DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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

STATISTICAL REVIEW AND EVALUATION
BLA 125089/395

BLA/Supplement Number:	STN 125089/395	
Product Name:	Menactra®	
Indication(s):	Active immunization against invasive meningococcal disease caused by Neisseria meningitides (serogroups A, C, Y and W-135 in healthy subjects below two years of age.	
Applicant:	Sanofi Pasteur	
Date(s):	Receipt Date:	6/24/2010
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Primary Statistical Reviewer:	Lihan Yan, Ph.D. Mathematical Statistician *Note: The review was originally finalized on March 9,2011. The document was modified to be 508 compliant and finalized on the stamped date*	
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1. EXECUTIVE SUMMARY

Menactra®, manufactured by Sanofi Pasteur Inc., is a meningococcal (Groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine indicated for active immunization in the prevention of invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y, and W-135. The vaccine was approved by FDA for used in adolescents and adults 11 through 55 years of age in January 2005 and subsequently for use in children 2 through 10 years of age in October 2007. Sanofi Pasteur Inc. submitted the current supplement Biologic License Application (sBLA) STN 125089 Amendment 395 on June 24, 2010 to seek an extended label indication for Menactra® vaccine to include a two dose series for infants and toddlers at 9 and 12 months of age.

1.1 Brief Overview of Clinical Studies

Four clinical studies were conducted to support the application for administration of Menactra® in children 9 and 12 months of age. An overall description of these studies is provided in Table 1.

Table 1. Description of the Clinical Studies and Size of the US Safety Population

Study	Description of Study	First Dose of Menactra®	Second Dose of Menactra®		
			Menactra® only	Menactra® + Concomitant Vaccine(s)*	Concomitant Vaccine(s)* only
MTA26	Phase II, schedule selection, safety and immunogenicity evaluation of 1 or 2 doses of Menactra® administered at 15 or 18 mos., or 9 and 12, 9 and 15, or 12 and 15 mos.	302	176	N/A	N/A
MTA44	Phase III, immunogenicity and safety evaluation of Menactra® administered to healthy subjects at 9 and 12 mos.	1118	386	644	N/A
MTA37	Phase III, immunogenicity, safety, and noninterference evaluation of pediatric vaccines administered concomitantly with Menactra® to healthy subjects at 9 and 12 mos.	1119	246	802	476
MTA48	Phase III, safety evaluation of Menactra® administered with other pediatric vaccines to healthy subjects at 9 and 12 mos.	1030	N/A	938	321
Total Vaccine(s) Recipients:		**3569**	**808**	**2384**	**797**

***** Concomitant vaccines (administered at 12 months of age) included one or more of the following:
- Measles, mumps, rubella, and varicella vaccine (MMRV)
- Pneumococcal conjugate vaccine (PCV)
- Hepatitis A vaccine (HepA)

Note: Subjects who received Hib vaccine or MMR and V vaccines are not included in this table.
Source: Table 1.1 in applicant's Clinical Overview

The statistical review focuses on the two Phase III studies (MTA37 and MTA44) that provided assessments for the immunogenicity objectives. Review of the safety data is primarily based on the three Phase III studies: MTA37, MTA44, and MTA48.

1.2 Conclusion, Major Statistical Findings and Recommendations

The objective of this application is to provide evidence of immunogenicity and safety of Menactra® administered utilizing a two dose series in infants and toddlers at 9 and 12 months of age. Two Phases III studies were conducted with the primary objectives of evaluating the immunogenicity of Menactra®, measles, Mumps, Rubella and Varicella (MMRV) and pneumococcal conjugate (PCV) vaccines when they were concomitantly administered.

Study MTA44
Study MTA44, a U.S. study was designed to primarily evaluate antibody responses to meningococcal serogroups A, C, Y and W-135, measured by serum bactericidal assay performed using human complement (SBA-HC). The immunogenicity cohort for the primary analysis included 277 subjects who received Menactra® alone for both vaccinations (Group 1). The primary endpoint was the proportion of subjects who received two doses of Menactra® with an SBA-HC titer ≥1:8 thirty days after the second vaccination. In this group, 95.6%, 100%, 96.4% and 86.4% of subjects achieved SBA-HC antibody titers of ≥1:8 after two doses for serogroups A, C, Y, and W-135, respectively (see Table 16). The secondary analysis compared the results of subjects administered Menactra® with and without other childhood vaccinations. Specifically, in the secondary analyses where non-inferiority of the group where Menactra® was administered concomitantly with MMRV or PCV to the group where Menactra® was administered alone was evaluated, the non-inferiority criteria were met for all serogroups for co-administration of Menactra® and MMRV (Table 18). However, for co-administration of Menactra® and PCV, the non-inferiority criteria were met for serogroups A, C and Y, but not for serogroup W-135 (Table 19).

Study MTA37
Study MTA37, a U.S. study was designed to primarily evaluate the antibody responses induced by MMRV or PCV vaccines when administered concomitantly with and without Menactra®. A total of 1281 subjects were included in the primary immunogenicity analysis. In the primary analyses, the antibody responses to measles, mumps, rubella, and varicella were measured by the proportions of the subjects with an antibody level on or above the corresponding pre-specified threshold. The antibody responses to PCV were measured by geometric mean concentrations (GMCs) to *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. As a result, the antibody responses to measles, mumps, rubella, and varicella induced by concomitant administration of MMRV (or MMR+V) and Menactra® were non-inferior to those induced by concomitant administration of MMRV and PCV, but without Menactra®, i.e., the upper bounds of the two-sided 95% CIs of the differences (the group without Menactra® minus the group with Menactra®) in proportions of subjects with an antibody level on or above the threshold were all below the corresponding non-inferiority margins (5% for measles, and 10% for mumps, rubella, and varicella) (see Table 24). On the other hand, the non-inferiority criterion (margin being 2.0 for GMC ratios) for the pneumococcal antibody responses to PCV was met for serotypes 14, 19F, 23F, was met (but marginally) for serotype 9V, but not met for serotypes 4, 6B and 18C (see

Table 26). It is worth noting that all lower bounds of the two-sided 95% CIs of the GMC ratio (Group without Menactra®/Group with Menactra®) were above 1.0, indicating that the GMCs in the group of subjects receiving concomitant administration of Menactra® tended to be statistically significantly lower (at 5% significance level for each serotype) than those in the group without concomitant administration of Menactra®. Therefore, there is a potential for an overall reduced response to the PCV vaccine if Menactra® and PCV are administered concomitantly. Whether these differences matter should be determined by the OVRR reviewers.

A summary of safety overview for three studies (MTA44, MTA37 and MTA48) is provided in the statistical review (see Section 3.3). Overall, the serious adverse event (SAE) rates ranged from 3.9% to 5.4%. The rates of AEs leading to study discontinuation were less than 1%. These rates were mostly similar among treatment 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 of note that all the serogroups (A, C, Y, and W-135) within Menactra® appeared to have seroresponse with rates above 85% when Menactra® was administered alone. No interference in seroresponse was observed when Menactra® was administered concomitantly with MMRV. However, there appeared to be potential interference between Menactra® and PCV (specifically, seroresponses to serogroup W-135 in Menactra® and to serotypes 4, 6B and 18C in PCV).

It is up to the review team to determine if the product is approvable and if so what language in the label may be considered for inclusion to note the possible interference between Menactra® and PCV.

2. INTRODUCTION

2.1 Overview

In this supplemental application to electronic Biologics License Application (e-BLA) 125089/395, the applicant is seeking to expand the label indication for Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra®) to include a two-dose regimen for infants and toddlers at 9 and 12 months of age.

Currently, Menactra® is indicated for active immunization of children, adolescents, and adults aged 2 through 55 years in the prevention of invasive meningococcal disease caused by *N. meningitides* serogroups A, C, Y, and W-135. This supplemental application presents three Phase III clinical studies (MTA44, MTA37, and MTA48) and one Phase II clinical study (MTA26) in support of administration of the vaccine in a 2-dose regimen to infants and toddlers 9 and 12 months of age. Each vaccine dose is administered via IM at a dosage level of 0.5 mL which contains 4 μg of each of the four serogroup–specific polysaccharide antigens. The overall description of the four clinical studies is provided in Table 1.

Study MTA26 (conducted in 2004 to 2005) was a Phase II trial designed to determine an optimal dosing schedule for infants and toddlers aged <2 years. The immunogenicity results from that study demonstrated that a two-dose administration schedule, with the first dose administered at 9 months and the second dose in the second year of life, at least 3 months after the first dose, would likely result in ≥ 85% of subjects achieving protective levels of antibodies (≥ 8) for all of the serogroups, as measured by serum bactericidal assay using human complement (SBA-HC).

Study MTA48 was Phase III, open label safety trial conducted in the US and Chile between May 2007 and January 2009. At enrollment, each 9-month old subject was to be assigned to receive two doses of Menactra® (one at 9 months of age and one at 12 months of age, with the second dose administered concomitantly with routine pediatric vaccines (MMRV, PCV and HepA vaccines). Another group of 12 month old subjects were assigned to receive the same pediatric vaccines at 12 months of age, but not Menactra®. A subset of the Group 1 subjects enrolled in Chile was to have blood draws at baseline and 30 days after the last study vaccinations in order to assess meningococcal antibody levels. The antibody responses of these subjects were evaluated as an observational objective and not included in the application and therefore are not included in the statistical review.

Clinical efficacy was primarily assessed in two US Phase III clinical studies (MTA44 and MTA37), conducted between 2006 and 2009. Menactra® was administered alone to subjects at 9 months of age, followed by a second dose injection at 12 months of age either alone (in Group 1) or concomitantly with a pediatric vaccine. The pediatric vaccine was ProQuad® (Measles, Mumps, Rubella and Varicella Virus Vaccine Live) (MMRV) (Group 2), or Prevnar® (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein]), a pneumococcal conjugate vaccine (PCV) indicated for active immunization against invasive disease caused by *Streptococcus (S.) pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F (Group 3). In addition, MMRV and PCV were administered concomitantly at 12 months to a control group of subjects in study MTA37 (Group 4).

The statistical review focuses on the two Phase III immunogenicity studies (MTA44 and MTA37) and the details are provided in Section 3.

2.2 Data Sources

The statistical review is based on the reports and datasets in the eCTD submission package provided by the applicant at time of the submission (STN 125089/395) dated June 24, 2010. The key materials include (but are not limited to):

- Clinical Overview (Module 2.5)
- Summary of Clinical Efficacy (Module 2.7.3)
- Summary of Clinical Safety (Module 2.7.4)
- Clinical Study Reports for MTA37, MTA44, and MTA48 (Module 5)
- Key data sets: ADSL, ADIM, ADAE for each study (Module 5)

3. STATISTICAL EVALUATION

3.1 Study Descriptions

The primary assay used for measuring the immune responses to Menactra® was the serum bactericidal assay using human complement (SBA-HC). This assay determined the level of complement-mediated killing of the target bacteria, *N. meningitidis* serogroups A, C, Y, and W-135. The SBA-HC was validated by assessing precision, accuracy, dilutability, specificity, lower limit of quantitation (LLOQ), and short-term stability. Immune responses to Menactra® were also measured for exploratory purposes using the serum bactericidal assay using baby rabbit complement (SBA-BR).

The following assays have been validated for the measurement of the antibody responses to the other study vaccines, i.e. MMRV (or measles, mumps, rubella vaccine [MMR] and varicella vaccine [V]), PCV, and *Haemophilus influenzae* type b vaccine (Hib).

- Measles immunoglobulin G (IgG) enzyme linked immunosorbent assay (ELISA) and ----------(b)(4)----------
- Mumps IgG ELISA and (b)(4)
- Rubella IgG ELISA
- ----------(b)(4)---------- IgG ELISA and fluorescent antibody to membrane antigen (FAMA)
- Pneumococcal Multiplexed Opsonophagocytic Killing Assay (MOPA) and capsular polysaccharide (CPS) IgG ELISA
- ----------(b)(4)----------

The following subsections evaluate the two immunogenicity studies (MTA44 and MTA37) which assessed the immune responses to Menactra® alone (Study MTA44) and those to MMRV and PCV (Study MTA37) when the vaccines were co-administered. The immune responses to the Hib vaccine were also measured in these studies but are not evaluated in this review.

For convenience, some tables and figures provided by the applicant in the submission are used and noted in the footnote to reference to the original sources.

3.1.1 Study MTA44

3.1.1.1 Study Design and Endpoints

This study was a modified single-blind (only the laboratory personnel were blinded), randomized, parallel-group, multicenter, comparative trial. A total of approximately 1200 subjects 9 months of age were to be randomized and enrolled at 1:1:1 ratio into one of the three groups described in Table 2.

Table 2: Study Groups and Trial Schedule: MTA44

Group	Visit 1 (at age 9 months)	Visit 2 (at age 12 months)	Visit 3 (30 days after Visit 2)
Group 1	Menactra®	Menactra®	Blood sample
Group 2	Menactra®	Menactra® + MMRV*	Blood sample
Group 3	Menactra®	Menactra® + PCV**	Blood sample

*Measles, mumps, rubella, varicella vaccine: ProQuad (Measles, Mumps, Rubella and Varicella [Oka/Merck] Virus Vaccine Live)
**Pneumococcal conjugate vaccine: Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM_{197} Protein])

Source: Table 3.1 on Page 48 in the applicant's clinical study report for Study MTA44.

The primary objective was to evaluate the antibody responses to meningococcal serogroups A, C, Y, and W-135, measured by SBA-HC, induced by two injections of Menactra® in subjects 9 months of age at the first vaccination visit and 12 months of age at the second vaccination visit (Group 1). The primary endpoints were the SBA-HC meningococcal serogroups A, C, Y, and W-135 antibody titers ≥ 1:8 in the serum specimens collected on Day 30 after the Visit 2 vaccination (Visit 3) in Group 1.

The secondary immunogenicity objectives were:

- To evaluate the antibody responses to meningococcal serogroups A, C, Y, and W-135, measured by SBA-HC, when Menactra® is administered concomitantly with MMRV vaccine(s) in Group 2, and when Menactra® is administered alone in Group 1.
- To evaluate the antibody responses to meningococcal serogroups A, C, Y, and W-135, measured by SBA-HC, when Menactra® is administered concomitantly with PCV in Group 3, and when Menactra® is administered alone in Group 1.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 1257 subjects were enrolled in this study (404 in Group 1, 430 in Group 2, and 423 in Group 3). Table 3 provides details about disposition of the subjects enrolled in the study. There were 129 subjects (128 subjects randomized to Group 2 and one randomized to Group 3) who received ActHIB and the other Group 2 vaccines at Visit 2 before Protocol Amendment 2 was approved and were excluded from all analyses. The remaining 1128 subjects were included in the analyses for "All" subject (404 subjects in Group 1, 302 subjects in Group 2, and 422 subjects in Group 3). Among these 1128 subjects, 10 subjects were excluded from the safety population. Among them, eight subjects were withdrawn from the study before receiving any injection of Menactra®; two subjects (one randomized to Group 2 and one randomized to Group 3) received vaccines that did not correspond to any of the pre-specified study group vaccinations. These two subjects along with the other 129 subjects who received ActHIB® were not considered in the primary analysis and were not included in the current application and therefore were not evaluated in this review.

Table 3: Summary of Subject Disposition of the Total Enrolled Population: MTA44

	Group 1	Group 2	Group 3	Total
All enrolled	404	430	423	1257
Removed from all analyses due to receipt of Hib vaccine	0	128	1	129
Included in the analyses performed on "All Subjects"	404	302	422	1128
Excluded from the safety population:				
Did not receive any study vaccine	1	6	1	8
Received vaccine(s) that did not correspond to any study group vaccinations	0	1	1	2
Included in the safety population as randomized	403	295	420	1118
Included in the safety population according to the vaccine received*	407	293	418	1118

*Four subjects (two randomized to Group 2 and two randomized to Group 3) were analyzed as Group 1 subjects according to the vaccine actually received.

Source: Table 4.2 on Page 93 in the applicant's clinical study report for Study MTA44.

The safety population, therefore, consisted of 1118 subjects who received Menactra® at Visit 1 and had available safety data. Table 4 provides additional details about the disposition of subjects in the safety population, immunogenicity intent-to-treat population, and immunogenicity per-protocol population. The immunogenicity per-protocol population included 277 subjects in Group 1, 180 subjects in Group 2 and 267 subjects in Group 3.

Table 4: Summary of Subject Disposition and Reasons for Early Discontinuation: MTA44

	Group 1 (N=407) n (%)	Group 2 (N=293) n (%)	Group 3 (N=418) n (%)	Total (N=1118) n (%)
Safety population	407 (100.0)	293 (100.0)	418 (100.0)	1118 (100.0)
Received Visit 2 vaccination(s)	386 (94.8)	253 (86.3)	391 (93.5)	1030 (92.1)
Completed vaccination phase of the study	375 (92.1)	247 (84.3)	385 (92.1)	1007 (90.1)
Did not complete the vaccination phase of the study due to:	32 (7.9)	46 (15.7)	33 (7.9)	111 (9.9)
Serious adverse event	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
Other adverse event	0 (0.0)	1 (0.3)	1 (0.2)	2 (0.2)
Non-compliance with the protocol	7 (1.7)	15 (5.1)	13 (3.1)	35 (3.1)
Lost to follow-up	11 (2.7)	13 (4.4)	3 (0.7)	27 (2.4)
Voluntary withdrawal not due to an adverse event	14 (3.4)	17 (5.8)	15 (3.6)	46 (4.1)
Were contacted at the end of the 6-month follow-up	365 (89.7)	252 (86.0)	372 (89.0)	989 (88.5)
Received Visit 2 vaccination(s) and had Visit 3 blood draw	365 (89.7)	235 (80.2)	365 (87.3)	965 (86.3)
Immunogenicity intent-to-treat population	365 (89.7)	235 (80.2)	364 (87.1)	964 (86.2)
Protocol violators included in the intent-to-treat population and excluded from the per-protocol population	88 (21.6)	55 (18.8)	97 (23.2)	240 (21.5)
Immunogenicity per-protocol population	277 (68.1)	180 (61.4)	267 (63.9)	724 (64.8)

Source: Table 4.3 on Page 95 in the applicant's clinical study report for Study MTA44.

Table 5 provides details about protocol violations. Among the subjects included in the safety population and analyzed according to the vaccine received, the proportion of subjects with at least one protocol violation during the study period was 31.9% (130/407) in Group 1, 38.6% (113/293) in Group 2, and 36.1% (151/418) in Group 3. All of these subjects were excluded from the immunogenicity per-protocol (PP) population.

Table 5: Summary of Protocol Violations: MTA44

n (%)	Group 1 (N=407)	Group 2 (N=293)	Group 3 (N=418)
Subjects with any protocol violations	130 (31.9)	113 (38.6)	151 (36.1)
Did not meet entry criteria	1 (0.2)	1 (0.3)	2 (0.5)
Did not come for Visit 2	15 (3.7)	24 (8.2)	20 (4.8)
Attended Visit 2 but did not receive all vaccines	9 (2.2)	15 (5.1)	7 (1.7)
Visit 2 out of window	60 (14.7)	44 (15.0)	69 (16.5)
Blood sample not obtained	18 (4.4)	14 (4.8)	23 (5.5)
Blood draw visit out of window	20 (4.9)	12 (4.1)	23 (5.5)
Received concomitant medication that could affect immunogenicity results	7 (1.7)	3 (1.0)	7 (1.7)
Note: Subjects with more than one protocol violation are counted only once and are classified in the category of violation listed first in this table.			

Source: Table 4.4 on Page 97 in the applicant's clinical study report for Study MTA44.

A summary of the distributions of demographic characteristics among the per-protocol and the safety populations is presented in Table 6. The distributions of sex, age and ethnic origin were similar between the two populations. There was a slightly higher proportion of males (56%, PP population) in Group 2 compared to Group 1 (48%, PP population) and Group 3 (50%, PP population). The majority of subjects were Caucasian (71%-79%).

Table 6: Summary of Subject Demographics: MTA44

	Group 1		Group 2		Group 3	
	PP (N=277)	**Safety (N=407)**	**PP (N=180)**	**Safety (N=293)**	**PP (N=267)**	**Safety (N=418)**
Sex n (%)						
Male	132 (47.7)	190 (46.7)	100 (55.6)	165 (56.3)	134 (50.2)	201 (48.1)
Female	145 (52.3)	217 (53.3)	80 (44.4)	128 (43.7)	133 (49.8)	217 (51.9)
Age (days)						
Mean	277.4	278.7	278.7	279.8	277.5	279.5
Median	277.0	278.0	278.0	279.0	277.0	279.0
SD	9.77	10.55	10.72	10.93	10.08	11.11
Minimum	249	249	250	249	249	249
Maximum	305	305	305	305	304	305
Ethnic Origin n (%)						
Asian	1 (0.4)	3 (0.7)	0 (0.0)	0 (0.0)	5 (1.9)	6 (1.4)
Black	29 (10.5)	45 (11.1)	16 (8.9)	33 (11.3)	37 (13.9)	46 (11.0)
Caucasian	219 (79.1)	316 (77.6)	140 (77.8)	219 (74.7)	189 (70.8)	304 (72.7)
Hispanic	8 (2.9)	15 (3.7)	14 (7.8)	25 (8.5)	17 (6.4)	31 (7.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.7)	2 (0.7)	4 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	19 (6.9)	27 (6.6)	8 (4.4)	14 (4.8)	17 (6.4)	26 (6.2)

Source: Table 4.5 on Page 99 and Table 9.9.2 on Page 177 in the applicant's CSR for Study MTA44.

Reviewer's comments:

- *The proportions of subjects being excluded from the per-protocol population ranged from 32% to 38%. The most frequent reasons for the exclusion were data collected out of window for either the vaccination visits and/or the blood draws. Because of these high "dropout" rates, sensitivity analyses are suggested to evaluate the robustness of the reported results. The primary analysis results for both the total vaccine cohort and the per-protocol cohort are presented in Section 3.2.*
- *The sex distributions were different among the treatment groups, when analyses are performed to compare results among the groups, covariate adjustment for sex may be needed.*

3.1.2 Study MTA37

3.1.2.1 Study Design and Endpoints

This was a modified single-blind (only the laboratory personnel were blinded), randomized, parallel-group, comparative, multicenter trial. A total of 92 study centers in US participated in the study. The study lasted from January 2007 to January 2009. At enrollment, each 9-month old subject was to be randomly assigned to one of four groups denoted by: Group 1A, Group 1B, Group 2, or Group 3 (see Table 7). These subjects were to receive one dose of Menactra® at 9 months of age, followed by a second dose at 12 months of age (administered concomitantly with routine pediatric vaccines in Group 2 [MMRV vaccine or MMR+V vaccines] and Group 3 [PCV]). Subjects in Groups 1A, 2, and 3 were to provide one blood sample 30 days after the second Menactra® administration. Subjects in Group 1B were to provide a blood sample 30 days after the first Menactra® administration. An additional control group consisted of 12-month old subjects enrolled in Group 4, and each subject was to receive the routine pediatric vaccines only (see Table 7). These subjects were to provide one blood sample 30 days after vaccination.

Table 7: Study Design in Study MTA 37

Group	N Planned	N Enrolled	Visit (Age at Vaccination), Vaccine (Route of Administration), Blood Sample			
			Visit 1 (at age 9 mos)	**Visit 1B (at age 10 mos)**	**Visit 2 (at age 12 mos)**	**Visit 2B (at age 13 mos)**
1A	200	201	Menactra® (IM)	-	Menactra® (IM)	BL - PV2†
1B	50	50	Menactra® (IM)	BL-PV1	Menactra® (IM)	
2	700	678*	Menactra® (IM)	-	Menactra® (IM) + MMRV (or MMR+V)‡ (SC)	BL - PV2
3	250	250	Menactra® (IM)	-	Menactra® (IM) + PCV (IM)	BL - PV2
4	625	485*	**Visit 1 (at age 12 months)**		**Visit 1B (at age 13 months)**	
			MMRV (SC) + PCV (IM)		BL – PV1	

IM = intramuscular; SC = subcutaneous; BL = blood sample; PV = post-vaccination visit
‡ Subjects in Group 2 could receive ProQuad or separate injections of M-M-RII and VARIVAX concomitantly with Menactra®.
*Number of subjects analyzed in this report; this does not include 24 Group 2 subjects and 601 Group 4 subjects who received ActHIB before Protocol Amendment 2.

Source: Table 3.1 on Page 53 of the applicant's CSR for MTA37.

The primary objectives are:

- To evaluate the antibody responses induced by MMRV vaccine (or MMR+V vaccines) when administered concomitantly with Menactra® (Group 2) and when MMRV vaccine was administered without Menactra® (Group 4).
- To evaluate the antibody responses induced by PCV when administered concomitantly with Menactra® (Group 3) and when PCV was administered without Menactra® (Group 4).

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

Sixty investigators at 82 clinical sites enrolled a total of 2289 subjects in this study. There were 625 subjects (24 subjects in Group 2 and 601 subjects in Group 4) who received ActHIB as part of their 12-month study vaccinations before Protocol Amendment 2 was approved. These subjects were excluded from all analyses. The remaining 1664 subjects were included in the analyses for "All Subjects" (201 in Group 1A, 50 in Group 1B, 678 in Group 2, 250 in Group 3, and 485 in Group 4). Of these, 21 subjects were excluded from the safety population because they were either withdrawn from the trial before receiving any study vaccine (N=11), or received vaccinations that did not correspond to any of the study group vaccinations (N=1) or enrolled at a clinical site (Site 40) that was found to be non-compliant with protocol procedures and ICH/GCP requirements. As a result, the safety population consisted of 1643 subjects. A summary of the subject disposition of the total enrolled population and safety population are presented in Table 8 and Table 9, respectively.

Table 8: Summary of Subject Disposition of the Total Enrolled Population in MTA37

	Group 1A	Group 1B	Group 2	Group 3	Group 4	Total
All enrolled [1]	201	50	702	250	1086	2289
Subjects who received ActHIB	0	0	24	0	601	625
Included in the analyses performed on "All Subjects"	201	50	678	250	485	1664
Excluded from the safety population:	3	0	8	1	9	21
Did not receive any study vaccine	3	0	3	0	5	11
Received vaccines that did not correspond to any study group vaccination	0	0	1	0	0	1
Enrolled at Site 40	0	0	4	1	4	9
Included in the safety population as randomized	198	50	670	249	476	1643
Included in the safety population according to the vaccine(s) received	207	50	664	246	476	1643
Received MMRV			616			
Received MMR+V			48			

[1] Total number of subjects enrolled, including ActHIB recipients.
Note: In this table, subjects are included in the study groups as they were randomized, with the exception of the last three rows. Subjects from Site 40 were excluded from all safety analyses.
Source: Tables 4.2 on Page 103 in the applicant's CSR for MTA37.

A subject was eligible for the immunogenicity per-protocol analysis set if the subject:

- Satisfied the inclusion /exclusion criteria.
- Received the assigned injections within the specified time window at Visit 1 and Visit 2, as applicable.

- Had blood drawn within the specified time window at Visit 1B (Group 1B and Group 4; BL - PV1) or at Visit 2B (Groups 1A, 2, and 3; BL - PV2), and had any valid serology results.
- Did not have any protocol violation that could have affected his/her immunogenicity response. (Examples of violations that would not have affected the immunogenicity response were administrative/documentation violations, missing diary cards, telephone call out of window, vaccine given in the left thigh rather than in the right thigh).

As shown in Table 9, the immunogenicity intent-to-treat population consisted of 1466 subjects (187 in Group 1A, 49 in Group 1B, 579 in Group 2, 222 in Group 3 and 429 in Group 4). The proportion of subjects included in the per-protocol population for immunogenicity was 71.5% (148/207) in Group 1A, 90.0% (45/50) in Group 1B, 75.0% (498/664) in Group 2, 77.6% (191/246) in Group 3, and 83.8% (399/476) in Group 4.

Table 9: Summary of Subject Disposition and Reasons for Early Discontinuation (Safety Population): MTA37

n (%)	Group 1A (N=207)	Group 1B (N=50)	Group 2 (N=664)	Group 3 (N=246)	Group 4 (N=476)
Safety population	**207 (100.0)**	**50 (100.0)**	**664 (100.0)**	**246 (100.0)**	**476 (100.0)**
Received 9-month vaccination	207 (100.0)	50 (100.0)	664 (100.0)	246 (100.0)	-
Received 9-month vaccination and had blood draw 30 days later	-	49 (98.0)	-	-	-
Received 12-month vaccination(s)	197 (95.2)	49 (98.0)	620 (93.4)	230 (93.5)	476 (100.0)
Completed vaccination phase of the study	192 (92.8)	47 (94.0)	598 (90.1)	224 (91.1)	452 (95.0)
Did not complete vaccination phase of the study due to:	15 (7.2)	3 (6.0)	66 (9.9)	22 (8.9)	24 (5.0)
Serious adverse event	1 (0.5)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)
Other adverse event	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Non-compliance with the protocol Lost to follow-up	2 (1.0)	2 (4.0)	25 (3.8)	8 (3.3)	5 (1.1)
Voluntary withdrawal not due to an adverse event	6 (2.9)	0 (0.0)	12 (1.8)	6 (2.4)	6 (1.3)
	5 (2.4)	1 (2.0)	25 (3.8)	7 (2.8)	13 (2.7)
Were contacted at the end of the 6-month follow-up	196 (94.7)	47 (94.0)	611 (92.0)	221 (89.8)	460 (96.6)
Received 12-month vaccination(s) and had blood draw 30 days later	187 (90.3)	-	581 (87.5)	222 (90.2)	431 (90.5)
Immunogenicity intent-to-treat population	187 (90.3)	49 (98.0)	579 (87.2)	222 (90.2)	429 (90.1)
Violators excluded from the per-protocol population	39 (18.8)	4 (8.0)	81 (12.2)	31 (12.6)	30 (6.3)
Did not meet entry criteria	2	0	6	4	1
Did not receive any vaccine	0	0	0	0	0
Did not receive all assigned vaccines	9	0	2	0	0
Visit out of window	11	0	17	6	0
Blood sample not obtained	0	0	0	0	0
Blood draw visit out of window	16	1	49	20	26
Invalid serology result	0	0	0	0	0
Received a concomitant medication that could have affected the immuno. results	1	1	7	1	3
Other	0	2	0 (0.0)	0 (0.0)	0 (0.0)
Immunogenicity per-protocol population	**148 (71.5)**	**45 (90.0)**	**498 (75.0)**	**191 (77.6)**	**399 (83.8)**

Source: Tables 4.3 and 4.4 in the applicant's CSR for MTA37.

A summary of demographic characteristics is given in Table 10 for the per-protocol population. The age distributions were similar among the treatment groups. However, the distributions for sex and ethnic origin appear to be slightly different among the treatment groups. The proportions of males in Groups 1, 3 and 4 (around 54%) tended to be higher than those of in Group 2 (48%). The proportion of Caucasians in Groups 1, 3 and 4 (around 65%) tended to be lower than that in Group 2 (77%). The statistical reviewer further examined the proportion of subjects who were excluded in the per-protocol population with regard to each of the sex and ethnicity categories (see Table 11). There were tendencies that the proportion of the excluded subjects in one category might be different from that in another category within or across the treatment groups. For example, Within Group 3 and Group 4, the proportions of males (26% and 20%, respectively) who were excluded tended to be higher than those of females (19% and 13%, respectively). However, it is difficult to conclude with regard to statistical significance of the differences because multiple pair-wise comparisons are made and thus an adjustment of Type I error may be necessary.

Table 10: Summary of Subject Demographics (Per-Protocol Population) in MTA37

	Total (N=1281)	**Group 1A (N=148)**	**Group 1B (N=45)**	**Group 2 (N=498)**	**Group 3 (N=191)**	**Group 4 (N=399)**
Sex n (%)						
Male	659 (51.4)	81 (54.7)	24 (53.3)	236 (47.4)	104 (54.5)	214 (53.6)
Female	622 (48.6)	67 (45.3)	21 (46.7)	262 (52.6)	87 (45.5)	185 (46.4)
Age (days)						
Mean	311.3	282.5	282.6	282.6	282.4	375.0
Median	289	280	282	281	281	372
Standard Deviation	44.0	11.5	10.8	11.4	10.0	8.6
Minimum	249	249	252	249	249	365
Maximum	400	304	305	305	305	400
Ethnic Origin n (%)						
Asian	23 (1.8)	2 (1.4)	1 (2.2)	4 (0.8)	0 (0.0)	16 (4.0)
Black	94 (7.3)	10 (6.8)	7 (15.6)	34 (6.8)	7 (3.7)	36 (9.0)
Caucasian	863 (67.4)	98 (66.2)	29 (64.4)	337 (67.7)	147 (77.0)	252 (63.2)
Hispanic	213 (16.6)	25 (16.9)	4 (8.9)	91 (18.3)	28 (14.7)	65 (16.3)
American Indian or Alaska native	1 (<0.1)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	5 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	3 (0.8)
Other	82 (6.4)	12 (8.1)	4 (8.9)	30 (6.0)	9 (4.7)	27 (6.8)

Source: Table 9.9.2 on Page 201 in the applicant's CSR for MTA37.

Table 11: Subjects Who were Excluded from the Per-Protocol Population With Demographic Categories

	Group 1			Group 2			Group 3			Group 4		
	N	# Excluded	%	N	# Excluded	%	N	# Excluded	%	N	# Excluded	%
SEX												
Female	119	31	26.1%	349	87	24.9%	118	31	26.3%	231	46	19.9%
Male	138	33	23.9%	315	79	25.1%	128	24	18.8%	245	31	12.7%
RACE												
American Indian	2	1	50.0%	0	N/A	N/A.	0	N/A	N/A.	0	N/A	N/A.
Asian	6	3	50.0%	5	1	20.0%	0	N/A	N/A.	16	0	0.0%
Black	25	8	32.0%	48	14	29.2%	9	2	22.2%	42	6	14.3%
Caucasian	160	33	20.6%	444	107	24.1%	189	42	22.2%	309	57	18.4%
Hispanic	38	9	23.7%	129	38	29.5%	35	7	20.0%	75	10	13.3%
Native American	0	N/A	N/A.	2	0	0.0%	0	N/A	N/A.	3	0	0.0%
Other	26	10	38.5%	36	6	16.7%	13	4	30.8%	31	4	12.9%

Source: Reviewer's analysis

Reviewer's comments:

- *The numbers in subject disposition presented in Table 8 and* Table 9 *were verified by the reviewer. The "dropout" (subjects being excluded from the per-protocol population) rates for the immunogenicity cohort and the primary analysis were between 16% and 25%.*
- *The demographic characteristics of the excluded subjects vary within and across treatment groups.*
- *Based on both points above, additional sensitivity analyses are needed to examine the impact of the exclusion of the subjects in the primary analysis. The primary analysis results for both the total vaccine cohort and the per-protocol cohort are presented in Section 3.2.*

3.1.3 Study MTA48

3.1.3.1 Study Design and Endpoints

This study was an open-label, controlled, parallel-group, multicenter trial in the US and Chile between May 2007 and January 2009. At enrollment, each 9-month old subject was to be assigned to Group 1, and each 12-month old subject was to be assigned to Group 2. Subjects in Group 1 were to receive 2 doses of Menactra® (one at 9 months of age and one at 12 months of age), with the second dose administered concomitantly with pediatric vaccines. A control group, Group 2, was to receive the same pediatric vaccines at 12 months of age, but not Menactra® (see Table 12). A subset of the Group 1 subjects enrolled in Chile was to have blood draws at baseline and 30 days after the last study vaccinations in order to assess meningococcal antibody levels.

Table 12: Study Design in MTA48

Group (Planned N)	Vaccine(s) Administered	
Group 1 N = 1320	**Vaccination Visit 1 (at age 9 months)** Menactra	**Vaccination Visit 2 (at age 12 months)** Menactra® + MMRV* + PCV† + HepA‡ vaccines
Group 2 N = 500	**Vaccination Visit 1 (at age 12 months)** MMRV* + PCV† + HepA‡ vaccines	

* Measles, mumps, rubella, varicella (MMRV) vaccine: ProQuad® (Measles, Mumps, Rubella and Varicella [Oka/Merck] Virus Vaccine Live)
† Pneumococcal conjugate vaccine (PCV): Prevnar® (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM197 Protein])
‡ Hepatitis A (HepA) vaccine: Vaqta® (Hepatitis A Vaccine, Inactivated)

Source: Table 3.1 on Page 45 in the applicant's CSR for MTA48.

The immunogenicity objective was to describe the antibody responses to meningococcal serogroups A, C, Y, and W-135, measured by serum bactericidal assay using baby rabbit complement (SBA-BR) at baseline and 30 days after the last study vaccinations. Since this objective was observational and only applied to subjects enrolled in Chile, the applicant did not include antibody response results in the application. Therefore, this objective is not being evaluated in this review.

3.1.3.2 Patient Disposition, Demographic and Baseline Characteristics

A summary of subject disposition of the total enrolled population in the US is presented in Table 13. A total of 400 subjects were enrolled at the 8 Chilean sites (200 in Group 1 and 200 in Group 2). No subject was misrandomized or received the wrong vaccine or vaccine dose. Therefore, the safety population included 1374 subjects in the US and all 400 subjects in Chile. A further disposition in terms of completion of the study in this safety population is given in Table 14.

Table 13: Summary of Subject Disposition of the Total Enrolled Population: MTA48

	Group 1	Group 2	Total
All enrolled [1]	1056	322	1378
Excluded from the safety population:	3	1	4
Did not receive any study vaccine	3	1	4
Received vaccine(s) that did not correspond to any study group vaccinations	0	0	0
Included in the safety population as randomized	1053	321	1374
Included in the safety population according to the vaccines received [2]	1053	321	1374
Received MMRV	935	320	1255
Received MMR+V	23	0	23

[1] Total number of subjects enrolled.
[2] Not all subjects in the safety population received MMRV or MMR+V.

Source: Table 3.1 on Page 45 in the applicant's CSR for MTA48.

Table 14: Summary of Subject Disposition and Reasons for Early Discontinuation (Safety Population): MTA48

	US Sites		Chile Sites	
	Group 1	**Group 2**	**Group 1**	**Group 2**
Safety population	1053 (100.0)	321 (100.0)	200 (100.0)	200 (100.0)
Received 9-month vaccination	1053 (100.0)	0 (0.0)	200 (100.0)	-
Received 12-month vaccinations	961 (91.3)	321 (100.0)	21 (10.5)	200 (100.0)
Completed vaccination phase of the study	951 (90.3)	308 (96.0)	21 (10.5)	200 (100.0)
Did not complete vaccination phase of the study due to:	102 (9.7)	13 (4.0)	179 (89.5)	0 (0.0)
Serious adverse event	3 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
Other adverse event	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with the protocol	28 (2.7)	9 (2.8)	171 (85.5)	0 (0.0)
Lost to follow-up	16 (1.5)	4 (1.2)	1 (0.5)	0 (0.0)
Voluntary withdrawal not due to an adverse event	52 (4.9)	0 (0.0)	6 (3.0)	0 (0.0)
Were contacted at the end of the 6-month follow-up	968 (91.9)	310 (96.6)	195 (97.5)	199 (99.5)

Source: Table 4.2 on Page 89 and Table 9.41A on Page 366 in the applicant's CSR for MTA48.

The demographic characteristics for the safety population in the US sites and the Chile sites are summarized in Table 15. The proportions of males and females were comparable between the two treatment groups in the US safety population but were slightly imbalanced in the Chile population. The mean ages were similar in both groups and in both countries. Specifically the mean ages were 282.8 days in Group 1 and 374.6 in Group 2 in the US safety population; and 279.2 in Group 1 and 379.5 in Group 2 among the Chilean subjects. The racial make up of subjects in the US were different than those in Chile. Most subjects were Caucasian (67.6% in Group 1 and 73.8% in Group 2) in the US sites whereas almost all subjects (except for one) were Hispanic in the Chile sites.

Table 15: Summary of Demographics by US and Chile Sites (Safety Population): MTA48

	US Sites		Chile Sites	
	Group 1 (N=1053)	**Group 2 (N=321)**	**Group 1 (N=200)**	**Group 2 (N=200)**
Sex n (%)				
Male	542 (51.5)	163 (50.8)	104 (52.0)	80 (40.0)
Female	511 (48.5)	158 (49.2)	96 (48.0)	120 (60.0)
Age (days)				
Mean	282.8	374.6	279.2	379.5
Median	281.0	372.0	279.0	377.0
SD	10.79	8.93	16.83	10.57
Minimum	249	365	247	365
Maximum	306	400	305	400
Ethnic Origin n (%)				
Asian	15 (1.4)	14 (4.4)	0 (0.0)	0 (0.0)
Black	158 (15.0)	18 (5.6)	0 (0.0)	0 (0.0)
Caucasian	712 (67.6)	237 (73.8)	1 (0.5)	0 (0.0)
Hispanic	126 (12.0)	38 (11.8)	199 (99.5)	200 (100)
American Indian or Alaska Native	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islands	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	37 (3.7)	13 (4.0)	0 (0.0)	0 (0.0)

Source: Table 4.5 on Page 95 and Table 9.42.1 on Page 368 in the applicant's CSR for MTA48.

3.2 Evaluation of Immunogenicity

3.2.1 Immunogenicity Responses to Menactra®

Immunogenicity responses to Menactra® were evaluated as primary and secondary objectives in Study MTA44. The data were also available and evaluated as observational objectives in Study MTA37.

3.2.1.1 Statistical Methodologies (MTA44)

According to the protocol, the proportion of subjects with an SBA-HC titer ≥ 8 in Group 1 30 days after the Visit 2 vaccination was calculated, and the 95% CI of this percentage was computed using the Clopper-Pearson Exact method. The percentage was calculated separately for each serogroup. With 320 evaluable subjects planned in Group 1 and a true percentage of subjects with an SBA-HC titer ≥ 8 of 88% for serogroup A and 90% for serogroups C, Y, and W-135, the probability of observing a 95% CI within of the point estimate was > 99.9%.

Primary Success Criterion:
The 95% confidence interval (CI) of the observed percentage of subjects in Group 1 with an SBA-HC titer ≥ 8, 30 days after the Visit 2 vaccination is within ± 5% of this percentage, assuming the true percentage is 88% for serogroup A and 90% for serogroups C, Y, and W-135.

The secondary objectives were evaluated by non-inferiority tests. The proportions of subjects with an SBA-HC titer ⩾ 1:8 thirty days after the Visit 2 vaccination(s) in Groups 2 (p_2) and 3 (p_3) were separately compared to those in Group 1 (p_1). Each serogroup was tested separately. The non-inferiority hypothesis was supported by the data if the upper limit of the two-sided 95% CI of the difference between these proportions (p_1-p_2 or p_1-p_3, for the first and the second secondary objectives, respectively), calculated using the normal approximation, was less than 10% for each serogroup.

Reviewer's comments:
- *The success criterion for evaluating the primary objective was unclear from the statistical perspective. It is unclear whether this criterion was based on the precisions (95% CI) of the estimates or a joint consideration of both the point estimates and their precisions. If it was based on the precisions only, with the targeted sample size, the criterion could be met for any proportions above 75% or below 25%. The observed proportions should imply the success of the vaccine; however, it is unclear how the observed proportions may be evaluated against the assumed proportions. The statistical reviewer defers to the clinical reviewer with regard to evaluation of the success of the study in addressing its primary objective.*

3.2.1.2 Results in MTA44 (Primary and Secondary Objectives)

For the primary objective, the observed proportions of subjects with an SBA-HC titer ⩾ 1:8 thirty days after the Visit 2 vaccination(s) in Group 1 are summarized in Table 16. Due to high "dropouts" rates, in addition to the primary results using subjects in the immunogenicity per-

protocol (PP) population, the results are also presented for all subjects in the immunogenicity intent-to-treat (ITT) population. The point estimates of the proportions using the ITT population were about 1% lower than those using the PP population. The statistical reviewer further explored the results by using logistic regression adjusting for different combinations of covariates (sex, race, blood draw date and/or the indicator whether or not the subject was in the PP population). The results (not presented) were consistent for the serogroups with those presented in Table 16.

Table 16: Proportions of Subjects with an SBA-HC Antibody Titer ≥ 1:8 after 30 Days after the Second Doses of Menactra® by Serogroup: MTA44

	Per-Protocol		Intent-To-Treat	
Serogroup	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
A	260/272	95.6 (92.4; 97.7)	338/360	93.9 (90.9, 96.1)
C	277/277	100.0 (98.7;100.0)	362/365	99.2 (97.6, 99.8)
Y	265/275	96.4 (93.4; 98.2)	348/363	95.9 (93.3, 97.7)
W-135	236/273	86.4 (81.8; 90.3)	308/361	85.3 (81.2, 88.8)

Source: Table 5.1 on Page 101 in the applicant's clinical study report for Study MTA44.

For the secondary objectives, the analyses were performed to compare the immunogenicity of Menactra® when co-administered with other vaccines with that when Menactra® was administered alone at 12 months. The comparisons of the proportions of subjects with an SBA-HC antibody titer of ≥1:8 on Day 30 after the Visit 2 vaccination between Group 1 and Group 2 are presented in Table 17. The upper bounds of the two-sided 95% confidence intervals of the differences for all serogroups were below 10%, the pre-specified non-inferiority margin. This finding indicates that the non-inferiority was met when comparing Group 2 with Group 1. Similarly, the comparisons of the proportions of subjects with an SBA-HC antibody titer of ≥1:8 on Day 30 after the Visit 2 vaccination between Group 1 and Group 3 are presented in Table 18. The non-inferiority criterion was met for Serogroups A, C and Y but was not met for Serogroup W-135. For Serogrous A and C, the lower bounds of the two-sided 95% CI of the differences were above 0, indicating a trend towards statistically significantly lower rates for these serogroups in Group 3 where subjects received co-administration of PCV and Menactra® at 12 months.

Table 17: Group 1 Versus Group 2 Subjects With SBA-HC Antibody Titers ≥1:8 After the Visit 2 Menactra® Vaccination, by Serogroup (Per-Protocol Population)

Serogroup	**Group 1 (Menactra) (N=277)**		**Group 2 (Menactra+MMRV) (N=180)**		**Difference ($p_1 - p_2$)**	**95% CI of the Difference**
	n/N	**% (95% CI)**	**n/N**	**% (95% CI)**		
A	260/272	95.6 (92.4; 97.7)	164/177	92.7 (87.8; 96.0)	2.9	(-1.6; 7.5)
C	277/277	100.0 (98.7; 100.0)	178/180	98.9 (96.0; 99.9)	1.1	(-0.4; 2.6)
Y	265/275	96.4 (93.4; 98.2)	173/179	96.6 (92.8; 98.8)	-0.3	(-3.7; 3.2)
W-135	236/273	86.4 (81.8; 90.3)	157/178	88.2 (82.5; 92.5)	-1.8	(-8.0; 4.5)

Source: Table 5.2 on Page 102 in the applicant's clinical study report for Study MTA44.

Table 18: Group 1 Versus Group 3 Subjects With SBA-HC Antibody Titers ≥1:8 After the Visit 2 Menactra® Vaccination, by Serogroup (Per-Protocol Population): MTA44

Serogroup	Group 1 (N=277)		Group 3 (N=267)		Difference (p_1 -p_3)	95% CI of the Difference
	n/N	% (95% CI)	n/N	% (95% CI)		
A	260/272	95.6 (92.4; 97.7)	239/264	90.5 (86.3; 93.8)	5.1	(0.8; 9.4)
C	277/277	100 (98.7; 100)	261/267	97.8 (95.2; 99.2)	2.2	(0.5; 4.0)
Y	265/275	96.4 (93.4; 98.2)	254/267	95.1 (91.8; 97.4)	1.2	(-2.2; 4.6)
W-135	236/273	86.4 (81.8; 90.3)	216/266	81.2 (76.0; 85.7)	5.2	(-1.0; 11.5)

Source: Table 5.3 on Page 103 in the applicant's clinical study report for Study MTA44.

A summary of the geometric mean titers (GMTs) for each treatment group are presented in Table 19. Overall, slightly lower titers were seen in Group 3 subjects compared to those in Group 1 and Group 2.

Table 19: Summary of SBA-HC Geometric Mean Titers after the Visit 2 Menactra Vaccination, by Serogroup (Per-Protocol Population): MTA44

Serogroup	Group 1 (N=277)			Group 2 (N=180)			Group 3 (N=267)		
	N	GMT	95% CI	N	GMT	95% CI	N	GMT	95% CI
A	272	54.9	(46.8 ; 64.5)	177	52.0	(41.8 ; 64.7)	264	41.0	(34.6 ; 48.5)
C	277	141.8	(123.5 ; 162.9)	180	161.9	(136.3 ; 192.3)	267	109.5	(94.1 ; 127.5)
Y	275	52.4	(45.4 ; 60.6)	179	60.2	(50.4 ; 71.7)	267	39.9	(34.4 ; 46.2)
W-135	273	24.3	(20.8 ; 28.3)	178	27.9	(22.7 ; 34.3)	266	17.9	(15.2 ; 21.0)

Source: Table 5.5 on Page 105 in the applicant's clinical study report for Study MTA44.

3.2.1.3 Results in MTA37 (Observational Objectives)

In Study MTA37, meningococcal antibody responses were measured in Groups 1A, 1B, and 3. There were no pre-specified statistical hypotheses to be tested on the data collected within this study. Simple descriptive statistics were to be examined and presented. The observed numbers and proportions of subjects who had SBA-HC antibody titer ≥4 and ≥8 on Day 30 after Menactra® vaccination are presented in Table 20. The observed GMTs by serogroup are presented in Table 21. The meningococcal antibody responses were generally observed to be higher after two doses of Menactra® when compared to after one dose of Menactra®. When co-administered with the PCV vaccine (Group 3), the meningococcal antibody responses were slightly lower compared to administration with Menactra® alone.

Table 20: Summary of Defined Levels of Serologic Response in SBA-HC Antibody Titer after Menactra® Vaccination in Groups 1A, 1B, and 3 (Per-Protocol Population): MTA37

Serogroup	SBA-HC Titer	Group 1A Post-Dose 2 (N=148) [1] n/M	% [2]	95% CI [3]	Group 1B Post-Dose 1 (N=45) [1] n/M	% [2]	95% CI [3]	Group 3 Post-Dose 2 (N=191) [1] n/M	% [2]	95% CI [3]
A	≥ 4	139/144	96.5	(92.1; 98.9)	37/43	86.0	(72.1; 94.7)	170/174	97.7	(94.2; 99.4)
	≥ 8	131/144	91.0	(85.1; 95.1)	34/43	79.1	(64.0; 90.0)	161/174	92.5	(87.6; 96.0)
C	≥ 4	147/147	100	(97.5; 100)	41/44	93.2	(81.3; 98.6)	177/178	99.4	(96.9; 100)
	≥ 8	147/147	100	(97.5; 100)	38/44	86.4	(72.6; 94.8)	176/178	98.9	(96.0; 99.9)
Y	≥ 4	141/145	97.2	(93.1; 99.2)	16/43	37.2	(23.0; 53.3)	170/174	97.7	(94.2; 99.4)
	≥ 8	138/145	95.2	(90.3; 98.0)	12/43	27.9	(15.3; 43.7)	164/174	94.3	(89.7; 97.2)
W-135	≥ 4	126/145	86.9	(80.3; 91.9)	8/43	18.6	(8.4; 33.4)	151/173	87.3	(81.4; 91.9)
	≥ 8	119/145	82.1	(74.8; 87.9)	6/43	14.0	(5.3; 27.9)	136/173	78.6	(71.7; 84.5)

[1] N: number of subjects in the per-protocol population.
[2] M: number of subjects with valid test results; n: number of subjects with the given titer levels. Proportions are based on M.
[3] CIs are calculated based on Clopper Pearson exact method.
Source: Table 5.5 on Page 119 in the applicant's clinical study report for Study MTA37.

Table 21: Summary of SBA-HC Geometric Mean Titers After Menactra® Vaccination in Groups 1A, 1B, and 3 (Per-Protocol Population): MTA37

Serogroup	Group 1A Post-Dose 2 (N=148) [1] M [2]	GMT	95% CI [3]	Group 1B Post-Dose 1 (N=45) [1] M [2]	GMT	95% CI [3]	Group 3 Post-Dose 2 (N=191) [1] M [2]	GMT	95% CI [3]
A	144	39.5	(31.5; 49.7)	43	14.1	(9.49; 20.8)	174	38.6	(31.9; 46.7)
C	147	161	(134; 192)	44	23.7	(16.4; 34.4)	178	109	(91.2; 131)
Y	145	65.9	(52.6; 82.5)	43	3.63	(2.77; 4.76)	174	45.1	(37.0; 55.0)
W-135	145	19.4	(15.6; 24.0)	43	2.90	(2.18; 3.85)	173	16.1	(13.3; 19.6)

[1] N: number of subjects in the per-protocol population.
[2] M: number of subjects with valid test results.
[3] The 95% CIs are based on a normal approximation.
Source: Table 5.6 on Page 120 in the applicant's clinical study report for Study MTA37.

3.2.1.4 Seroresponses to Menactra® by Sex and Race

Subgroup analyses by sex and by race with regard to the proportions (95% CIs) of the subjects with a titer ≥ 1:8 were further described in Table 22 and Table 23, respectively, for the per-protocol population in MTA44. In general, the results in the subgroups were consistent with the overall results. The reliability of the information provided by some of the subgroups (e.g. minority racial groups) may be limited due to small sample size.

Table 22: Proportions of Subjects with an SBA-HC Antibody Titer ≥ 1:8 after 30 Days after the Second Doses of Menactra® by Serogroup and Sex (Per-Protocol Population): MTA44

PP	Females		Males	
Serogroup	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
A	137/140	97.9% (93.9%, 99.6%)	123/132	93.2% (87.5%, 96.8%)
C	145/145	100% (97.5%, 100%)	132/132	100% (97.2%, 100%)
Y	137/143	95.8% (91.1%, 98.4%)	128/132	97.0% (92.4%, 99.2%)
W-135	125/141	88.7% (82.2%, 93.4%)	111/132	84.1% (76.7%, 89.9%)

Source: Reviewer's analysis

Table 23: Proportions of Subjects with an SBA-HC Antibody Titer ≥ 1:8 after 30 Days after the Second Doses of Menactra® by Serogroup and Race (Per-Protocol Population): MTA44

	Serogroup A		Serogroup C		Serogroup Y		Serogroup W-135	
RACE	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
Asian	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)
Black	23/28	82.1% (63.1%, 93.9%)	29/29	100% (88.1%, 100%)	26/29	89.7% (72.6%, 97.8%)	25/29	86.2% (68.3%, 96.1%)
Caucasian	210/216	97.2% (94.1%, 99.0%)	219/219	100% (98.3%, 100%)	212/218	97.2% (94.1%, 99.0%)	188/216	87.0% (81.8%, 91.2%)
Hispanic	8/8	100% (63.1%, 100%)	8/8	100% (63.1%, 100%)	7/8	87.5% (47.3%, 99.7%)	5/8	62.5% (24.5%, 91.5%)
Native	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)	1/1	100% (2.50%, 100%)
Other	17/18	94.4% (72.7%, 99.9%)	19/19	100% (82.4%, 100%)	18/18	100% (81.5%, 100%)	16/18	88.9% (65.3%, 98.6%)

Source: Reviewer's analysis

3.2.2 Immunogenicity Responses to MMRV and PCV Vaccines

Immunogenicity responses to MMRV and PCV vaccines were evaluated in Study MTA37. Note that these objectives do not including serotypes contained in the Menactra® vaccine; however, these immune responses provide insight about potential interactions between Menactra® and other childhood vaccines

3.2.2.1 Statistical Methodologies in MTA37

The hypotheses and corresponding statistical methods for addressing the success criteria for the two co-primary objectives are described below:

Primary Hypothesis 1

Thirty days after MMRV (or MMR+V) vaccination, the proportion of subjects in Group 2 (those administered Menactra® at 9 months followed by Menactra® and MMRV vaccines at 12 months) with the antibody concentrations specified below was non-inferior to the corresponding proportion of subjects in Group 4 (the control group of subjects not administered Menactra).

- Measles ≥300 mIU/mL (measured by ELISA) or ≥ 120 mIU/mL (measured by neutralization assay when the ELISA concentration was < 300 mIU/mL)
- Mumps ≥500 U/mL (measured by ELISA) or ≥ 60 (1/dil) (measured by neutralization assay when the ELISA concentration was < 500 U/mL)
- Rubella ≥10 IU/mL (measured by ELISA)
- Varicella ≥300 mIU/mL (measured by ELISA) or ≥4 (1/dil) (measured by FAMA assay when the ELISA concentration was < 300 mIU/mL)

In support of primary hypothesis 1, the null hypothesis (H0: $p4 - p2 \geq \delta$) was tested against the alternative hypothesis (H1: $p4 - p2 < \delta$), where $p4$ and $p2$ were the proportions of subjects in Group 4 and Group 2, respectively, who had the concentrations of antibodies defined above with $\delta = 0.10$ if $p4 \leq 0.95$ and $\delta = 0.05$ if $p4 > 0.95$. If the upper limit of the two-sided 95% confidence interval (CI) of the difference between the two proportions was less than δ for each antibody, and assuming the difference between the two proportions was normally distributed, the inferiority assumption was to be rejected. Each measles, mumps, rubella, and varicella antigen was tested separately.

Primary Hypothesis 2

Thirty days after PCV vaccination, the geometric mean concentration (GMC) of antibodies (measured by ELISA) to each of the *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in subjects in Group 3 (those administered Menactra® at 9 months followed by Menactra® and PCV vaccines at 12 months) was non-inferior to the corresponding GMC in subjects in Group 4.

In support of primary hypothesis 2, the null hypothesis (H_0: $GMC_4 / GMC_3 > 2$) was tested against the alternative hypothesis (H_1: $GMC_4 / GMC_3 \leq 2$), where GMC_4 and GMC_3 were the GMCs of anti-pneumococcal antibodies in subjects in Group 4 and Group 3, respectively. If the upper limit of the two-sided 95% CI of the ratio of the two GMCs was less than 2 for each serotype, the inferiority assumption was to be rejected. Each of the serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F was tested separately. There was an estimated 89.9% power to reject the null hypotheses 1 and 2 simultaneously.

To be considered successful, both primary hypothesis 1 and primary hypothesis 2 must be considered co-primary hypothesis and must both meet pre-specified criteria.

Reviewer's comments:

- *Group 1 is not used for the primary analysis.*
- *The non-inferiority margins for the first primary hypothesis were arbitrary to some extent because they were determined based on the observed proportions of subjects with antibody response in Group 4. Because there were variations in the observed proportions, the non-*

inferiority margins became arbitrary (between the choice of 5% and 10%) and could be more or less stringent than the intended margin in the case where the true proportions in the comparison group were actually on the opposite side of 95% comparing with the observed. Nevertheless, the degree of precision is acceptably high because of the large sample size in the study. Therefore, the probability for the derived non-inferiority margin being different from the intended margin is small. The study results presented in the following subsection indicated a success even if the non-inferiority margins were 5% for all the antigens.

3.2.2.2 Results in MTA37

The primary analysis results for the comparisons of antibody responses for measles, mumps, rubella, and varicella in the per-protocol population are presented in Table 24. Based on the observed point estimates of the proportions of subjects with response, the non-inferiority margins were set at 5% for measles and 10% for mumps, rubella and varicella according to the protocol. All the upper bounds of the two-sided 95% CIs of the differences [Group 4-Group2] based on the proportion of subjects with antibody concentrations above the thresholds were below 5%. These findings indicate that the non-inferiority criteria were met for antibody responses for measles, mumps, rubella, and varicella when comparing the group of subjects receiving Menactra® and MMRV (Group 2) with the group of subjects receiving MMRV and PCV (Group 4). Similar results were observed in the ITT population (see Table 25).

Table 24: Comparisons of Measles, Mumps, Rubella, and Varicella Antibody Responses between Group 4 and Group 2 Subjects (Per-Protocol Population): MTA37

Antigen	Concentration Level (Assay Type)	Group 4 MMRV + PCV (N=429)		Group 2 Menactra® + (MMRV or MMR+V) (N=579)		Difference in Proportions (Group 4 - Group 2)	
		n/N	%	n/N	%	%	95% CI
Measles	>= 300 mIU/mL (ELISA) or >= 120 mIU/mL (neutralization)	386/395	97.7	488/498	98.0	-0.3	(-2.2; 1.6)
Mumps	>= 500 U/mL (ELISA) or >= 60 1/dil (neutralization)	373/394	94.7	474/498	95.2	-0.5	(-3.4; 2.4)
Rubella	>= 10 IU/mL (ELISA)	348/394	88.3	463/498	93.0	-4.6	(-8.5; -0.8)
Varicella	>= 300 mIU/mL (ELISA) or >= 4 1/dil (FAMA)	342/395	86.6	463/498	93.0	-6.4	(-10.4; -2.3)

Source: Table 5.1 on Page 113 in the applicant's CSR for MTA37.

Table 25: Comparisons of Measles, Mumps, Rubella, and Varicella Antibody Responses between Group 4 and Group 2 (Intent-to-Treat Population): MTA37

Antigen	Concentration Level (Assay Type)	Group 4 MMRV + PCV (N=429)		Group 2 Menactra® + (MMRV or MMR+V) (N=579)		Difference in Proportions (Group 4 - Group 2)	
		n/N	%	n/N	%	%	95% CI
Measles	>= 300 mIU/mL (ELISA) or >= 120 mIU/mL (neutralization)	416/425	97.9	566/577	98.1	-0.2	(-2.0; 1.6)
Mumps	>= 500 U/mL (ELISA) or >= 60 1/dil (neutralization)	402/424	94.8	548/577	95.0	-0.2	(-2.9; 2.6)
Rubella	>= 10 IU/mL (ELISA)	374/424	88.2	539/577	93.4	-5.2	(-8.9; -1.5)
Varicella	>= 300 mIU/mL (ELISA) or >= 4 1/dil (FAMA)	361/425	84.9	538/577	93.2	-8.3	(-12.3; -4.3)

Source: Table 9.35 on Page 480 in the applicant's CSR for MTA37.

The primary analysis results for the comparisons of the GMC of antibodies (measured by ELISA) to each of the *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in the per-protocol population between Group 4 and Group 3 are presented in Table 26. The upper bounds of the two-sided 95% CIs of the GMC ratio (Group 4/Group 3) exceeded 2.0 for serotypes 4, 6B, 18C, was exactly 2.0 for serotype 9V and were below 2.0 for serotypes 14, 19F, and 23F. Similar results were observed in the ITT population (see Table 27). The non-inferiority criteria were not fully met in terms of immunogenicity response to PCV.

It is worth noting that the lower bounds of the 95% CIs for all the serotypes were above 1.0, indicating a tendency towards significant lower responses to PCV in the group where Menactra® and PCV were co-administered when compared to the group in which PCV and MMRV were co-administered without Menactra®. The statistical reviewer further explored the GMC results separated by females and males (see Table 30). The results were consistent with the overall conclusions. The lower bounds of the 95% CIs of the GMC ratios were all above 1.0, indicating tendency toward statistically significant lower GMC in Group 3. It appears that GMC ratios (Group 4/Group 3) tended to be slightly higher in males than females. However, there was no formal statistical testing performed and confirmation of the findings would require a larger sample size. Similarly, the GMC ratios by race were presented in Table 31.

Table 26: Geometric Mean Concentrations of Anti-Pneumococcal Antibodies (Measured by ELISA) 30 Days after PCV Vaccination in Groups 4 and 3 (Per-Protocol Population): MTA37

Serotype	Group 4 (N=399) MMRV + PCV GMC	Group 3 (N=191) Menactra + PCV GMC	Group 4 GMC / Group 3 GMC	
			GMC Ratio	95% CI
4	3.33	1.82	1.83	(1.58, 2.11)
6B	10.8	5.40	1.99	(1.72, 2.31)
9V	3.57	2.06	1.74	(1.51, 2.00)
14	10.5	6.73	1.56	(1.35, 1.80)
18C	2.91	1.58	1.84	(1.59, 2.12)
19F	4.03	2.50	1.61	(1.42, 1.84)
23F	7.03	4.62	1.52	(1.29, 1.79)

Source: Table 5.3 on Page 116 in the applicant's CSR for MTA37.

Table 27: Geometric Mean Concentrations of Anti-Pneumococcal Antibodies (Measured by ELISA) 30 Days after PCV Vaccination in Groups 4 and 3 (ITT Population): MTA37

Serotype	Group 4 (N=399) MMRV + PCV GMC	Group 3 (N=191) Menactra + PCV GMC	Group 4 GMC / Group 3 GMC	
			GMC Ratio	95% CI
4	3.23	1.81	1.78	(1.55; 2.05)
6B	10.5	5.52	1.91	(1.66; 2.19)
9V	3.49	2.06	1.69	(1.48; 1.94)
14	10.3	6.67	1.54	(1.35; 1.77)
18C	2.83	1.60	1.77	(1.54; 2.02)
19F	3.96	2.48	1.59	(1.40; 1.81)
23F	6.85	4.67	1.47	(1.26; 1.71)

Source: Table 9.37 on Page 483 in the applicant's CSR for MTA37.

3.2.2.3 Seroresponses to MMRV and PCV by Gender and Race

The reviewer further evaluated the results by sex and by race. The primary analysis results of seroresponse to MMRV vaccine by sex and by race are provided in Table 28 and Table 29, respectively. The seroresponse results to PCV vaccine by sex and by race are provided in Table 30 and Table 31, respectively. The results in males and females were consistent with the overall conclusion. The results were also consistent in the subgroup of whites, the majority of the study population. Because the sample sizes in the other racial subgroups were small, the statistical powers were reduced and non-inferiority criteria were not all met.

Table 28: Comparisons of Measles, Mumps, Rubella, and Varicella Antibody Responses between Group 4 and Group 2 Subjects by Sex (Per-Protocol Population): MTA37

		Proportion of Subjects with antibody level above threshold							
		Females				Males			
		N	%	Lower 95% CI	Upper 95% CI	N	%	Lower 95% CI	Upper 95% CI
MEASLES	Group 4	184	97.8	94.5	99.4	211	97.6	94.6	99.2
	Group 2	262	98.1	95.6	99.4	236	97.9	95.1	99.3
	Difference	-	-0.3	-2.9	2.4	-	-0.3	-3.0	2.5
MUMPS	Group 4	183	95.6	91.6	98.1	211	93.8	89.7	96.7
	Group 2	262	95.0	91.7	97.3	236	95.3	91.8	97.7
	Difference	-	0.6	-3.4	4.6	-	-1.5	-5.7	2.7
RUBELLA	Group 4	183	90.2	84.9	94.1	211	86.7	81.4	91.0
	Group 2	262	95.4	92.1	97.6	236	90.3	85.7	93.7
	Difference	-	-5.3	-10.3	-0.3	-	-3.5	-9.5	2.4
VARICELLA	Group 4	184	88.0	82.5	92.4	211	85.3	79.8	89.8
	Group 2	262	92.4	88.5	95.3	236	93.6	89.7	96.4
	Difference	-	-4.3	-10.0	1.4	-	-8.3	-14.0	-2.6

Source: Reviewer's analysis

Table 29: Comparisons of Measles, Mumps, Rubella, and Varicella Antibody Responses between Group 4 and Group 2 Subjects by Race (Per-Protocol Population): MTA37

Proportion of Subjects with antibody level above threshold		MEASLES			MUMPS			RUBELLA			VARICELLA		
		%	Lower 95% CI	Upper 95% CI	%	Lower 95% CI	Upper 95% CI	%	Lower 95% CI	Upper 95% CI	%	Lower 95% CI	Upper 95% CI
Asian	Group4	100.0	79.4	100.0	93.8	69.8	99.8	87.5	61.7	98.4	87.5	61.7	98.4
	Group 2	75.0	19.4	99.4	75.0	19.4	99.4	75.0	19.4	99.4	100.0	39.8	100.0
	Difference	25.0	-17.4	67.4	18.8	-25.3	62.8	12.5	-32.9	57.9	-12.5	-28.7	3.7
Black	Group 4	97.2	85.5	99.9	N/A			97.2	85.5	99.9	13.9	4.7	29.5
	Group 2	100.0	89.7	100.0				97.1	84.7	99.9	17.6	6.8	34.5
	Difference	-2.8	-8.1	2.6				0.2	-7.7	8.0	-3.8	-20.8	13.3
Caucasian	Group 4	97.2	94.3	98.9	92.7	88.8	95.6	85.9	80.9	90.0	87.6	82.8	91.4
	Group 2	97.9	95.8	99.2	95.0	92.0	97.0	92.3	88.9	94.9	93.5	90.3	95.9
	Difference	-0.7	-3.3	1.8	-2.2	-6.2	1.8	-6.4	-11.6	-1.2	-5.9	-10.8	-1.0
Hispanic	Group 4	98.5	91.7	100.0	98.5	91.7	100.0	93.8	85.0	98.3	83.1	71.7	91.2
	Group 2	97.8	92.3	99.7	94.5	87.6	98.2	93.4	86.2	97.5	95.6	89.1	98.8
	Difference	0.7	-3.6	4.9	4.0	-1.6	9.5	0.4	-7.3	8.2	-12.5	-22.6	-2.5
Other	Group 4	N/A			96.2	80.4	99.9	84.6	65.1	95.6	84.6	65.1	95.6
	Group 2				96.7	82.8	99.9	96.7	82.8	99.9	90.0	73.5	97.9
	Difference				-0.5	-10.3	9.3	-12.1	-27.3	3.2	-5.4	-22.9	12.2

Source: Reviewer's analysis

Table 30: Geometric Mean Concentrations of Anti-Pneumococcal Antibodies (Measured by ELISA) 30 Days after PCV Vaccination in Groups 4 and 3 by Sex (PP Population): MTA37

PNEUMOCOCCAL SEROTYPE		Females				Males			
		N	GMT	Lower 95% CI	Upper 95% CI	N	GMT	Lower 95% CI	Upper 95% CI
4	Group 4	180	3.43	3.01	3.90	209	3.25	2.91	3.63
	Group 3	86	2.10	1.75	2.52	104	1.62	1.39	1.88
	GMT Ratio	-	1.63	1.30	2.04	-	2.01	1.66	2.43
6B	Group 4	181	11.29	9.91	12.86	208	10.32	9.24	11.52
	Group 3	86	5.89	4.96	6.98	104	5.03	4.25	5.97
	GMT Ratio	-	1.92	1.54	2.39	-	2.05	1.69	2.49
9V	Group 4	181	3.60	3.17	4.09	209	3.55	3.20	3.95
	Group 3	86	2.32	1.97	2.74	104	1.86	1.60	2.16
	GMT Ratio	-	1.55	1.25	1.92	-	1.91	1.59	2.30
14	Group 4	181	10.69	9.46	12.09	209	10.27	9.21	11.45
	Group 3	86	7.15	5.95	8.60	104	6.39	5.42	7.55
	GMT Ratio	-	1.50	1.20	1.86	-	1.61	1.32	1.95

PNEUMOCOCCAL SEROTYPE		Females				Males			
		N	GMT	Lower 95% CI	Upper 95% CI	N	GMT	Lower 95% CI	Upper 95% CI
18C	Group 4	180	2.82	2.48	3.21	209	2.99	2.65	3.37
	Group 3	86	1.69	1.47	1.94	104	1.50	1.30	1.74
	GMT Ratio	-	1.67	1.35	2.06	-	1.99	1.63	2.43
19F	Group 4	181	4.26	3.80	4.77	209	3.84	3.48	4.24
	Group 3	86	2.61	2.25	3.03	104	2.41	2.06	2.81
	GMT Ratio	-	1.63	1.34	1.98	-	1.59	1.34	1.90
23F	Group 4	181	6.96	5.96	8.12	209	7.09	6.30	7.98
	Group 3	86	4.98	4.06	6.10	104	4.34	3.67	5.13
	GMT Ratio	-	1.40	1.08	1.82	-	1.63	1.33	2.00

Source: Reviewer's analysis

Table 31: Geometric Mean Concentrations Ratio of Anti-Pneumococcal Antibodies (Measured by ELISA) between Groups 4 and 3 by Race (PP Population): MTA37

Serotype	Black			Caucasian			Hispanic			Other		
	GMC Ratio	Lower 95% CI	Upper 95% CI	GMC Ratio	Lower 95% CI	Upper 95% CI	GMC Ratio	Lower 95% CI	Upper 95% CI	GMC Ratio	Lower 95% CI	Upper 95% CI
4	1.92	0.94	3.89	1.74	1.48	2.05	1.91	1.24	2.93	1.30	0.74	2.29
6B	2.35	1.24	4.44	1.68	1.43	1.98	2.67	1.76	4.06	2.54	1.44	4.47
14	1.82	1.07	3.07	1.49	1.26	1.76	1.78	1.17	2.70	1.00	0.55	1.81
18C	2.88	1.23	6.74	1.65	1.40	1.94	2.13	1.45	3.13	1.54	0.91	2.61
19F	2.28	1.21	4.30	1.48	1.28	1.72	1.77	1.27	2.47	1.49	0.82	2.73
23F	1.58	0.69	3.59	1.30	1.08	1.56	2.12	1.41	3.18	1.64	0.80	3.38
9V	2.03	0.99	4.19	1.56	1.33	1.83	2.04	1.41	2.95	1.88	0.94	3.77

Source: Reviewer's analysis

3.3 Evaluation of Safety

3.3.1 Safety Overviews for Studies MTA37, MTA44, and MTA48

Please refer to the clinical review for details and discussion of the clinical relevance of the findings. Brief summaries of safety overview for the three Phase III studies are presented in Table 32 for MTA37, Table 33 for MTA44, and Table 34 for MTA48 separately for the US sites and the Chile sites.

Table 32: Safety Overview After Any Vaccination (Safety Population) in MTA37

	Group 1 (N=257)	Group 2 (Proquad) (N=616)	Group 3 (N=246)	Group 4 (N=476)
Subjects with at least one	n/M (%)	n/M (%)	n/M (%)	n/M (%)
- Immediate unsolicited adverse event	0/257 (0.0)	0/616 (0.0)	0/246 (0.0)	2/476 (0.4)
- Solicited injection site reaction				
Menactra at 9 months	111/241 (46.1)	253/584 (43.3)	114/234 (48.7)	
Menactra at 12 months	100/228 (43.9)	244/534 (45.7)	122/216 (56.5)	
MMRV		201/534 (37.6)		223/457 (48.8)
PCV			117/215 (54.4)	284/458 (62.0)
- Solicited systemic reaction	193/249 (77.5)	488/591 (82.6)	205/238 (86.1)	351/458 (76.6)
After the 9-month vaccination	160/242 (66.1)	405/587 (69.0)	165/234 (70.5)	
After the 12-month vaccination(s)	127/228 (55.7)	375/536 (70.0)	149/216 (69.0)	351/458 (76.6)
- Unsolicited adverse event	154/256 (60.2)	393/610 (64.4)	152/245 (62.0)	218/463 (47.1)
After the 9-month vaccination	121/256 (47.3)	258/610 (42.3)	117/245 (47.8)	
After the 12-month vaccination(s)	87/231 (37.7)	279/563 (49.6)	98/223 (43.9)	218/463 (47.1)
- Medically significant AE	7/243 (2.9)	13/565 (2.3)	4/221 (1.8)	15/460 (3.3)
- AE leading to study discontinuation	2/257 (0.8)	4/616 (0.6)	1/246 (0.4)	0/476 (0.0)
- SAE	14/257 (5.4)	24/616 (3.9)	10/246 (4.1)	17/476 (3.6)
- Death	0/257 (0.0)	1/616 (0.2)	0/246 (0.0)	0/476 (0.0)

Source: Table S9 on Page 35 in the applicant's CSR for MTA37.

Table 33: Safety Overview After Any Vaccination (Safety Population) in MTA44

	Group 1 (N=407)	Group 2 (N=293)	Group 3 (N=418)
Subjects with at least one:	**n/M (%)**	**n/M (%)**	**n/M (%)**
- Immediate unsolicited adverse event	1/407 (0.2)	1/293 (0.3	0 (0
- Solicited injection site reaction **Menactra dose 1** **Menactra dose 2** **MMRV** **PCV**	 158/388 (40.7) 158/369 (42.8) -- --	 130/272 (47.8) 120/243 (49.4) 105/242 (43.4) --	 173/399 (43.4) 204/381 (53.5) -- 204/380 (53.7)
- Solicited systemic reaction [3]	314/392 (80.1)	222/278 (79.9)	341/404 (84.4)
Visit 1	265/388 (68.3)	175/272 (64.3)	268/399 (67.2)
Visit 2	233/366 (63.7)	179/243 (73.7)	258/380 (67.9)
- Unsolicited adverse event [2] [4]	264/407 (64.9)	180/291 (61.9)	272/418 (65.1)
Visit 1	179/407 (44.0)	113/291 (38.8)	192/418 (45.9)
Visit 2	178/383 (46.5)	129/253 (51.0)	184/387 (47.5)
- Medically significant AE	9/365 (2.5)	7/252 (2.8)	9/373 (2.4)
- AE leading to study discontinuation	0 (0)	1/293 (0.3)	2/418 (0.5)
- SAE	16/407 (3.9)	9/293 (3.1)	17/418 (4.1)
- Death	0 (0)	0 (0)	0 (0)

Source: Table S7 on Page 17 in the applicant's CSR for MTA44.

Table 34: Safety Overview After Any Vaccination (Safety Population) in MTA48

U.S. Sites

	Group 1 (ProQuad) (N=1030)			Group 2 (N=321)		
Subjects with at least one:	**n/M % (95% CI)**			**n/M % (95% CI)**		
-Immediate unsolicited adverse event	5/1030	0.5	(0.2; 1.1)	0/321	0.0	(0.0; 1.1)
-Solicited injection site reaction						
Menactra at 9 months	520/998	52.1	(49.0; 55.2)	--	--	--
Menactra at 12 months	520/904	57.5	(54.2; 60.8)	--	--	--
MMRV	399/899	44.4	(41.1; 47.7)	182/307	59.3	(53.6; 64.8)
PCV	473/901	52.5	(49.2; 55.8)	170/304	55.9	(50.1; 61.6)
HepA	451/900	50.1	(46.8; 53.4)	158/304	52.0	(46.2; 57.7)
-Solicited systemic reaction [3]	854/1008	84.7	(82.4; 86.9)	231/307	75.2	(70.0; 80.0)
After the 9-month vaccination	696/1005	69.3	(66.3; 72.1)	--	--	--
After the 12-month vaccinations	665/908	73.2	(70.2; 76.1)	231/307	75.2	(70.0; 80.0)
-Unsolicited adverse event [2] [4]	673/1028	65.5	(62.5; 68.4)	152/319	47.6	(42.1; 53.3)
After the 9-month vaccination	490/1028	47.7	(44.6; 50.8)	--	--	--
After the 12-month vaccinations	431/921	46.8	(43.5; 50.1)	152/319	47.6	(42.1; 53.3)
-Medically significant AE	40/947	4.2	(3.0; 5.7)	13/311	4.2	(2.2; 7.0)
-AE leading to study discontinuation	6/1030	0.6	(0.2; 1.3)	0/321	0.0	(0.0; 1.1)
-SAE	42/1030	4.1	(3.0; 5.5)	5/321	1.6	(0.5; 3.6)
-Death	2/1030	0.2	(0.0; 0.7)	0/321	0.0	(0.0; 1.1)

Chile Sites

	Group 1 (N=200)			Group 2 (N=200)		
Subjects with at least one:	**n/M % (95% CI)**			**n/M % (95% CI)**		
-Immediate unsolicited adverse event	0/200	0.0	(0.0; 1.8)	0/ 200	0.0	(0.0; 1.8)
-Solicited injection site reaction						
Menactra at 9 months	80/200	40.0	(33.2; 47.1)	--	--	--
Menactra at 12 months	16/21	76.2	(52.8; 91.8)	--	--	--
MMRV	10/21	47.6	(25.7; 70.2)	108/200	54.0	(46.8; 61.1)
PCV	16/21	76.2	(52.8; 91.8)	142/200	71.0	(64.2; 77.2)
HepA	14/21	66.7	(43; 85.4)	95/200	47.5	(40.4; 54.7)
-Solicited systemic reaction [3]	146/200	73.0	(66.3; 79.0)	174/200	87.0	(81.5; 91.3)
After the 9-month vaccination	145/200	72.5	(65.8; 78.6)	--	--	--
After the 12-month vaccinations	17/21	81.0	(58.1; 94.6)	174/200	87.0	(81.5; 91.3)
-Unsolicited adverse event	73/200	36.5	(29.8; 43.6)	119/200	59.5	(52.3; 66.4)
After the 9-month vaccination	67/200	33.5	(27.0; 40.5)	--	--	--
After the 12-month vaccinations	8/21	38.1	(18.1; 61.6)	119/200	59.5	(52.3; 66.4)
-Medically significant AE	0/195	0.0	(0.0; 1.9)	0/199	0.0	(0.0; 1.8)
-AE leading to study discontinuation	1/200	0.5	(0.0; 2.8)	0/200	0.0	(0.0; 1.8)
-SAE	8/200	4.0	(1.7; 7.7)	7/200	3.5	(1.4; 7.1)
-Death	0/200	0.0	(0.0; 1.8)	0/200	0.0	(0.0; 1.8)

Source:: Table S5 on Page 18, Table 6.3 on Page 107 in the applicant's CSR for MTA48

3.3.2 Safety Overview by Sex

Three key safety measures (medically significant AEs, AEs leading to study discontinuation and SAEs) were also tabulated separately for males and females in Table 35. The event rates appear to be similar between genders. The event rates also didn't appear to be out of proportion when examined by racial groups (results not shown). In summary, the subgroup analysis results were consistent with the overall findings.

Table 35: Overview of Significant AEs by Sex

Males

n/M % 95% CI	**MTA44**			**MTA37**				**MTA48**	
Subjects with at least one:	**Group 1 (N = 178)**	**Group 2 (N = 137)**	**Group 3 (N = 185)**	**Group 1 (N = 131)**	**Group 2 (N = 271)**	**Group 3 (N = 119)**	**Group 4 (N = 245)**	**Group 1 (N = 484)**	**Group 2 (N = 163)**
Medically significant AE	2/168	5/140	5/181	5/129	6/275	2/115	7/239	22/491	4/158
	1.2	3.6	2.8	3.9	2.2	1.7	2.9	4.5	2.5
	(0.1; 4.2)	(1.2; 8.1)	(0.9; 6.3)	(1.3; 8.8)	(0.8; 4.7)	(0.2; 6.1)	(1.2; 5.9)	(2.8; 6.7)	(0.7; 6.4)
AE leading to study discontinuation	0/190	1/165	2/201	1/138	1/292	0/128	0/245	3/529	0/163
	0.0	0.6	1.0	0.7	0.3	0.0	0.0	0.6	0.0
	(0.0; 1.9)	(0.0; 3.3)	(0.1; 3.5)	(0.0; 4.0)	(0.0; 1.9)	(0.0; 2.8)	(0.0; 1.5)	(0.1; 1.6)	(0.0; 2.2)
SAE	7/190	6/165	7/201	12/138	10/292	6/128	11/245	17/529	5/163
	3.7	3.6	3.5	8.7	3.4	4.7	4.5	3.2	3.1
	(1.5; 7.4)	(1.3; 7.7)	(1.4; 7.0)	(4.6; 14.7)	(1.7; 6.2)	(1.7; 9.9)	(2.3; 7.9)	(1.9; 5.1)	(1.0; 7.0)
Death	0/190	0/165	0/201	0/138	0/292	0/128	0/245	2/529	0/163
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0
	(0.0; 1.9)	(0.0; 2.2)	(0.0; 1.8)	(0.0; 2.6)	(0.0; 1.3)	(0.0; 2.8)	(0.0; 1.5)	(0.0; 1.4)	(0.0; 2.2)

Females

n/M % 95% CI	**MTA44**			**MTA37**				**MTA48**	
Subjects with at least one:	**Group 1 (N = 208)**	**Group 2 (N = 116)**	**Group 3 (N = 206)**	**Group 1 (N = 115)**	**Group 2 (N = 305)**	**Group 3 (N = 101)**	**Group 4 (N = 231)**	**Group 1 (N = 454)**	**Group 2 (N = 158)**
Medically significant AE	7/197	2/112	4/192	2/114	7/290	2/106	8/221	18/456	9/153
	3.6	1.8	2.1	1.8	2.4	1.9	3.6	3.9	5.9
	(1.4; 7.2)	(0.2; 6.3)	(0.6; 5.2)	(0.2; 6.2)	(1.0; 4.9)	(0.2; 6.6)	(1.6; 7.0)	(2.4; 6.2)	(2.7; 10.9)
AE leading to study discontinuation	0/217	0/128	0/217	1/119	3/324	1/118	0/231	3/501	0/158
	0.0	0.0	0.0	0.8	0.9	0.8	0.0	0.6	0.0
	(0.0; 1.7)	(0.0; 2.8)	(0.0; 1.7)	(0.0; 4.6)	(0.2; 2.7)	(0.0; 4.6)	(0.0; 1.6)	(0.1; 1.7)	(0.0; 2.3)
SAE	9/217	3/128	10/217	2/119	14/324	4/118	6/231	25/501	0/158
	4.1	2.3	4.6	1.7	4.3	3.4	2.6	5.0	0.0
	(1.9; 7.7)	(0.5; 6.7)	(2.2; 8.3)	(0.2; 5.9)	(2.4; 7.1)	(0.9; 8.5)	(1.0; 5.6)	(3.3; 7.3)	(0.0; 2.3)
Death	0/217	0/128	0/217	0/119	1/324	0/118	0/231	0/501	0/158
	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0
	(0.0; 1.7)	(0.0; 2.8)	(0.0; 1.7)	(0.0; 3.1)	(0.0; 1.7)	(0.0; 3.1)	(0.0; 1.6)	(0.0; 0.7)	(0.0; 2.3)

Source: Tables 7.3.1B and 7.3.2B in the applicant's Integrated Summary of Safety (ISS).

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

Because the study subjects were infants and toddlers (9 months or 12 months old), there is no need for subgroup analysis by age. Subgroups analyses by sex and race for various primary immunogenicity and safety endpoints were provided in the respective subsections of the statistical evaluation section of this review. Due to small sample size, no other subgroups analyses were performed since results by subgroup analysis are unlikely to provide any meaningful information.

4. SUMMARY AND CONCLUSIONS

4.1 Summary of Statistical Results

The objective of this application is to provide evidence of immunogenicity and safety of Menactra® administered following a two dose series in infants and toddlers at 9 and 12 months of age. Two Phases III studies were conducted with the primary objectives of evaluating the immunogenicity of Menactra®, MMRV and PCV vaccines when concomitantly administered.

Study MTA44
Study MTA44, a U.S. study was designed to primarily evaluate antibody responses to meningococcal serogroups A, C, Y and W-135, measured by serum bactericidal assay performed using human complement (SBA-HC). The immunogenicity cohort for the primary analysis included 277 subjects who received Menactra® alone for both vaccinations (Group 1). The primary endpoint was the proportion of subjects who received two doses of Menactra® with an SBA-HC titer ≥1:8 thirty days after the second vaccination. In this group, 95.6%, 100%, 96.4% and 86.4% of subjects achieved SBA-HC antibody titers of ≥1:8 after two doses for serogroups A, C, Y, and W-135, respectively (see Table 16). The secondary analysis compared the results of subjects administered Menactra® with and without other childhood vaccinations. Specifically, in the secondary analyses where non-inferiority of the group where Menactra® was administered concomitantly with MMRV or PCV to the group where Menactra® was administered alone was evaluated, the non-inferiority criteria were met for all serogroups for co-administration of Menactra® and MMRV (Table 18). However, for co-administration of Menactra® and PCV, the non-inferiority criteria were met for serogroups A, C and Y, but not for serogroup W-135 (Table 19).

Study MTA37
Study MTA37, a U.S. study was designed to primarily evaluate the antibody responses induced by MMRV or PCV vaccines when administered concomitantly with and without Menactra®. A total of 1281 subjects were included in the primary immunogenicity analysis. In the primary analyses, the antibody responses to measles, mumps, rubella, and varicella were measured by the proportions of the subjects with an antibody level on or above the corresponding pre-specified threshold. The antibody responses to PCV were measured by geometric mean concentrations (GMCs) to *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. As a result, the antibody responses to measles, mumps, rubella, and varicella induced by concomitant administration of MMRV (or MMR+V) and Menactra® were non-inferior to those induced by concomitant

administration of MMRV and PCV, but without Menactra®, i.e., the upper bounds of the two-sided 95% CIs of the differences (the group without Menactra® minus the group with Menactra®) in proportions of subjects with an antibody level on or above the threshold were all below the corresponding non-inferiority margins (5% for measles, and 10% for mumps, rubella, and varicella) (see Table 24). On the other hand, the non-inferiority criteria (margin being 2.0 for GMC ratios) for the pneumococcal antibody responses to PCV were met for serotypes 14, 19F, 23F, was met (but marginally) for serotype 9V, but not met for serotypes 4, 6B and 18C (see Table 26). It is worth noting that all lower bounds of the two-sided 95% CIs of the GMC ratio (Group without Menactra®/Group with Menactra®) were above 1.0, indicating that the GMCs in the group of subjects receiving concomitant administration of Menactra® tended to be statistically significantly lower (at 5% significance level for each serotype) than those in the group without concomitant administration of Menactra®. Therefore, there is a potential for an overall reduced response to the PCV vaccine if Menactra® and PCV are administered concomitantly. Whether these differences matter should be determined by the OVRR reviewers.

Study MTA48
Study MTA48 was primarily a safety study and did not provide immunogenicity and efficacy response data from a subgroup of the enrolled subjects in a foreign country (Chile).

A summary of safety overview for three studies (MTA44, MTA37 and MTA48) is provided in the statistical review (see Section 3.3). Overall, the serious adverse event (SAE) rates ranged from 3.9% to 5.4%. The rates of AEs leading to study discontinuation were less than 1%. These rates were mostly similar among treatment group. Please refer to the clinical review for more safety details and assessment of clinical significance of some of the observed differences.

Additional Comments:
Below are additional comments from the statistical reviewer:

- The applicant's results were verified through independent analyses by the statistical reviewer.
- Due to the high rates (25%-30%) of exclusion of subjects in the primary analysis, additional analyses were performed by the reviewing statistician to incorporate efficacy responses of the excluded subjects in the primary cohort as a sensitivity analysis. The results were similar and did not change the conclusion from the primary analyses. The statistical reviewer further explore the result by including adjustment of demographic covariates in logistic regressions, the results were also consistent with the conclusions above.
- There were no blood draws at pre-vaccination in the studies; therefore the precision of the estimates for the post-vaccination seroresponse may be affected. Nevertheless, because the study subjects were children less than one year old, it is expected the impact on the estimates from baseline is small.
- The success criteria for the primary objective for MTA44 targeted at the precision of the estimated proportion of subject achieving threshold level. Although such criteria can be addressed statistically, the clinical interpretation of the success may be different. Therefore the evaluation of the success of the study should defer to the clinical review.

4.2 Conclusions and Recommendations

A regulatory decision based on this submission depends on evaluation of the clinical significance of these findings. It is of note that all the serogroups (A, C, Y, and W-135) within Menactra® appeared to have seroresponse with rates above 85% when Menactra® was administered alone. No interference in seroresponse was observed when Menactra® was administered concomitantly with MMRV. However, there appeared to be potential interference between Menactra® and PCV (specifically, seroresponses to serogroup W-135 in Menactra® and to serotypes 4, 6B and 18C in PCV).

It is up to the review team to determine if the product is approvable and if so what language in the label may be considered for inclusion to note the possible interference between Menactra® and PCV.

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