on March 31, 2010 Novartis submitted a supplement Biologics License Application (sBLA) STN 125300/95 to seek an extension of the use of Menveo® vaccine in children 2 through 10 years of age.

Four clinical studies were included in the submission to support the applicant's proposal for licensure:

- V59P20: 2-10 years of age (N=1278)
- V59P10: 2-10 years of age (N=950)
- V59P8: 2-10 years of age (N=309)
- V59P7: 2-5 years of age (N=228)

The immunogenicity data presented in this sBLA submission were intended to assess the following key objectives in the studies with US-licensed comparator vaccines:

- Compare the functional immune response from a single dose of MenACWY or Menactra® in children aged 2-10 years (V59P20);
- Compare the functional immune response from a single dose of MenACWY or Menomune® in children aged 2-10 years (V59P8 and V59P10).

The data also permitted the applicant to assess the following secondary objectives:

- Compare the immune response from 1 vs 2 doses of MenACWY in children aged 2-5 years (V59P20). The response to 2 doses was also assessed in V59P7, although it was not a declared objective.
- Assess the immune response to a booster dose of MenACWY administered at 12 months following a single dose of MenACWY or Mencevax® in children aged 2-5 years (V59P7)
- Assess the persistence of immune response at 6 or 12 months following a single dose of MenACWY (V59P7, V59P8, and V59P10).

2.2 Data Sources

This review is based on the clinical study reports (CSRs) for the pivotal study (V59P20) and three supportive studies (V59P7, V59P8, and V59P10). Various SAS transport datasets are used for verification of the results and the statistical reviewer's independent analyses. The CSRs and SAS datasets as well as other related materials were provided by the applicant at the time of the sBLA submission (STN 123500/95) dated March 31, 2010 and were primarily located in Module 5 of the eCTD submission package ("m5-clinical-study-reports").

The key materials reviewed include (but are not limited to):
- m1-1-14-labeling
- m2-5-clinical-overview
- m2-7-clinical-summary
- m5-3-5-reports of efficacy and safety studies
- Key (but not limited to) Datasets: DEMOG, ADVERSE, IMMUN, POP, PROTDEV, LABDATA

A full statistical review was performed based on immunogenicity and safety data in Study V59P20. The primary objective of the submission was to seek an expansion of the license of the product, Menveo®. The statistical review will address results from the primary study (V59P20) as well as key information submitted in support of the new label claims also directly relevant to this study. Relevant review and comments may also be based on the supportive studies and will be noted in this statistical review.

3. STATISTICAL EVALUATION

To be consistent with the vaccine name used in the clinical study reports submitted by the applicant, Menveo® is also referred to as MenACWY in the following review sections. For convenience, some tables or graphs presented in the submission may be used and noted in the footnotes, if applicable.

3.1 Evaluation of Immunogenicity in Pivotal Study V59P20

3.1.1 Study Design and Endpoints

This trial was designed as a Phase III, multi-center, observer-blind, randomized study to evaluate the safety and immune response at one month following vaccination with one dose of either MenACWY or Menactra® in healthy children 2 through 10 years of age. The study was

designed to also explore, in an open-label format, the immune response in children 2 to 5 years of age after a second vaccination of MenACWY at least 2 months after the first vaccination of MenACWY. The overall study design is shown in Table 2. The randomization was stratified by age with the following targets per age stratum: children 2-5 years of age (planned sample size, N = 1700), and children 6-10 years of age (planned sample size, N = 1120). Subjects 2 through 5 years of age were randomized in a 1:2:2 ratio to receive either 2 doses of MenACWY, one dose of MenACWY, or one dose of Menactra®. The subjects ages 6 through 10 years old were randomized in a 1:1 ratio to receive a single dose of either MenACWY or Menactra®. The study was conducted within the US and Canada at 67 study centers.

Table 2: Study Design and Plan/Actual in V59P20

Vaccine Group	Age group	Subjects Enrolled (Planned/ Actual)	Day 1	Day 29	Day 61	Day 89
I	2-5 Years	340/359	MenACWY (blood draw)	n/a	MenACWY	(blood draw)
II	2-5 Years	680/696	MenACWY (blood draw)	(blood draw)	n/a	n/a
III	2-5 Years	680/696	Menactra (blood draw)	(blood draw)	n/a	n/a
IV	6-10 Years	560/582	MenACWY (blood draw)	(blood draw)	n/a	n/a
V	6-10 Years	560/574	Menactra (blood draw)	(blood draw)	n/a	n/a

Source: Table 9.1-1 on Page 44 in the applicant's Clinical Study Report for V59P20.

The immunogenicity was measured by the ability of MenACWY vaccine to elicit functional bactericidal antibodies against each serogroup in the presence of human complement (human Serum Bactericidal Activity, hSBA).

The primary objective was 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 directed against *N. meningitidis* serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy children 2 to 5 and 6 to 10 years of age. Seroresponse was defined as a post-vaccination hSBA titer of 1:8 or greater if the subject's pre-vaccination hSBA titer was <1:4; or a ≥ four-fold increase over baseline at post-vaccination if the subject's pre-vaccination hSBA titer was ≥1:4. The success criteria for this study were based upon these primary objectives for the per protocol population. This study was to be considered a success if, for both age strata and for all four serogroups, the lower limits of the two-sided 95% confidence intervals around the differences (MenACWY-Menactra®) in the percentage of subjects with seroresponse were greater than -10%.

Three pre-specified secondary objectives included:

- 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;
- 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 GMTs directed against N. meningitides serogroups A, C, W-135, and Y, at 1 month after vaccination, when administered to healthy subjects 2 to 10 years of age;
- 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 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.

Reviewer's comments:

- *The primary objective was changed to measure seroresponse within each age group (2-5, 6-10) in the amendment (dated Jan. 28, 2008) rather than in the total group of children aged 2-10 in the original protocol (dated Sept. 20, 2007). As a result, the targeted sample size increased from 1418 to approximately 2820 healthy children.*
- *Subjects in the two-dose MenACWY group (Group I) were administered the vaccine in an open-label fashion. There was no control group or complete blinding mechanism applied to this treatment group. Therefore, these features need to be considered when interpreting results for the subjects in this treatment group.*

3.1.2 Statistical Methodologies

The null and alternative hypotheses for the primary non-inferiority objectives concerning proportion of subjects with response were:

H_0: $(P_{MenACWY} - P_{Menactra}) \leq -10\%$ for serogroups A, C, W-135, or Y
H_A: $(P_{MenACWY} - P_{Menactra}) > -10\%$ for serogroups A, C, W-135, and Y,

where $P_{MenACWY}$ was the proportion of MenACWY subjects and $P_{Menactra}$ was the proportion of Menactra® subjects with seroresponse at 1 month after vaccination. The two-sided 95% CIs for each serogroup for the difference in proportions (MenACWY - Menactra®) were constructed. If the CI was entirely to the right of -10%, then noninferiority was declared for that serogroup.

Immunogenicity of MenACWY is considered non-inferior to the immunogenicity of Menactra® in both age groups (2-5 years, 6-10 years), for any of the four serogroups, if the lower limit of the two-sided 95% CI around the difference in the percentage of subjects with seroresponse for that serogroup (MenACWY minus Menactra®) is greater than -10%. If the CI is entirely to the right of -10%, then non-inferiority is declared for that serogroup. Moreover, if the CI is entirely to the right of 0%, then the MenACWY serogroup is considered to have a

statistically significantly higher immune response compared to that same serogroup of Menactra®. The combined hypothesis testing for non-inferiority and statistical superiority does not require any adjustment for multiplicity. The success criteria for this study are based upon only the primary objective for the per protocol population. The study is considered a success if all four serogroup analyses meet the non-inferiority criteria identified for the endpoint noted above.

The immunogenicity response was also measured by geometric mean titers (GMTs) as stated in the secondary objectives. MenACWY was considered non-inferior to the immunogenicity of Menactra®, in any of the age groupings, if the lower limit of the two-sided 95% CI around the ratio of hSBA GMTs between MenACWY and Menactra®, one month after vaccination, was greater than 0.5.

Reviewer's comment:

- *The applicant considered statistical tests for both non-inferiority and superiority in this study. The planned sample size (N=680 per group for 2-5 years; N=560 per group for 6-10 years) was powered to test for non-inferiority.*

3.1.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 2907 healthy children 2 to 10 years of age were randomly assigned to either MenACWY or Menactra®. The randomization was stratified by age with the following targets per age strata: children 2 to 5 years of age (n = 1751), and children 6 to 10 years of age (n = 1156). 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 MenACWY, one dose of MenACWY, 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 MenACWY or Menactra®. A total of 2898 subjects were vaccinated (356 in the MenACWY 2-dose group, 1279 received MenACWY and 1263 were administered Menactra®). A total of 105 subjects withdrew prematurely from the study, while 2802 completed the protocol. Of the 105 subjects who withdrew prematurely, 26 were in the MenACWY 2-dose group, 51 were in the 2 to 5 year age group (27 in the MenACWY group and 24 in the Menactra® group), while 28 were in the 6 to 10 year age group (11 in the MenACWY group and 17 in the Menactra® group). The overview of the study population is presented in Table 3.

The primary analysis is based on the per-protocol (PP) population of 2628 subjects. A total of 279 subjects were excluded due to major protocol deviations, including pre or post vaccination blood draw, post-vaccination blood draw out of window, and prior vaccination with less than four DTP-containing vaccines. The rate of observed deviations was similar between the MenACWY and Menactra® groups. Overall, about 11% of the enrolled subjects in each of the MenACWY and Menactra® groups in the 2-5 year old group were excluded from the PP population. Likewise, 5% of the enrolled subjects in each of the MenACWY and Menactra® groups in the 6-10 year old group were excluded from the PP population. A summary of early terminations is provided in Table 4.

The demographic and other baseline characteristics for the PP population are presented in Table 5. It can be observed that these characteristics were similar among the MenACWY 2-dose, MenACWY and Menactra® groups within each age group.

Table 3: Overview of Study Population in V59P20

	2-5 Years			6-10 Years		2-10 Years	
Population	**MenACWY 2-doses**	**MenACWY**	**Menactra**	**MenACWY**	**Menactra**	**MenACWY**	**Menactra**
Randomized	359	696	696	582	574	1278	1270
Exposed (%)	356 (99)	696 (100)	691 (99)	583 (100)	572 (100)	1279 (100)	1263 (99)
Safety (%)	351 (98)	693 (100)	684 (98)	582 (100)	571 (99)	1275 (100)	1255 (99)
Safety - 6 Month Follow-up (%)	335 (93)	672 (97)	675 (97)	573 (98)	558 (97)	1245 (97)	1233 (97)
MITT (%)	315 (88)	636 (91)	641 (92)	565 (97)	557 (97)	1201 (94)	1198 (94)
Per Protocol (%)	297 (83)	616 (89)	619 (89)	554 (95)	542 (94)	1170 (92)	1161 (91)

Note: The percentages in parentheses were based on the number of subjects randomized within the treatment group.
Source: Table 11.1-1 on Page 76 of the applicant's Clinical Study Report for V59P20.

Table 4: Summary of Study Termination

	2-5 Years			6-10 Years		2-10 Years	
	MenACWY 2-doses	**MenAC WY**	**Menactra**	**MenACWY**	**Menactra**	**MenAC WY**	**Menactra**
Total Number Of Subjects Enrolled	359	696	696	582	574	1278	1270
Completed	333 (93%)	669 (96%)	672 (97%)	571 (98%)	557 (97%)	1240 (97%)	1229 (97%)
Completed Protocol	333 (93%)	669 (96%)	672 (97%)	571 (98%)	557 (97%)	1240 (97%)	1229 (97%)
Premature Withdrawal	26 (7%)	27 (4%)	24 (3%)	11 (2%)	17 (3%)	38 (3%)	41 (3%)
Withdrawal Of Consent	9 (3%)	9 (1%)	7 (1%)	2 (< 1%)	1 (< 1%)	11 (< 1%)	8 (< 1%)
Lost To Follow-Up	12 (3%)	18 (3%)	16 (2%)	8 (1%)	14 (2%)	26 (2%)	30 (2%)
Inappropriate Enrollment	3 (< 1%)	0	1 (< 1%)	0	0	0	1 (< 1%)
Administrative Reason	1 (< 1%)	0	0	0	0	0	0
Protocol Deviation/Violation	0	0	0	1 (< 1%)	2 (< 1%)	1 (< 1%)	2 (< 1%)
Unable To Classify	1 (< 1%)	0	0	0	0	0	0

Source: Table 14.1.1.2 on Page 119 of the applicant's Clinical Study Report for V59P20.

Table 5: Demographic and Other Baseline Characteristics: PP Population in V59P20

	2-5 Years			6-10 Years		2-10 Years	
	MenACWY 2-doses	MenACWY	Menactra	MenACWY	Menactra	MenACWY	Menactra
	(N=297)	(N=616)	(N=619)	(N=554)	(N=542)	(N=1170)	(N=1161)
Mean age Years (SD)	3.6 (1.1)	3.6 (1.1)	3.6 (1.1)	7.9 (1.4)	8.1 (1.4)	5.6 (2.5)	5.7 (2.6)
Female N (%)	142 (48%)	304 (49%)	297 (48%)	265 (48%)	237 (44%)	569 (49%)	534 (46%)
Race: N (%)							
Asian	18 (6%)	35 (6%)	24 (4%)	27 (5%)	30 (6%)	62 (5%)	54 (5%)
Black	33 (11%)	72 (12%)	80 (13%)	77 (14%)	77 (14%)	149 (13%)	157 (14%)
Caucasian	187 (63%)	381 (62%)	381 (62%)	368 (66%)	356 (66%)	749 (64%)	737 (63%)
Hispanic	42 (14%)	84 (14%)	82 (13%)	38 (7%)	38 (7%)	122 (10%)	120 (10%)
Other	17 (6%)	44 (7%)	52 (8%)	44 (8%)	41 (8%)	88 (8%)	93 (8%)
Mean Weight in kg (SD)	17.54 (4.12)	17.46 (3.98)	17.48 (3.93)	31.93 (10.09)	31.01 (9.21)	24.31 (10.42)	23.80 (9.66)
Mean Height in cm (SD)	102.39 (9.75)	102.54 (10.10)	102.71 (9.77)	130.98 (11.03)	131.44 (10.68)	116.04 (17.69)	116.17 (17.60)
Met study criteria	295 (99%)	606 (98%)	612 (99%)	548 (99%)	539 (99%)	1154 (99%)	1151 (99%)

SD=standard deviation

Source: Table 14.11.3.3 on Page 124 of the applicant's Clinical Study Report for V59P20.

3.1.4 Results and Conclusions

The immunogenicity results for the primary endpoint in V59P20 are presented in Table 6. In the 2 to 5 years old age group, the percentages of seroresponders at 1 month postvaccination was consistently higher in the MenACWY group than in the Menactra® group for serogroups C (60% vs. 56% for MenACWY and Menactra®, respectively), W (72% vs. 58%), and Y (66% vs. 45%), but lower for serogroup A (72% vs. 77%). Similarly, in the 6 to 10 age group, the percentages of seroresponders was consistently higher in the MenACWY group than in the Menactra® group for serogroups C (63% vs. 57%), W (57% vs. 44%), and Y (58% vs. 39%), but lower for serogroup A (77% vs. 83%). In both groups, the non-inferiority was met for serogroups C, W, and Y, but not for serogroup A. The seroresponse rates in the MenACWY group were statistically higher than those in the Menactra® group for serogroups W and Y (the lower bound of the 95% CI was above 0). On the other hand, the seroresponse rate in the MenACWY group was statistically lower than those in the Menactra® group for serogroup A (the upper bound of the 95% CI was below 0). The proportions of subjects with a titer of ≥1:8 post single vaccination were similar to the seroresponse rates in the corresponding age and treatment groups.

Table 6: Percentage (95% CI) of Subjects with hSBA Seroresponse at One Month Post-vaccination by Age Group, PP Population

	2-5 Years			6-10 Years		
Serogroup	**MenACWY**	**Menactra**	**Vaccine Group Difference MenACWY - Menactra**	**MenACWY**	**Menactra**	**Vaccine Group Difference MenACWY - Menactra**
A	434 (72%) (68-75) N=606	469 (77%) (73-80) N=611	-5% (-10-0)	422 (77%) (73-80) N=551	447 (83%) (79-86) N=541	-6% (-11--1)
C	363 (60%) (56-64) N=607	346 (56%) (52-60) N=615	4% (-2-9)	349 (63%) (59-67) N=554	309 (57%) (53-62) N=539	6% (0-11)
W	426 (72%) (68-75) N=594	349 (58%) (54-62) N=605	14% (9-19)	308 (57%) (53-61) N=542	236 (44%) (40-49) N=533	13% (7-18)
Y	394 (66%) (62-70) N=593	271 (45%) (41-49) N=600	21% (16-27)	316 (58%) (54-62) N=545	212 (39%) (35-44) N=539	19% (13-24)

Source: Table 11.4.1.1-1 on Page 81 in the applicant's Clinical Study Report V59P20.

The summary of geometric mean titers (GMTs) is presented in Table 7. The GMTs were similar between the two vaccine groups at baseline (Day 1) (GMT ratios (MenACWY/Menactra®) ranged between 0.99 and 1.11.) The GMT ratios at Day 29 post vaccination ranged between 1.04 to 2.36 in the 2-5 year old age group and 1.01 to 2.41 in the 6-10 year old age groups. The lower bounds of the 95% confidence intervals of the ratios (ranging from 0.83 to 1.95) were all above 0.5, the pre-specified non-inferiority margin. This finding indicates that the secondary objective of the non-inferiority in terms of GMTs was met.

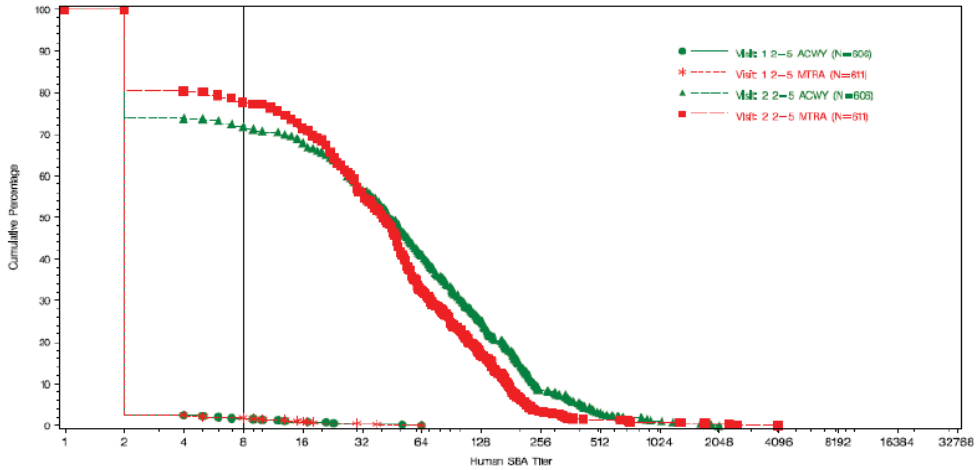
Table 7: hSBA GMTs at One Month Post Vaccination: PP Population

	2-5 years			6-10 years		
Serogroup	**MenACWY**	**Menactra**	**Vaccine group Ratio (95% CI)**	**MenACWY**	**Menactra**	**Vaccine group Ratio (95% CI)**
A	26 (22-30) N=606	25 (21-29) N=611	1.04 (0.86-1.27)	35 (29-42) N=551	35 (29-41) N=541	1.01 (0.83-1.24)
C	18 (15-20) N=607	13 (11-15) N=615	1.33 (1.11-1.6)	36 (29-45) N=554	27 (21-33) N=539	1.36 (1.06-1.73)
W-135	43 (38-50) N=594	21 (19-25) N=605	2.02 (1.71-2.39)	61 (52-72) N=542	35 (30-42) N=533	1.72 (1.44-2.06)
Y	24 (20-28) N=593	10 (8.68-12) N=600	2.36 (1.95-2.85)	34 (28-41) N=545	14 (12-17) N=539	2.41 (1.95-2.97)

Source: Table 11.4.1.2-5 on Page 88 in the applicant's Clinical Study Report V59P20.

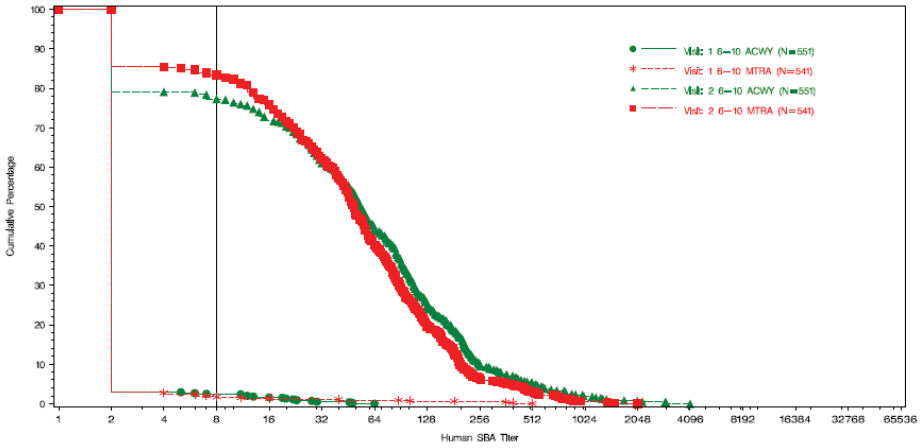
For both age groups, the GMTs for serogroup A were similar following a dose of MenACWY when compared with a single dose of Menactra® (26 vs. 25 for 2-5 years, 35 vs. 35 for 6-10 years); yet the proportions of seroresponders were lower for this serogroup. The explanation can be found through inspection of the reverse cumulative distribution (RCD) curves for serogroup A. As can be seen in Figure 1 for the 2-5 age group and Figure 2 for the 6-10 age group, the curves for MenACWY and Menactra® cross. Thus, although the percentage of subjects with an hSBA ≥ 1:8 post-vaccination did not meet the non-inferiority criteria when comparing MenACWY to Menactra®, among those that did achieve positive titers, the titers were higher after MenACWY. This can be seen in the RCD curves where the MenACWY group has a longer "tail" than Menactra®.

Figure 1: Reverse Cumulative Distribution (RCD) of hSBA Titers Before and 1 Month After 1st Dose by Serogroup (Age 2-5 years) : –PP population



Source: Figure 14.4.1.2-1 on Page 89 in the applicant's Clinical Study Report V59P20.

Figure 2: Reverse Cumulative Distribution (RCD) of hSBA Titers Before and 1 Month After 1st Dose by Serogroup (Age 6-10 years) : –PP population



Source: Figure 14.4.1.2-2 on Page 89 in the applicant's Clinical Study Report V59P20.

Finally, as pre-specified in the secondary objectives, immunogenicity data comparisons were made between subjects receiving one dose of MenACWY (N=593 to 607 varying by serogroup) to subjects receiving two doses of MenACWY (N=288 to 293 varying by serogroup). As shown in Table 8, the baseline (Day 1) hSBA data were similar between the two groups. At Day 29, the percentages of seroresponders were consistently higher in the MenACWY 2-dose group than in the MenACWY single dose group for all four serogroups (A 91% vs. 72%, C: 98% vs. 60%, W: 89% vs. 72%, and Y: 95% vs. 66%). Similarly, the percentages of subjects with hSBA ≥ 1:8 showed a large increase for all four serogroups in both vaccine groups, but were consistently higher for all four serogroups in the MenACWY 2-dose group (A: 91% vs. 72%, C: 99% vs. 68%, W: 99% vs. 90%, and Y: 98% vs. 76%). The GMTs showed a large increase for all four serogroups in both vaccine groups, but were significantly higher ($p<0.001$) for all four serogroups in MenACWY 2-dose group (A: 64 vs. 27, C: 144 vs. 18, W: 132 vs. 41, and Y: 102 vs. 23). Therefore, not only were the non-inferiority objectives met, the two-dose group exhibited substantial improvement in serological response than in the one-dose group.

Table 8: Percentage of Subjects with hSBA Titer ≥ 1:8 and GMTs of Subjects at Day 1 and at One Month Post-Vaccination, Children 2 to 5 years of age (2 doses v/s 1 dose), PP Population

		hSBA Titer ≥ 1:8 n (%) (95% CI)		Seroresponse n (%) (95% CI)		GMT (95% CI)	
Serogroup		MenACWY 2 Doses	MenACWY 1 Dose	MenACWY 2 Doses	MenACWY 1 Dose	MenACWY 2 Doses	MenACWY 1 Dose
Day 1	A	4 (1%) (0-3)	9 (1%) (1-3)	NA	NA	2.1 (2.02-2.18)	2.1 (2.04-2.16)
	C	27 (9%) (6-13)	61 (10%) (8-13)	NA	NA	2.92 (2.65-3.23)	3.05 (2.83-3.29)
	W	61 (21%) (17-26)	143 (24%) (21-28)	NA	NA	4.07 (3.42-4.84)	4.38 (3.84-5.01)
	Y	26 (9%) (6-13)	81 (14%) (11-17)	NA	NA	2.75 (2.44-3.09)	3 (2.74-3.28)
Day 28	A	266 (91%) (88-94)	436 (72%) (68-75)	264 (91%) (87-94)	434 (72%) (68-75)	64 (51-81)	27 (23-32)
	C	289 (99%) (97-100)	413 (68%) 64-72)	286 (98%) (95-99)	363 (60%) (56-64)	144 (118-177)	18 (15-21)
	W	286 (99%) (98-100)	532 (90%) (87-92)	256 (89%) (85-92)	426 (72%) (68-75)	132 (111-157)	41 (36-47)
	Y	280 (98%) (95-99)	448 (76%) (72-79)	271 (95%) (91-97)	394 (66%) (62-70)	102 (82-126)	23 (20-27)

Source: Table 11.4.1.2-6 on Page 91 in the applicant's Clinical Study Report V59P20.

Reviewer's comments:

- *The applicant's analyses were consistent with the statistical analysis plan. The reviewer performed independent analyses by using a logistic regression model adjusting for treatment group, log10(baseline titer), different demographic variables such as Sex, and Country. The conclusions are consistent with the applicant's conclusions.*
- *It is important to note that the non-inferiority margin of -10% for serogroup A for the primary endpoint based on a single dose of MenACWY was not met (although the results were -10.1%*

and -10.8% for the different age groups). The review team may want to discuss whether and how this should be noted in the label..

- *The reviewer examined time of assay for each of the treatment groups to investigate the potential bias due to different time of assay runs. The reviewer did not find obvious lag/drift of the assay time in one group when compared to the other.*

3.1.5 Gender, Race, Age and Other Special/Subgroup Populations

The statistical reviewer performed exploratory analyses for the primary endpoint, percentage of subjects with seroresponse at 1 month post vaccination, separately by baseline (whether or not baseline titer is ≥1:4) (Table 9), gender (females vs. males) (Table 10), or country (U.S. vs. Canada) (Table 11) for each of the age groups. The seroresponse rates , the differences in seroresponse rate between MenACWY and Menactra®, as well as the lower bounds of the two-sided 95% confidence intervals of the differences using the unconditional exact method (SAS 9.2: PROC FREQ, the EXACT RISKDIFF option) are presented. Due to small sample sizes in some of the subgroups, e.g., subjects enrolled in Canada, or subjects with a baseline titer of ≥1:4 in some of the serogroups, the point estimates are not stable, i.e., the confidence intervals are wide. There may be a slight trend for male subjects to have a lesser immune response for the various serotypes when compared to females. In addition, the seroresponse rates for the subjects enrolled in Canada tended to be lower than those for the subjects enrolled in U.S. The seroresponse rates are higher among subjects with a baseline titer of <1:4 than those among subjects with a baseline titer of ≥1:4. However, the differences between the subgroups are not formally tested and may not reach statistical significance due to the small sample size. Overall, the results within the subgroups comparing the seroresponses between the Menveo and the Menactra® groups are consistent regarding the conclusions related to the non-inferiority objectives for the four serogroups.

Table 9: Seroresponse Rate by Baseline and Age Group

		Age class 2-5 years				Age class 6-10 years			
		MenACWY	Menactra	Diff.	Lower 95% CI	MenACWY	Menactra	Diff.	Lower 95% CI
A	Seroresponse-baseline < 4	71.7% (N=591)	77.3% (N=596)	-5.6%	-10.6%	76.8% (N=535)	83.3% (N=526)	-6.4%	-11.2%
	Seroresponse-baseline >= 4	66.7% (N=15)	53.3% (N=15)	13.3%	-21.4%	68.8% (N=16)	60.0% (N=15)	8.8%	-24.9%
	Overall Seroresponse	71.6% (N=606)	76.8% (N=611)	-5.1%	-10.1%	76.6% (N=551)	82.6% (N=541)	-6.0%	-10.8%
C	Seroresponse-baseline < 4	62.3% (N=491)	58.4% (N=503)	3.9%	-2.2%	66.6% (N=347)	62.6% (N=334)	4.0%	-3.2%
	Seroresponse-baseline >= 4	49.1% (N=116)	46.4% (N=112)	2.7%	-10.3%	57.0% (N=307)	48.8% (N=205)	8.2%	-1.4%
	Overall Seroresponse	59.8% (N=607)	56.3% (N=615)	3.5%	-2.0%	63.0% (N=554)	57.3% (N=539)	5.7%	-0.1%
W-135	Seroresponse-baseline < 4	86.7% (N=442)	68.4% (N=469)	18.2%	12.9%	83.9% (N=285)	71.4% (N=294)	12.4%	5.7%
	Seroresponse-baseline >= 4	28.3% (N=152)	20.6% (N=136)	7.7%	-2.2%	26.8% (N=257)	10.9% (N=239)	16.0%	9.3%
	Overall Seroresponse	71.7% (N=594)	57.7% (N=605)	14.0%	8.7%	56.8% (N=542)	44.3% (N=533)	12.5%	6.6%
Y	Seroresponse-baseline < 4	71.5% (N=492)	49.6% (N=496)	21.9%	16.0%	70.1% (N=344)	48.7% (N=347)	21.4%	14.2%
	Seroresponse-baseline >= 4	41.6% (N=101)	24.0% (N=104)	17.5%	4.9%	37.3% (N=201)	22.4% (N=192)	14.9%	6.0%
	Overall Seroresponse	66.4% (N=593)	45.2% (N=600)	21.3%	15.8%	58.0% (N=545)	39.3% (N=539)	18.6%	12.8%

Table 10: Seroresponse Rate by Gender and Age Group

Serogroup	Gender	Age class 2-5 years				Age class 6-10 years			
		MenACWY	Menactra	Diff.	Lower 95% CI	MenACWY	Menactra	Diff.	Lower 95% CI
A	FEMALE	73.2% (N=299)	78.5% (N=293)	-5.3%	-10.1%	79.2% (N=264)	85.2% (N=237)	-6.1%	-10.8%
	MALE	70.0% (N=307)	75.2% (N=319)	-5.1%	-10.1%	74.2% (N=287)	80.6% (N=304)	-6.4%	-11.1%
C	FEMALE	63.3% (N=300)	58.4% (N=293)	5.0%	-0.6%	58.5% (N=265)	58.1% (N=236)	0.4%	-5.7%
	MALE	56.4% (N=307)	54.3% (N=322)	2.0%	-3.5%	67.1% (N=289)	56.8% (N=303)	10.4%	4.9%
W-135	FEMALE	71.9% (N=295)	59.5% (N=289)	12.3%	6.9%	59.5% (N=257)	46.8% (N=231)	12.8%	6.6%
	MALE	71.6% (N=299)	56.0% (N=316)	15.6%	10.3%	54.4% (N=285)	42.4% (N=302)	12.0%	6.3%
Y	FEMALE	68.3% (N=293)	50.7% (N=284)	17.6%	12.0%	58.7% (N=259)	45.3% (N=236)	13.3%	7.2%
	MALE	64.7% (N=300)	40.2% (N=316)	24.5%	19.1%	57.3% (N=286)	34.7% (N=303)	22.7%	17.1%

Table 11: Seroresponse Rate by Country and Age Group

Serogroup	Country	Age class 2-5 years				Age class 6-10 years			
		MenACWY	Menactra	Diff.	Lower 95% CI	MenACWY	Menactra	Diff.	Lower 95% CI
A	USA	72.5% (N=527)	76.9% (N=533)	-4.4%	-8.1%	78.8% (N=307)	84.6% (N=311)	-5.7%	-10.0%
	CANADA	65.8% (N=79)	75.6% (N=78)	-9.8%	-19.8%	73.8% (N=244)	80.0% (N=230)	-6.2%	-11.6%
C	USA	60.3% (N=527)	56.6% (N=537)	3.7%	-0.5%	68.3% (N=309)	62.1% (N=309)	6.1%	0.8%
	CANADA	56.3% (N=80)	53.8% (N=78)	2.4%	-8.6%	56.3% (N=245)	50.9% (N=230)	5.5%	-0.9%
W-135	USA	72.8% (N=515)	59.1% (N=528)	13.7%	9.7%	58.3% (N=302)	43.5% (N=308)	14.8%	9.2%
	CANADA	64.6% (N=79)	48.1% (N=77)	16.5%	5.6%	55.0% (N=240)	45.3% (N=225)	9.7%	3.3%
Y	USA	67.9% (N=514)	46.7% (N=523)	21.2%	17.1%	62.6% (N=305)	40.6% (N=310)	22.0%	16.5%
	CANADA	57.0% (N=79)	35.1% (N=77)	21.9%	11.1%	52.1% (N=240)	37.6% (N=229)	14.5%	8.2%

3.1.6 Immunogenicity Results in Supportive Studies (V59P7, V59P8, V59P10)

V59P7 was a Phase II, multicenter, controlled, randomized, observer blind study, conducted in one center in Finland and in two centers in Poland. The subjects in the study were between 1 year and 5 years of age. Relevant data to this applicant's submission only include the MenACWY group of 2-5 year olds and the Mencevax® (non U.S. licensed vaccine) group of 3-5 year olds.

V59P8 was a Phase II, single-center U.S. trial conducted during 2005/06 in children 1-10 years of age. An open-label component of this study performed in toddlers 12-23 months was designed to evaluate the concomitant use of diphtheria-containing vaccines. Only the immunogenicity data among the children 2-10 years of age are evaluated.

V59P10 was a Phase III, observer-blind, multi-center, randomized, controlled study in healthy children aged 2 to 10 years of age conducted in Argentina during 2006/07. Immunogenicity was evaluated in a subset of subjects, and data from this subset are evaluated.

A summary of the immunogenicity results is presented in Table 12. The results among the studies vary, likely due to a variety of factors since the studies were conducted at different time periods and locations.

Table 12: Summary of Immunogenicity Results at 1 Month after a Single Vaccination of MenACWY in All Studies

		Seroresponse N, % (95% CI))		% Subjects with hSBA Titer ≥ 1:8 (95% CI)		GMT (95% CI)	
Sero-group	**Study**	**2-5 yeas**	**6-10years**	**2-5 yeas**	**6-10years**	**2-5 yeas**	**6-10years**
A	V59P7	N = 198 62 (55, 69)	N/A	63 (55, 69)	N/A	14 (12, 18)	N/A
	V59P8	N = 133 77 (69, 84)	N = 147 82 (74, 88)	77 (69, 84)	82 (74, 88)	28 (22, 37)	45 (34, 60)
	V59P10	N = 72 93 (85, 98)	N = 76 92 (84, 97)	94 (86, 98)	95 (87, 99)	54 (38, 76)	77 (55, 107)
	V59P20	N = 606 72 (68, 75)	N = 551 77 (73, 80)	72 (68, 75)	77 (74, 81)	26 (22, 30)	35 (29, 42)
C	V59P7	N = 196 40 (33, 48)	N/A	46 (39, 54)	N/A	6.63 (5.57, 7.88)	N/A
	V59P8	N = 135 52 (43, 61)	N = 146 76 (68, 83)	63 (54, 71)	83 (76, 89)	14 (11, 19)	47 (34, 67)
	V59P10	N = 72 76 (65, 86)	N = 75 87 (77, 93)	81 (70, 89)	96 (89, 99)	26 (18, 38)	64 (45, 92)
	V59P20	N = 607 60 (56, 64)	N = 554 63 (59, 67)	68 (64, 72)	77 (73, 80)	18 (15, 20)	36 (29, 45)
W-135	V59P7	N = 198 67 (60, 73)	N/A	78 (71, 83)	N/A	20 (17, 25)	N/A
	V59P8	N = 135 62 (53, 70)	N = 144 71 (63, 78)	87 (81, 92)	96 (91, 98)	43 (34, 56)	80 (65, 99)
	V59P10	N = 70 89 (79, 95)	N = 73 60 (48, 72)	99 (92, 100)	100 (95, 100)	58 (42, 82)	87 (63, 122)
	V59P20	N = 594 72 (68, 75)	N = 542 57 (53, 61)	90 (87, 92)	91 (88, 93)	43 (38, 50)	61 (52, 72)
Y	V59P7	N = 196 63 (56, 70)	N/A	65 (58, 72)	N/A	17 (13, 21)	N/A
	V59P8	N = 134 72 (63, 79)	N = 146 78 (70, 84)	83 (75, 89)	92 (86, 96)	42 (31, 56)	68 (51, 90)
	V59P10	N = 71 79 (68, 88)	N = 75 84 (74, 91)	83 (72, 91)	95 (87, 99)	34 (22, 51)	64 (43, 95)
	V59P20	N = 593 66 (62, 70)	N = 545 58 (54, 62)	76 (72, 79)	79 (76, 83)	24 (20, 28)	34 (28, 41)

3.2 Evaluation of Safety

The evaluation of safety is based on the safety data collected in four clinical trials (V59P7, V59P8, V59P10, and V59P20). Detailed discussion of the safety data can be found in the clinical review and epidemiological review. The overall extent of exposure to MenACWY is summarized in Table 13. Based on the safety responses of AE's, SAE's, and reactogenicity to the vaccine, similar safety events were observed when examining MenACWY and the comparator in the various studies examined in this submission.

Table 13: MenACWY Studies in Subject Ages 2 to 10 Years: Number of Subjects Exposed to at Least One Injection of Meningococcal Vaccination

		Single Meningococcal Vaccination			Two Doses of Meningococcal Vaccination (ages 2 to 5 years only)		Total MenACWY[c]
	Study	MenACWY	Menactra	Menomune	MenACWY→ MenACWY[a]	Mencevax→ MenACWY[b]	
2-5 years	V59P7	--	--	--	224	74	298
	V59P8	151	--	153	--	--	151
	V59P10	451	--	265	--	--	451
	V59P20	693	684	--	351	--	1044
	Total	**1295**	**684**	**418**	**575**	**74**	**1944**
6-10 years	V59P8	157	--	157	--	--	157
	V59P10	498	--	286	--	--	498
	V59P20	582	571	--	--	--	582
	Total	**1237**	**571**	**443**	**--**	**--**	**1237**
2-10 years	V59P7	--	--	--	224	74	298
	V59P8	308	--	310	--	--	308
	V59P10	949	--	551	--	--	949
	V59P20	1275	1255	--	351	--	1626
	Total	**2532**	**1255**	**861**	**575**	**74**	**3181**

Source: section 5.3.5.3, ISS Tables, Table 1 and section 5.3.5.3, ISE Tables, Table 1 P7;
[a]Subjects who received two doses of MenACWY (studies V59P7 and V59P20);
[b]Subjects who received MenACWY after Mencevax (study V59P7);
[c]Subjects who received one or two doses of MenACWY or Mencevax followed by MenACWY.

Source: Table 1.2-1 in the applicant's Integrated Summary of Safety report.

3.2.1 Local and Systemic Reactogenicity

Summaries of the local reactogenicity after a single dose of Meningococcal vaccine for the 2-5 year old and 6-10 year old groups by study are presented in Table 14 and Table 15, respectively. Pain was the most reported local reaction (20% to 45% depending on the study). The percentages of 2 to 5 year olds reporting erythema ranged from 7% to 28%, and those reporting induration ranged from 3% to 18%. The percentages reporting local symptoms tended to be lower in Studies V59P8 and V59P10. In the pivotal study (V59P20), the percentage of subjects who reported severe erythema (>50mm) after the MenACWY vaccination (7% in either of the 2-5 year old and 6-10 year old age groups) was higher than that after the Menactra® vaccination (4% in the 2-5 year old group, 2% in the 6-10 year old group).

Table 14: Percentage of Children Ages 2 to 5 Reporting Any and (Severe) Local Reaction after First/Single Meningococcal Vaccination, Day 1 to 7 and 1 to 3, by Study

	V59P7				V59P8				V59P10				V59P20			
	MenACWY		Mencevax		MenACWY		Menomune		MenACWY		Menomune		MenACWY		Menactra	
Days / Reaction	1-7 N=224	1-3 N=224	1-7 N=74	1-3 N=74	1-7 N=151	1-3 N=151	1-7 N=153	1-3 N=153	1-7 N=451	1-3 N=451	1-7 N=265	1-3 N=265	1-7 N=1044	1-3 N=1044	1-7 N=684	1-3 N=684
Pain[a]	33% (1,<1%)	33% (1,<1%)	45% (4%)	45% (4%)	28% (1%)	28% (1%)	20% (0)	18% (0)	20% (0)	19% (0)	26% (0)	25% (0)	32% (1%)	32% (1%)	35% (3,<1%)	35% (3,<1%)
Erythema (>50mm)	21% (1%)	21% (1%)	16% (0)	16% (0)	15% (3%)	15% (3%)	7% (0)	7% (0)	17% (1%)	16% (1%)	13% (0)	13% (0)	28% (7%)	28% (7%)	25% (4%)	25% (4%)
Induration (>50mm)	13% (1,<1%)	13% (1,<1%)	14% (0)	14% (0)	11% (2%)	11% (2%)	3% (0)	3% (0)	13% (0)	12% (0)	9% (0)	9% (0)	18% (2%)	18% (2%)	18% (2%)	18% (2%)

[a]Tenderness in study V59P7; pain/tenderness were graded as none, mild (defined as "minor light reaction to touch"), moderate (defined as "cried or protested to touch"), or severe (defined as "cried when injected limb was moved").

Source: Table 2.1.1.1-3 on Page 31 in the applicant's Integrated Summary Safety report

Table 15: Percentage of Children Ages 6 to 10 Reporting Any and (Severe) Local Reaction after First/Single Meningococcal Vaccination, Day 1 to 7 and 1 to 3, by Study

	V59P8				V59P10				V59P20			
	MenACWY		Menomune		MenACWY		Menomune		MenACWY		Menactra	
Reaction \ Days	1-7 N=157	1-3 N=157	1-7 N=157	1-3 N=157	1-7 N=498	1-3 N=498	1-7 N=286	1-3 N=286	1-7 N=582	1-3 N=582	1-7 N=571	1-3 N=571
Pain[a]	36% (1%)	34% (1%)	27% (0)	26% (0)	27% (0)	26% (0)	35% (1,<1%)	35% (1,<1%)	39% (1%)	38% (1%)	45% (2%)	44% (2%)
Erythema (>50mm)	17% (4%)	17% (4%)	6% (0)	5% (0)	18% (1%)	18% (1%)	13% (0)	13% (0)	28% (7%)	27% (6%)	22% (2%)	22% (2%)
Induration (>50mm)	17% (4%)	16% (4%)	4% (0)	3% (0)	17% (2,<1%)	16% (2, <1%)	13% (0)	12% (0)	17% (2%)	16% (2%)	13% (2%)	12% (2%)

[a]Pain was graded as none, mild (defined as "minor light reaction to touch"), moderate (defined as "cried or protested to touch"), or severe (defined as "cried when injected limb was moved").

Source: Table 2.1.1.1-5 on Page 33 in the applicant's Integrated Summary Safety report

Summaries of the systemic reactogenicity for the 2-5 year old and 6-10 year old groups by vaccine and study are presented in Table 16 and Table 17, respectively. The categories of symptoms may be collected differently among studies. The most commonly reported systemic reaction to MenACWYwas irritability (range across vaccine groups: 11% to 22%), followed by: sleepiness (range: 9% to 18%), change in eating habits (10% in all three vaccine groups), malaise (range: 8% to 12%), headache (range: 9% to 11%), myalgia (range: 7% to 10%), and diarrhea (6% to 8%).

Table 16: Percentages of Children Ages 2 to 5 Reporting Any and (Severe) Systemic Reactions after First/Single Meningococcal Vaccination, Days 1 to 7 and 1 to 3, by Study

Vaccination	V59P7[a]				V59P8				V59P10				V59P20			
	MenACWY		Mencevax		MenACWY		Menomune		MenACWY		Menomune		MenACWY		Menactra	
Reaction \ Days	1-7 N=224	1-3 N=224	1-7 N=74	1-3 N=74	1-7 N=151	1-3 N=151	1-7 N=153	1-3 N=153	1-7 N=451	1-3 N=451	1-7 N=265	1-3 N=265	1-7 N=1044	1-3 N=1044	1-7 N=684	1-3 N=684
Change in eating habits	10% (0)	7% (0)	8% (0)	3% (0)	12% (0) N=145	9% (0) N=144	11% (0) N=150	8% (0) N=150	8% (2,<1%) N=449	6% (1,<1%) N=449	9% (0)	6% (0)	10% (5,<1%) N=1024	8%(3,<1%) N=1023	10% (2,<1%) N=671	8%(1,<1%) N=667
Sleepiness	15% (0)	13% (0)	14% (0)	12% (0)	17% (1%)	15% (0)	16% (1%)	14% (1%)	6% (2,<1%)	4% (0)	5% (0)	4% (0)	16%(1%) N=1043	14%(1%) N=1043	18% (1%)	17% (2,<1%) N=683
Irritability	17% (0)	15% (0)	11% (0)	9% (0)	19% (0)	17% (0)	17% (0)	16% (0)	8% (2,<1%)	6% (0)	7% (0)	5% (0)	21%(2%) N=1042	20%(1%) N=1042	22% (1%)	20%(1%) N=683
Vomiting	3% (0)	1,<1% (0)	0	0	8% (1%)	5% (0)	4% (0)	3% (0)	5% (0)	3% (0)	3% (0)	2% (0)	3%(2,<1%) N=1043	2%(2,<1%) N=1043	3% (0)	2%(0) N=683
Diarrhea	6% (0)	4% (0)	0	0	7% (0)	5% (0)	4% (0)	3% (0)	7% (2,<1%)	5% (1,<1%)	8% (0)	5% (0)	7%(1,<1%) N=1043	5%(0) N=1043	8% (0)	6%(0) N=683
Fever[b]	5% (1%)	2% (0)	5% (3%)	1% (1%)	5% (1%)	3% (0)	5% (2%)	3% (1%)	8% (2%)	4% (1,<1%)	7% (1%)	3% (1,<1%)	2%(6,<1%) N=1043	1%(1,<1%) N=1043	2% (2,<1%)	1% (0)
Headache*					4% (0)	4% (0)	2% (0)	1% (0)	10% (0)	8% 0	8% (0)	5% (0)	5% (1,<1%)	3% (1,<1%)	6% (2,<1%)	5% (1,<1%)
Arthralgia*					2% (1%)	2% (1%)	5% (0)	4% (0)	6% (1,<1%)	5% 0	4% (0)	4% (0)	4% (3,<1%)	3% (2,<1%)	4% (0)	3% (0)
Rash*													5%(2%)[c]	4%(2%)[c]	5%(1%)[c]	4%(1%)[c]

[a]Study V59P7 collected systemic reactions as "present" or "absent" without grading severity.

[b]Fever: temperature (regardless of method of collection) ≥ 38°C, severe fever ≥ 39°C

*Greyed out area indicates that data were not collected in the study.

Source: Table 2.1.1.1-7 on Page 43 in the applicant's Integrated Summary Safety report

Table 17: Percentages of Children Ages 6 to 10 Reporting Any and (Severe) Systemic Reactions after a Single MenACWY Vaccination, Days 1 to 7 and 1 to 3, by Study

	V59P8				V59P10				V59P20			
	MenACWY[b]		Menomune		MenACWY		Menomune		MenACWY		Menactra	
Reaction \ Days	1-7 N=157	1-3 N=157	1-7 N=157	1-3 N=157	1-7 N=498	1-3 N=498	1-7 N=286	1-3 N=286	1-7 N=582	1-3 N=582	1-7 N=571	1-3 N=571
Chills	8% (1%)	6% (0)	3% (1%)	3% (0)	4% (0)	3% (0)	6% (0)	4% (0)	5% (0)	4%(0) N=581	5% (2,<1%)	3% (1,<1%)
Nausea	4% (0)	2% (0)	4% (1%)	3% (0)	3% (1,<1%)	2% (0)	4% (1,<1%)	3% (1,<1%)	8% (1%)	7%(1%) N=581	6% (2,<1%)	5% (2,<1%)
Malaise	8% (2%)	6% (1%)	6% (1%)	4% (0)	10% (2,<1%)	8% (1,<1%)	10% (0)	8% (0)	14% (1%)	11%(1%) N=581	11% (1%)	8% (1%)
Myalgia	8% (2%)	7% (1%)	3% (1%)	2% (0)	7% (1,<1%)	6% (1,<1%)	9% (0)	8% (0)	10% (1%)	9%(2,<1%) N=581	10% (1%)	9% (1%)
Arthralgia	3% (1%)	2% (0)	2% (0)	1% (0)	4% (0)	3% (0)	5% (1,<1%)	5% (1,<1%)	6% (0)	5% (0)	4% (2,<1%)	4% (1,<1%)
Headache	19% (2%)	14% (1%)	11% (1%)	8% (0)	15% (2,<1%)	11% (1,<1%)	16% (0)	12% (0)	18% (1%)	15% (1%)	13% (1%)	11% (1%)
Fever[c]	2% (1%)	1% (0)	2% (1%)	2% (1%)	4% (1%)	2% (1%)	6% (1%)	2% (1,<1%)	2% (1%)	2% (2,<1%)	2%(2,<1%) N=570	1%(2,<1%) N=570
Rash*									5%(2%[d])	4%(1%[d])	3%(3%[d])	2%(2%[d])

[a]For the grading of severity refer to the applicant's Tables 1.1.2-3 and 1.1.2-4 in the ISS report.
[b]Except for fever, N=156
[c]Fever: temperature (regardless of method of collection) ≥38°C, severe fever ≥39°;
[d]Percentage of urticarial rash.
*Greyed out area indicates that data were not collected in the study.
Source: Table 2.1.1.1-9 on Page 45 in the applicant's Integrated Summary Safety (ISS) report

3.2.2 Unsolicited Adverse Events (AEs)

Subjects were followed up between 6 to 12 months after the first vaccination, varying by study. A summary of the follow-up time in each of the studies is provided in Table 18. The median follow-up time was about 6 months in Studies V59P20 and V59P10, and 12 months in Studies V59P7 and V59P8.

Table 18: Summary of Follow-up Time Since the First Vaccination by Study

Study	Treatment	N	Follow-up Time (Days)				
			Mean	Std	Min	Median	Max
V59P20	MenACWY 10/5/5/5 mcg	1275	170	27	3	176	290
	MenACWY 10/5/5/5 mcg 2 doses	351	219	41	3	221	287
	Menactra	1255	170	25	3	177	247
V59P7	MenACWY 10/5/5/5 mcg 2 doses	224	282	92	29	350	412
	Mencevax, MenACWY 10/5/5/5 mcg	81	270	97	30	338	386
V59P8	MenACWY 10/5/5/5 mcg	308	344	68	1	358	460
	Menomune	310	348	65	1	359	460
V59P10	MenACWY 10/5/5/5 mcg	949	180	8	44	181	200
	Menomune	551	181	6	167	181	231

In the overall 2 to 10 years age group, the percentage of subjects reporting unsolicited AEs (any and possibly related) within 1 month of the first/single meningococcal vaccination were similar after MenACWY and comparator vaccines Menactra® and Menomune® (any AE: range, 18% to 21%, possibly vaccine related AE: range, 3% to 5%, See Table 19). The AE event rates by gender and race are also summarized in Table 20.

Table 19: Percentages of Subjects Reporting Unsolicited AEs within 1 Month of Meningococcal Vaccination by Age Group, Pooled Analysis

	2-5 years					
	1 Month after 1st Vaccination				1 Month after 2nd Vaccination	
	MenACWY N=1870	Menactra N=684	Menomune N=418	Mencevax N=74	MenACWY→MenACWY N=550	Mencevax→MenACWY[b] N=74
Any AE	24%	20%	22%	31%	19%	19%
At least possibly related AEs	4%	5%	3%	0	2%	1%

	6-10 years (1 Month after Single Vaccination)		
	MenACWY 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)		
	MenACWY N=3107	Menactra N=1255	Menomune N=861
Any AE	21%	18%	18%
At least possibly related AEs	4%	5%	3%

[a]MenACWY pooled analysis: studies V59P7 (only 2-5 years age group), V59P8, V59P10, and V59P20, Menactra: study V59P20; Menomune pooled analysis: studies V59P8 and V59P10;
[b]Mencevax: study V59P7 (only 3-5 years age group).

Source: Table 2.1.1.2-1 on Page 48 in the applicant's Integrated Summary Safety report.

Table 20: Unsolicited AE Rates by Gender and Race Observed in Study V59P20

			MenACWY: 1 Dose			MenACWY: 2 doses			Menactra		
			N	n	%	N	n	%	N	n	%
2-5 years	Gender	Female	339	99	29.2%	164	77	47.0%	328	89	27.1%
		Male	354	111	31.4%	187	75	40.1%	356	104	29.2%
	Race	Asian	36	8	22.2%	19	7	36.8%	25	13	52.0%
		Black	87	23	26.4%	43	14	32.6%	91	14	15.4%
		Caucasian	417	144	34.5%	215	107	49.8%	418	120	28.7%
		Hispanic	108	23	21.3%	53	15	28.3%	96	24	25.0%
		Other	45	12	26.7%	21	9	42.9%	54	22	40.7%
6-10 years	Gender	Female	281	53	18.9%				248	43	17.3%
		Male	301	64	21.3%				323	68	21.1%
	Race	Asian	31	6	19.4%				34	4	11.8%
		Black	79	5	6.3%	N/A			80	9	11.3%
		Caucasian	387	89	23.0%				376	81	21.5%
		Hispanic	40	9	22.5%				39	9	23.1%
		Other	45	8	17.8%				42	8	19.0%

3.2.3 Serious Adverse Events (SAE)

Table 21 provides a summary of serious adverse events is presented by study and age group. There were no deaths in any of the four studies used to support this application. In addition, a summary of the serious adverse event rates by gender and race in the pivotal Study V59P20 is provided in Table 22. Please refer to the clinical review for detailed discussions on SAEs.

Table 21: Summary of Serious Adverse Events by Study and Age Group

Study	Age Group	MenACWY 1 dose	MenACWY 2 doses	Menactra	Menomune	Mencevax, MenACWY
V59P7	2-5 years		17/224 (7.6%)			9/81 (11.1%)
V59P8	2-5 years	2/151 (1.3%)			1/153 (0.7%)	
	6-10 years	0/157 (0.0%)			0/157 (0.0%)	
V59P10	2-5 years	4/451 (0.9%)			1/265 (0.4%)	
	6-10 years	5/498 (1.0%)			0/286 (0.0%)	
V59P20	2-5 years	5/693 (0.7%)	2/351 (0.6%)	5/684 (0.7%)		
	6-10 years	3/582 (0.5%)		2/571 (0.4%)		
All Studies	2-5 years	11/1295 (0.8%)	19/575 (3.3%)	5/684 (0.7%)	2/418 (0.5%)	9/81 (11.1%)
	6-10 years	8/1237 (0.6%)		2/571 (0.4%)	0/443 (0.0%)	
All		19/2532 (0.8%)	19/575 (3.3%)	7/1255 (0.6%)	2/861 (0.2%)	9/81 (11.1%)

Table 22: Serious Adverse Event Rates by Gender and Race Observed in Study V59P20

			MenACWY: 1 Dose			MenACWY: 2 doses			Menactra		
			N	n	%	N	n	%	N	n	%
2-5 years	Gender	Female	339	4	1.2%	164	1	0.6%	328	2	0.6%
		Male	354	1	0.3%	187	1	0.5%	356	3	0.8%
	Race	Asian	36	0	0.0%	19	0	0.0%	25	0	0.0%
		Black	87	2	2.3%	43	0	0.0%	91	1	1.1%
		Caucasian	417	3	0.7%	215	2	0.9%	418	3	0.7%
		Hispanic	108	0	0.0%	53	0	0.0%	96	0	0.0%
		Other	45	0	0.0%	21	0	0.0%	54	1	1.9%
6-10 years	Gender	Female	281	2	0.7%				248	1	0.4%
		Male	301	1	0.3%				323	1	0.3%
	Race	Asian	31	0	0.0%				34	0	0.0%
		Black	79	0	0.0%	N/A			80	0	0.0%
		Caucasian	387	1	0.3%				376	1	0.3%
		Hispanic	40	1	2.5%				39	1	2.6%
		Other	45	1	2.2%				42	0	0.0%

Reviewer's comment:

- *There is a discrepancy in the total number of subjects in the Mencevax®-MenACWY----(b)(4)---------- group in Study V59P7. The applicant reported the number to be 74, while the statistical*

reviewer determined the number to be 81 based on the ADVERSE dataset in the ISS (Integrated Safety Summary) analysis datasets provided by the applicant. Nevertheless, this discrepancy does not change the conclusion and the safety profile based on all studies.

3.2.4 Safety Results for Post Two-Doses of MenACWY

In Study V59P20, the percentage of subjects with at least one local and/or systemic reaction after any vaccination was higher in MenACWY 2-dose group when compared with MenACWY single dose (72% and 60%, respectively). However, the percentage of subjects with at least one local and/or systemic reaction after first vaccination in the MenACWY 2-dose group and MenACWY single dose group were similar (63% and 60%, respectively). The percentage of subjects with at least one local and/or systemic reaction was lower after second vaccination than after first vaccination in the MenACWY 2-dose group (47% and 63%, respectively). The percentages of subjects experiencing at least one severe local and/or systemic reaction were also lower after second vaccination than after first vaccination in the MenACWY 2-dose group (8% and 13%, respectively).

Overall, the percentage of subjects experiencing any unsolicited AE was higher in the MenACWY 2-dose group, as was expected because of the longer reporting period. The MedDRA System Organ Class (SOC) most commonly affected by unsolicited AEs was "infections and infestations" (22% and 13% MenACWY 2-dose group and MenACWY single dose group, respectively). Similar numbers of subjects reported possibly or probably related unsolicited AEs (6% and 5% in MenACWY 2-dose group and MenACWY single dose group, respectively). All possibly or probably related unsolicited AEs were reported within 29 days of vaccination.

4. SUMMARY AND CONCLUSIONS

4.1 Summary of Statistical Results

The objective of this application is to provide evidence of the non-inferiority of immunogenicity and safety of MenACWY as compared to the US-licensed meningococcal ACWY conjugate vaccine Menactra when administered to healthy children 2 through 10 years of age.

The pivotal study (Study V59P20) conducted in the U.S. and Canada was designed to evaluate and ideally demonstrate the non-inferiority of Menveo® to Menactra®, an approved comparator in both the 2-5 years and 6-10 years age groups for serogroups A, C, W-135, and Y. The study results indicated that non-inferiority was demonstrated for the primary immunogenicity endpoint, seroresponse at one month after a single vaccination, for serogroups C, W-135, and Y. However, for serogroup A, the non-inferiority criterion was narrowly missed, i.e., the lower bounds of the 95% confidence interval for the difference in seroresponse for Serogroup A between the Menveo® and the Menactra® groups (Menveo®-Menactra®) were slightly below the pre-specified non-inferiority margin of -10% for both of the age groups (-10.1% and -10.8% for the 2-5 years and 6-10 years age groups, respectively. See Table 6). The study results also indicated that the seroresponse rates for serogroups W-135 and Y were statistically higher in the Menveo® group

than in the Menactra® group (lower bound of the 95% CI of the seroresponse rate difference, Menveo®-Menactra®, was above 0), while it was statistically lower for the serogroup A (upper bound of the 95% CI of the seroresponse rate difference was below 0.) The statistical reviewer performed independent analyses and confirmed the above findings in pivotal Study V59P20.

Three secondary objectives concerning various endpoints were examined in Study V59P20. When the endpoints were proportions of subjects achieving a post-vaccination titer ≥1:4 or ≥1:8 in age groups 2-5 years and 6-10 years, the conclusions were similar to those based on the seroresponses (primary objective) described above, i.e., non-inferiority was not strictly met. However, the secondary objective of non-inferiority measured by geometric mean titers (GMTs) was met in both age groups for all the serogroups. In addition, two other secondary objectives were met. Specifically, when the seroresponse data were compared among children 2 through 10 years age, i.e., the 2-5 years and 6-10 years were combined, the non-inferiority criteria measured by seroresponse were met. The combination of both age groups likely met the non-inferiority margin because of the larger sample size which narrowed the confidence interval. Finally, regarding another secondary objective in which the seroresponse rates were compared between the two-dose and one-dose Menveo® groups (see Table 8), the seroresponse rates were notably higher after two doses of Menveo® (91%-98%) than those after one single dose of Menveo® (60%-72%). The secondary objective of establishing the non-inferiority of the two-dose group to the single dose group was met.

The safety profile of Menveo® was evaluated in all four studies. A total of 3,181 children were exposed to Menveo®. The overall serious adverse event rates (see Table 21) were around 0.6% (excluding the events related to varicella among the unvaccinated subjects in Study V59P7). Only one of the SAEs (a subject in Study V59P10 experienced febrile convulsion two days after vaccination) was considered to be possibly related to vaccine. All other SAEs were considered not related to vaccine. For local and systemic reactogenicity, pain was the most reported local reaction (20% to 45%). The event rates for Menveo® varied by study but the majority of them were comparable with the reference groups (the rate differences were within 3%). In Study V59P20, it appears that there was an increase in event rates for erythema (>50mm) and headache in children 6-10 years of age in the Menveo® group when compared to the Menactra® group. Please refer to the clinical review for more safety details and clinical significance of some of the observed differences.

4.2 Conclusions and Recommendations

A regulatory decision based on this submission depends on evaluation of the clinical significance of these findings. It is important to note that the non-inferiority margin of -10% for seroresponse was nearly met when examining the 2-5 and 6-10 year old individuals, with observed lower 95% confidence limits of -10.1% and -10.8%, respectively.

There was an observed trend that within a small subset of the subjects in the pivotal study, a second dose of Menveo® administered two months after the first vaccine provided a noticeable increase in seroresponse when compared to the one dose group. If a claim for two doses is desired in the future, CBER may consider whether additional studies on dosing interval, persistence of antibody response, or further safety monitoring are desirable.

4.3 Additional Comments Regarding the "Statistically Higher" Language in the Label

In the approved Menveo® label dated February 19, 2010 and the originally proposed added label information for children 2 through 10 years of age, the immunogenicity results were described with regard to not only the non-inferiority but also the superiority (statistically higher) of Menveo® when compared to Menactra® for each of the serogroups A, C, W-135, and Y. In multiple places (text and footnotes), the seroresponse rates for Menveo® were claimed to be "statistically higher" than those for Menactra® with regard to specific serogroups. The statistical reviewer recommended that the "statistically higher" language be removed from the label based on the following rationale:

> The pivotal study was designed, with attention to avoid type I and type II errors, to establish the non-inferiority of Menveo® to Menactra® based on all serogroup (A, C, W-135, and Y) responses. Therefore, if a non-inferiority criterion is not met for any one of the serogroups, then the overall claim of non-inferiority is not supported by the data. This type of hypothesis test (an "intersection-union test") does not require adjustment to control the Type I error probability (typically 5%) for each test for the individual serogroup. The Type I error is controlled as long as success of the product is based on the overall claim for all serogroups simultaneously. Therefore, it is not consistent with this hypothesis test to make a non-inferiority claim based on any individual test, particularly when success is not achieved for all serogroups. The setup for testing "statistically higher" follows the same principle. From a statistical perspective, in the pivotal study (V59P20) among children 2 through 10 years of age, the non-inferiority of Menevo® to Menactra® was not established. Analogously, the data also did not support the conclusion that responses to Menveo® were "statistically higher" compared to Menactra®.
>
> Although the two-sided 95% CI was computed and compared to the pre-specified non-inferiority margin (-10%) for each of the serogroups in order to test the hypothesis, each individual test result should be considered descriptive and only described in the context of addressing the overall hypothesis testing. Statistical statements regarding such descriptive results violate the Type I error assumptions and can be misleading if appearing in the product label.

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