

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and and Related Product Applications**

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Subject: Clinical Review of Menactra[®] (Meningococcal (Groups A, C, Y and W-135)
Polysaccharide Diphtheria Toxoid Conjugate Vaccine) for use in children as young as 9
months old

To: STN 125089\395

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1.0 General Information

1.1 Contents

Clinical review of supplemental biologics license application to extend Menactra use to children as young as 9 months of age

1.1.1 STN#: 125089.395

1.1.2 Submission Received by FDA

July 24, 2010

1.2 Product

1.2.1 Proper Name

Meningococcal (Groups A, C, Y, W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

1.2.2 Trade Name: Menactra

1.2.3 Product Formulation: Each 0.5ml dose contains

- 4ug of polysaccharide (PS) for serogroup A
- 4ug of polysaccharide (PS) for serogroup C
- 4ug of polysaccharide (PS) for serogroup Y
- 4ug of polysaccharide (PS) for serogroup W-135

48ug diphtheria toxoid protein total (Each PS is conjugated to diphtheria toxoid)

0.6 mg sodium phosphate

4.4mg sodium chloride

The vaccine contains neither an adjuvant nor preservative.

1.3 Applicant: Sanofi Pasteur, Inc.

1.4 Pharmacologic Class: Vaccine

1.5 Proposed Indication

Active immunization for prevention of invasive disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135.

1.6 Proposed New Population

Menactra is currently approved for use in individuals 2 years through 55 years of age.

The applicant submitted the current clinical supplemental biologics license application (sBLA) to extend Menactra use to children as young as 9 months of age.

1.7 Dosage Form and Route of Administration: Liquid, intramuscular

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3.0 Executive Summary

Menactra is a tetravalent meningococcal (Group A, C, Y, and W-135) conjugate vaccine that contains diphtheria toxoid as a carrier protein. The clinical immunogenicity and safety data included in this supplemental BLA application support the approval of Menactra for use in children 9 months through 23 months of age. The vaccination schedule consists of a 2-dose series administered three months apart. Menactra is indicated for the prevention of invasive disease caused by *Neisseria meningitidis* serogroups contained in the vaccine.

Menactra vaccine effectiveness against invasive meningococcal disease was inferred from an immunological measure of protection, serum bactericidal antibody. For purposes of U.S. licensure, seroresponses achieved at or above a pre-defined titer indicated that the meningococcal-specific functional antibodies measured post-vaccination were considered protective against systemic infection. The described approach was discussed at a Vaccines and Related Biological Products Advisory Committee meeting, held April 6-7, 2011. The committee concurred with CBER's approach to use serum bactericidal activity with human complement (SBA-H) as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children <2 years old.

The clinical evaluation of Menactra in children 9 months to 23 months of age included four studies in which a total of 3993 children received at least one dose of Menactra, 2582 children received a second Menactra dose concomitantly with ≥ 1 U.S. licensed childhood vaccine, and 1583 children received concomitant childhood vaccines without Menactra. The safety population of U.S. participants included 3569 participants who received at least one dose of Menactra, 2384 participants who received a second Menactra dose with one or more childhood vaccine (MMRV, PCV7, HepA), and 797 participants who received childhood vaccines without Menactra. Studies MTA-48 and MTA-44 were pivotal trials designed to evaluate Menactra safety and immunogenicity, respectively. Menactra was administered as a 2-dose series at 9 months and 12 months of age. The first dose was given alone, and the second dose was administered alone or concomitantly with U.S. licensed childhood vaccine(s). Study MTA-37 was primarily a trial designed to evaluate the safety and immunogenicity of routine childhood vaccines concomitantly given with Menactra. Study MTA-26 was a dose selection trial that included evaluations of other 2-dose regimens.

In study MTA-44, the primary immunogenicity endpoint was the percentage of participants who achieved an SBA-H titer $\geq 1:8$, measured thirty days after the 2nd Menactra vaccination, for each serogroup. The primary success criteria were defined as at least 90% of participants who achieved the primary endpoint, and 95% confidence limits for the estimate that were within a 5% margin. Except for serogroup W-135 (86%; 95% CI 82, 90), the success criteria were met. The percentage of study participants who achieved an SBA-H $\geq 1:8$ to serogroup W-135 was similar to respective seroresponses in a historical group of children 4-10 years old (85%; 95% CI 75, 92), after a single Menactra dose.

The safety of Menactra (after each vaccination) included the following parameters: immediate reactions (30-minute observational period); solicited local and systemic adverse events (7-day period); other non-serious, unexpected AEs (30-day period); medically significant AEs, defined as events that prompted medical advice/attention from a physician's office or emergency room, that occurred between 30 days and 6 months after the last vaccination, and SAEs reported from study start through the 6-months after the last vaccination. In the main safety trial, the most frequently solicited Menactra injection site reaction reported by U.S. participants, after either Menactra dose, was localized tenderness (37%, 1st dose; 49% 2nd dose + concomitant vaccines [MMRV, PCV7, HepA]). Irritability was the most frequently reported solicited systemic adverse event (57%, 1st dose; 62% 2nd dose + concomitant vaccines). The frequencies of systemic adverse events after a second Menactra dose when given concomitantly with routine childhood vaccines (study group 1) were generally similar to systemic adverse event frequencies when the childhood vaccines were administered without Menactra (study group 2). Overall, analyses of serious adverse events in all participants did not reveal imbalances in distribution between study groups who received Menactra (with or without childhood vaccines) or childhood vaccines alone. The SAEs reported in the first month after the 9

month and 12 month vaccination(s) were similar to SAEs reported during subsequent months. Rates of serious adverse events leading to discontinuation represented less than 1% of each study group. Three deaths occurred during the four trials, all which were unrelated to vaccination. In this clinical reviewer's opinion, no safety signals were identified in the review of this BLA supplement.

Immune responses to measles, mumps, rubella and varicella antigens were comparable when MMRV was administered with or without and a second Menactra dose. Reduced pneumococcal IgG antibody responses to serotypes 4, 6B and 18C were observed following co-administration of Menactra vaccine and a 4th dose of PCV7. For each of these serotypes, the upper limit of the 95% CI for the GMC ratio exceeded the 2.0-fold criterion for non-inferiority. Pneumococcal opsonophagocytic activity (OPA) antibody responses were consistent the IgG antibody responses. Possible explanations for the observed findings include carrier-protein related interference. PCV7 contains a carrier protein (CRM₁₉₇) that is antigenically similar to the carrier protein in Menactra (diphtheria toxoid). Due to the indirect effects of routine PCV7 immunization in the U.S., reduced pneumococcal antibody responses to the three serotypes may not have a population effect. Further discussion was included in the body of the review. Continued assessment of the effectiveness of pneumococcal CRM₁₉₇ conjugate vaccines through post-licensure surveillance would be important, particularly since immunological interference was observed following the last administered dose of the pneumococcal primary immunization series.

The applicant agreed to conduct two post-licensure studies: 1) a descriptive, epidemiological surveillance study, to provide additional safety data in children in the newly approved age group; 2) a safety and immunogenicity study of Menactra when co-administered with DTaP-IPV/PRP-T at 15 to 18 months of age.

FDA's Pediatric Review Committee concluded that the assessment of Menactra safety and effectiveness for the claimed indication satisfied PREA requirements.

4.0 Background

Neisseria meningitidis is a primary cause of bacterial meningitis, especially in young children. A timely clinical diagnosis is difficult, and, even with available treatments, approximately 10-20% of individuals with invasive meningococcal disease experience sequelae (e.g., limb loss, neurosensory hearing loss, cognitive deficits, seizure disorder).

In the U.S., the highest incidence of meningococcal disease occurs in children younger than one year of age. During 1999-2008, the average annual incidence of meningococcal disease in children <1 years old was 5.65 cases/per 100,000 population; serogroups Y, C and W-135/other serogroups accounted for approximately 25%, 10% and 5% of meningococcal disease.[1] Also, the largest disease burden occurred among children ages 0 to 8 months of age.[2] In 2009, preliminary data indicated that the incidence of meningococcal serogroup Y, C, W-135 disease in children <1 year old was 0.58, 0.19, and 0.19/ per 100,000 population, respectively.[3]

4.1 Immune marker of protection: serum bactericidal antibody

An approach to demonstrating effectiveness of meningococcal conjugate vaccines in young children was discussed at a Vaccines and Related Biological Products Advisory Committee meeting held April 6-7, 2011. At the time, a meningococcal conjugate vaccine for use in children younger than 2 years old had not been licensed in the U.S. In individuals 2 years of age and older, clinical trials had been designed to demonstrate non-inferiority of serum bactericidal antibody responses of a new meningococcal vaccine to responses in a randomized, control group who received a U.S. licensed meningococcal vaccine.

The committee concurred that serum bactericidal activity with human complement could be used as an immune measure to infer effectiveness of meningococcal conjugate vaccines in children <2 years old. Also, seroresponses achieved at or above a pre-defined SBA-H titer indicated that the meningococcal-specific functional antibodies measured post-vaccination were considered protective against systemic infection.

5.0 Materials Reviewed

Clinical study reports and appendices for studies MTA37, MTA44, and MTA48 (module 5), clinical overview (module 2.5), summary of clinical safety (module 2.7.4), summary of clinical efficacy (Module 2.7.3), information pertaining pediatric research equity act (PREA) requirements (module 1.9), package insert (module 1.14), risk management plan (module 1.16).

6.0 Overview Clinical Studies

Table 1. Summary of Clinical Studies

Study	Description	Number of Vaccinated Participants			
		First Vaccination (9 months of age)	Second Vaccination (12 months of age)		
		Menactra only	Menactra only	Menactra + Concomitant Vaccine(s)*	Concomitant Vaccine(s) only*
Pivotal Studies					
MTA-44 USA	Phase III Safety and immunogenicity (Pivotal immunogenicity)	1247	386	773	N/A
MTA-37 USA	Phase III, Safety and immunogenicity Com vx: MMRV (or MMR+V), PCV7	1191	246	850	1062
MTA-48 USA, Chile	Phase III Safety study Com vx (safety): MMRV, PCV7, HepA	1253	N/A	959	521
Total number of participants		3691		2582	1583
Supportive study					
MTA-26 USA	Phase II Dose ranging study 1-dose: 15m, 18m; 2-dose: (9m,12m); (9m,15m); (12m,15m) Menomune, 1 dose, children 3-5 years old	302	176	N/A	N/A

*Number of subjects who received concomitant PRP-T (MTA-44 n=128; MTA-37 n=24 [study group 2], n=601 [study group 4])

7.0 Clinical Studies

7.1 Study MTA-44: An Immunogenicity and Safety Evaluation of Two Doses of Menactra (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) Given to Healthy Subjects at 9 and 12 Months of Age

7.1.1 NCT#00384397

7.1.1.1 Objectives

Primary Objective

To evaluate antibody responses to meningococcal serogroups A, C, Y, and W- 135, measured by a SBA-H assay, one month after completion of a 2-dose Menactra vaccination schedule (Study Group 1).

Secondary Objectives

Immunogenicity

- To compare SBA-H antibody responses to each serogroup when Menactra is co-administered with a combination measles, mumps, rubella, varicella vaccine (MMRV) (Study Group 2) to Menactra administered alone (Study Group 1).

- To compare SBA-H antibody responses to each serogroup when Menactra is co-administered with a 7-valent pneumococcal CRM₁₉₇ conjugate vaccine (PCV7) (Study Group 3) to Menactra is administered alone (Study Group 1).

Safety

To describe the safety profile (immediate adverse events, solicited and unsolicited AEs, medically significant AEs and serious adverse events (SAEs) in study groups 1-3.

Other Objectives

- To describe the SBA-H antibody titer 30 days after the second vaccination visit (Visit 2) (Study Groups 1-3).
- To describe the antibody response to each serogroup, measured by a serum bactericidal assay with a baby rabbit complement source (SBA-BR), 30 days after Visit 2.

7.1.1.2 Design Overview

The study was viewed by CBER as an open-label trial since the number of administered injections and routes of administration differed among study groups. Laboratory personnel were blinded to the treatment assignment.

Table 2. MTA-44. Study Design

Study group	Visit 1 (at age 9 months)	Visit 2 (at age 12 months)
Group 1	Menactra	Menactra
Group 2	Menactra	Menactra + MMRV*
Group 3	Menactra	Menactra + PCV7†

* Measles, mumps, rubella, varicella vaccine: ProQuad (Measles, Mumps, Rubella and Varicella Vaccine [Oka/Merck] Virus Vaccine Live)

† Pneumococcal conjugate vaccine: Prevnar (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria CRM₁₉₇ Protein])

The study was conducted from September 2006 to August 2008, at 71 centers in the United States.

7.1.1.3 Populations

Inclusion criteria

- Healthy
- Aged 9 months (249 to 305 days) at the time of enrollment
- Informed consent obtained

Exclusion criteria

- Serious acute or chronic disease (i.e., cardiac, renal, neurologic)
- Known or suspected impairment of immunologic function
- History of seizures, including febrile seizures, or any other neurologic disorder
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Suspected or known hypersensitivity to any vaccine component or to dry natural rubber latex
- Receipt of a 4th PCV dose or their first MMRV vaccination before enrollment
- Receipt of any vaccine within 30-day period prior to administration of study vaccine, or, scheduled to receive a vaccine other than influenza vaccine* or hyposensitization therapy in the 30-day period after a study vaccine. *Can be administered at least 2 weeks before or after study vaccination.
- Receipt of immune globulin or other blood products within 12 weeks prior to the administration of study vaccine
- Thrombocytopenia or a bleeding disorder contraindicating intramuscular (IM) vaccination
- Personal or family history of Guillain-Barre Syndrome (GBS)
- Unable to comply with scheduled visits or study procedures

- Participating in another clinical trial
- Oral or injected antibiotic therapy within 72 hours prior to any blood draw
- Acute medical illness in the 72h prior to enrollment, or temperature $\geq 38.0^{\circ}\text{C}$ at the time of enrollment

7.1.1.4 Study Products

Menactra: Each 0.5 mL dose of vaccine contains 4 ug of PS/serogroup each conjugated to diphtheria toxoid protein (~48ug total). The vaccine is a clear to slightly turbid liquid given IM.

MMRV (ProQuad; Merck & Co., Inc., Whitehouse Station, NJ): Each 0.5 mL dose contains the following active ingredients: measles virus (not $< 3.00 \log_{10} \text{TCID}_{50}$), mumps virus (not $< 4.30 \log_{10} \text{TCID}_{50}$), rubella virus (not $< 3.00 \log_{10} \text{TCID}_{50}$), varicella virus (a minimum of $3.99 \log_{10} \text{PFU}$). After reconstitution, the vaccine appears as a clear, pale yellow to light pink solution. Given subcutaneously.

PCV7 (Prevnar; Wyeth Pharmaceuticals Inc., Pearl River, NY): Each 0.5 mL dose of vaccine contains 2ug of each saccharide, except for 6B (4ug), that is individually conjugated to CRM₁₉₇ carrier protein (~20ug total), and 0.125mg Al. The vaccine is a liquid given IM.

7.1.1.5 Endpoints

Primary Endpoints

% of participants with SBA-H titer $\geq 1:8$ for each serogroup

Secondary Endpoints

- % of participants with SBA-H titer $\geq 1:4$ and $\geq 1:8$ for each serogroup (study groups 2 and 3)
- Occurrence of solicited and unsolicited adverse events (AEs)
- Medically significant AEs
- Serious adverse events (SAEs)

Observational Endpoints

SBA using human (H) or baby rabbit (BR) complement: distribution of titers, reverse cumulative distribution curves, GMTs with 95%CI

7.1.1.6 Surveillance/Monitoring

Safety: Study participants were monitored for immediate reactions (30-minute observation period) after each vaccination. Pre-specified AEs included injection site reactions (erythema, swelling, tenderness) and systemic adverse events (fever, vomiting, inconsolable crying, drowsiness, loss of appetite and irritability). These events were recorded daily on a diary card during the 7 days after each vaccination, and by telephone interview eight days after vaccination. Other non-serious, unexpected AEs, including rash, were obtained by telephone interview eight and twenty-eight days after each vaccination.

Information about medically significant AEs, defined as events that prompted medical advice/attention from a physician's office or emergency room, was obtained by telephone interview for events occurring between 30 days and 6 months after the last vaccination. SAEs were reported and recorded from study start through the 6-months after the last vaccination.

Immunogenicity: Blood samples for analyses were obtained on Day 30 (range: Day 30-44) after the second vaccination visit. Sera available after primary and secondary objectives were completed were used for SBA-BR analyses. Laboratory testing was performed at Sanofi Pasteur, Inc. The lower limit of quantitation (LLOQ) for the SBA-H assay was 1:4.

7.1.1.7 Statistical Analysis Plan

Primary Success Criterion

To demonstrate that at least 90% of participants in study group 1 achieved an SBA-H titer $\geq 1:8$, measured thirty days after the 2nd Menactra vaccination, for each serogroup. Also, the 95% confidence limits for the percentage of participants achieving the primary endpoint would be within $\pm 5\%$. The probability of achieving success based on the chosen sample size was estimated to be $>99.9\%$ for each serogroup. The primary analysis was based on the per-protocol population.

Secondary Hypotheses

The secondary immunogenicity objectives, to compare SBA-H antibody responses when Menactra is administered alone or co-administered with other childhood vaccines, were evaluated by non-inferiority tests. The hypotheses would be supported by the data if the upper limit of the two-sided 95% CI for the difference between two proportions ($p_{\text{study group 1}} - p_{\text{study group 2}}$ or $p_{\text{study group 1}} - p_{\text{study group 3}}$), was less than 10% for each serogroup, where p represented the percentage of participants with an SBA-H titer $\geq 1:8$ thirty days after the Visit 2 vaccination(s).

Safety analyses: For each solicited reaction, the number and percentage of participants were tabulated by any reaction, severity, and treatment group, during the 7 days after each vaccination. Temperature results were reported without a conversion factor. Unsolicited adverse events, including immediate AEs occurring within 30 minutes post-vaccination, were collected and coded by system organ class and preferred term, using the MedDRA dictionary. For each unsolicited reaction, the number and percentage of participants with at least one instance of the event were tabulated by any severity, relatedness to the study product and by treatment group, during the 28 days after each vaccination. Serious adverse events were described and presented separately.

Populations analyzed

Safety: The full analysis set included all participants who received at least one Menactra injection and for whom safety data was available. Immunogenicity: The per-protocol population included all eligible participants who received the assigned study vaccinations, complied with scheduled vaccination and blood sampling visits, had sufficient quantities of sera was available for analysis, and did not have protocol violation(s) that affected antibody responses to the vaccine antigens (e.g., missing diary card, administration/ documentation errors, telephone contact visit outside scheduled window, error in site of administration). The intent-to-treat population consisted of all participants who received at least one Menactra injection and had a valid (i.e., blood sample obtained and sufficient quantities of sera available for analysis) test result.

7.1.2 Results

Main protocol revisions

Hib immunizations, administered to study group 2, were deferred until after the vaccination phase in order to be consistent with the age for prescribed use of ActHIB (Haemophilus b Conjugate Vaccine [Tetanus Toxoid Conjugate]).

Population

A total of 1257 (group 1, n=404; group 2, n=430; group 3, n=423) children were enrolled, and 84%-95% of participants completed the study. Prior to the protocol revision, 129 participants had received concomitant Hib vaccine (group 2, n=128; group 3, n=1). In this review, Hib participants were excluded from the below described populations and described separately in sections 7.2.2 (population characteristics) and 7.2.2.2 (immunogenicity). The description of serious adverse events in section 7.1.2.1 accounts for all study participants (including Hib recipients).

Safety analysis set: Ten participants (group 1, n=1; group 2, n=6; group 3, n=1) did not receive study vaccines or received vaccines inconsistent with the treatment assignment. The safety population categorized by the vaccine(s) received included 1118 participants (group 1, n=407; group 2, n=293; group 3, n=418).

Immunogenicity population: The intent-to-treat population included 964 participants (group 1 n=365; group 2, n=235; group 3, n=364). The drop-out rate ranged from 7.9% (groups 1, 3) to 15.7% (group 2). Voluntary withdrawal, lost to follow-up and non-compliance with protocol procedures were the main reasons for not completing the vaccination phase. The number of participants who did not complete the vaccination phase (i.e., attendance at the 12-month vaccination visit [Visit 2] or post-vaccination blood draw [Visit 3]) was higher in study group 2 for each of the three reasons. One participant withdrew from the study due to an SAE (See section 7.1.2.1 (Safety outcomes) for additional details). Approximately 20% of participants (group 1, n=88; group 2, n=55; group 3, n=97) in each study group were excluded from the per-protocol population. The most frequent reasons for exclusion were visits outside the scheduled interval, blood sample was not obtained, or absence at Visit 2. The per-protocol population therefore consisted of 724 participants (group 1, n=277; group 2, n=180; group 3, n=267).

Demographic characteristics: Except for study group 2, the distribution of participants, based on age, gender and ethnicity, was similar among the three vaccine groups. The study population enrolled was predominately Caucasian (75.5%), but also included African American (0.5%), Hispanic (6.4%), Asian populations (0.8%).

7.1.2.1 Safety Outcomes

Immediate adverse events (30 minute observation period)

Two participants (study group 1, 2) developed a non-descript truncal rash after the Visit 2 vaccination(s). The rashes resolved the same day.

Menactra injection site reactions (within 7 days after each vaccination visit)

After the first Menactra dose, the percentage of participants with at least one injection site reaction ranged from 40.7% to 47.8%. After the second Menactra dose, administered alone or with childhood vaccine, the percentage of participants with at least one injection site reaction was 42.8% (Menactra only), 49.4% (Menactra+MMRV) and 53.5% (Menactra+PCV7), respectively.

Injection site tenderness was the event most frequently reported after the first Menactra dose (31.7%-34.6%), and in each of the three study groups after the second Menactra dose. The frequency of injection site tenderness after the second vaccination visit ranged from 35.8% (Menactra only) to 47.8% (Menactra + PCV7). Of the injection site reactions categorized as grade 3, erythema (diameter ≥ 5.0 cm) was the adverse event that occurred most often after the first Menactra dose (n=11) and after the second vaccination visit (group 1 n=3; group 2, n=5; group 3, n=10). Over 98% of injection site reactions started between Day 0 (day of vaccination) and Day 3, and were present for 1 to 3 days.

Solicited systemic adverse events (within 7 days after each vaccination visit)

Irritability was the adverse event most frequently reported after the first Menactra dose (range 52.9% to 57.0%) and after the second vaccination visit (group 1, 51.9%; group 2, 60.7%; group 3, 57.4%). After the first Menactra dose, 33 participants (3.1%) experienced irritability that ranged from 8 to 24 days. After the second vaccination visit, 34 participants (study group 1, n=16; group 2, n=10, group 3, n=9) developed irritability that lasted between 8 and 30 days. Abnormal crying was also common after Menactra dose 1 (range 33.2% to 35.7%), and in any of the study groups after Menactra dose 2 (range 35.45 to 39.3%).

After the first Menactra dose, 11.9% to 13.4% of participants developed fever ($T \geq 38.0^\circ\text{C}$; any route of temperature measurement), and 12 participants (1.1%) developed a $T > 39.5^\circ\text{C}$; 99.5% of temperatures were measured rectally. After the second vaccination visit, fever by any temperature route ranged from 15.8% (n=58/366, study group 1) to 26.4% (n=63/239, study group 2), and 17 participants (1.7%) developed a $T > 39.5^\circ\text{C}$. Temperatures were measured rectally in 99.0% of all subjects.

Serious Adverse Events (*Day of vaccination through 6 months after the last vaccination(s)*)

One participant withdrew from the study due to an SAE: an 11-month old boy (group 3) experienced a febrile convulsion 64 days after receiving the first Menactra vaccination. He had a $T 38.9^\circ\text{C}$ and irritability that developed the previous day. According to his mother, the seizure experienced by the participant was generalized and lasted <1 minute. Other than a $T 39.4^\circ\text{C}$, the physical examination and laboratory evaluation was unremarkable. The participant fully recovered.

Forty-two participants (group 1, n=16; group 2, n=9; group 3, n=17) experienced an SAE during the study period between the first vaccination visit through 6 months after the second vaccination visit. The events were commonly due to bronchiolitis and gastroenteritis. Eight febrile seizures were reported in 5 participants (group 1, n=2; study group 3, n=3), all of which occurred >40 days after vaccination (range 44-144 days).

7.1.2.2 Immunogenicity Outcomes

Except for serogroup W-135, more than 90% of participants achieved a SBA-H titer $\geq 1:8$. Also, the lower 95% CI limit for the percentage of children achieving a SBA-H titer $\geq 1:8$ was $\geq 90\%$ for serogroups A, C, and Y.

A trend towards a lower percentage of participants who achieved serogroup-specific SBA-H titer $\geq 1:8$ was observed in the study group who received Menactra (2nd dose) concomitantly with PCV7 (4th dose), compared to the study group who received Menactra alone or with MMRV. The difference between serogroup-specific SBA-H GMTs among participants who received Menactra + PCV7 or Menactra alone were within 2-fold, and 95% CIs were largely non-overlapping. The reverse cumulative distribution curves among the study groups 1-3 were similar for each serogroup (not shown in this review).

Table 3. MTA-44. SBA-H Antibody Responses After the Second Menactra Dose Given Alone or Concomitantly with MMRV or PCV7 Vaccines, Per-protocol population

Serogroup	Immune Parameter	Vaccine(s) administered at 12 months of age					
		Menactra (study group 1)		Menactra+MMRV (study group 2)		Menactra+PCV7 (study group 3)	
		N=272-277 ^a		N=177-180 ^a		N=264-267 ^a	
			(95% CI)		(95% CI)		(95% CI)
A	% $\geq 1:8$	95.6%	(92.4, 97.7)	92.7%	(87.8, 96.0)	90.5%	(86.3, 93.8)
	GMT	55	(47, 65)	52	(42, 65)	41	(35, 49)
C	% $\geq 1:8$	100%	(98.7, 100)	98.9%	(96.0, 99.9)	97.8%	(95.2, 99.2)
	GMT	142	(124, 163)	162	(136, 192)	110	(-94, 128)
Y	% $\geq 1:8$	96.4%	(93.4, 98.2)	96.6%	(92.8, 98.8)	95.1%	(91.8, 97.4)
	GMT	52	(45, 61)	60	(50, 72)	40	(34, 46)
W-135	% $\geq 1:8$	86.4%	(81.8, 90.3)	88.2%	(82.5, 92.5)	81.2%	(76.0, 85.7)
	GMT	24	(21, 28)	28	(23, 34)	18	(15, 21)

^a N= Number of participants with at least one valid serology result at Day 30 (range: Days 30-44) after the second Menactra dose.

Menactra was administered at 9 months and 12 months of age.

Source: adapted from 125089.395.0, m5.3.5.1, MTA44 report.pdf, Tables 5.4 and 5.5.

For the study group that received a second dose of Menactra alone at 12 months old, the intent-to-treat analysis results were consistent with the per-protocol analysis results.

Table 4. MTA-44. SBA-H Antibody Responses after the Second Menactra Dose (given alone) by Serogroup, Per-protocol and Intent-to-Treat Populations

Serogroup	Immune Parameter	Menactra given at 12 months of age (study group 1)			
		Per-Protocol N=272-277		Intent-To-Treat N= 360-365	
		(95% CI)		(95% CI)	
A	% ≥1:8	95.6%	(92.4, 97.7)	93.9%	(90.9, 96.1)
	GMT	55	(47, 65)	51	(44, 59)
C	% ≥1:8	100.0%	(98.7, 100.0)	99.2%	(97.6, 99.8)
	GMT	142	(124, 163)	137	(121, 155)
Y	% ≥1:8	96.4%	(93.4, 98.2)	95.9%	(93.3, 97.7)
	GMT	52	(45, 61)	51	(45, 58)
W-135	% ≥1:8	86.4%	(81.8, 90.3)	85.3%	(81.2, 88.8)
	GMT	24	(21, 28)	23	(20, 27)

Menactra was administered at 9 months and 12 months of age.

Source: adapted from 125089.395.0, m5.3.5.1, MTA44 report.pdf, Tables 9.32A, 9.32B and 9.37B.

7.1.3 Summary and Conclusions

Study MTA-44 was the main trial for inferring Menactra effectiveness in children immunized at 9 months and 12 months old. The first Menactra dose was given alone at 9 months of age. At 12 months of age, the second dose of Menactra was given alone, with MMRV or with PCV7. Serum bactericidal antibody responses were measured with a SBA-H assay.

Safety

After the first dose of Menactra, the most commonly reported solicited adverse events were injection site tenderness and irritability; 11.9% to 13.4% of participants developed fever ($T \geq 38.0^\circ\text{C}$). The Menactra safety profile after the second dose in part depended on the co-administered vaccine. Local tenderness, the most frequently reported Menactra injection site reaction, occurred most often when PCV7 was a co-administered vaccine. Irritability was the solicited systemic adverse event reported most often by participants after the 12-month old vaccination(s), and occurred similarly in participants who received Menactra with MMRV or PCV7. Fever ($T > 38.0^\circ\text{C}$) was more frequently reported in subjects when Menactra was administered concomitantly with MMRV (26.4%), than when Menactra was given with PCV7 (22.3%) or when Menactra was given alone (15.8%) at the second visit. There was no proportional increase in study group 2 participants with grade 3 fever ($T > 39.5^\circ\text{C}$). SAEs reported after both vaccination visits were illnesses, such as bronchiolitis and gastroenteritis, which commonly occur in childhood. No deaths occurred during the study.

Immunogenicity

The primary success criteria were met, except for serogroup W-135 (86%; 95% CI 82, 90). The percentage of participants who achieved an SBA-H $\geq 1:8$ to serogroup W-135 was similar to respective seroresponses in a historical group of children 4-10 years old (85%; 95% CI 75, 92), after a single Menactra dose.[4] The lower 95% confidence limit for the percentage of participants achieving an SBA-H titer $\geq 1:8$ was $\geq 90\%$ for serogroups A, C and Y. Approximately 10% of participants/per group did not complete the vaccination phase (non-safety reasons) and another 20% of participants/per group were excluded from the per-protocol immunogenicity population (blood sampling reasons). Immunogenicity results from the primary intent-to-treat analyses were consistent with the per-protocol analyses.

7.2 Study MTA-37: An Immunogenicity, Safety, and Non-Interference Evaluation of Pediatric Vaccines Administered Concomitantly with Menactra (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) to Healthy Toddlers

7.2.1 NCT#00422292

7.2.1.1 Objectives

Primary Objectives

1. To compare the immune responses to antigens contained in MMRV vaccine, when concomitantly administered with Menactra, to corresponding immune responses when MMRV is given without Menactra (study group 2 vs. 4). MMRV could be given as separate injections of MMR+V.
2. To compare the immune responses to antigens contained in PCV7 vaccine, when concomitantly administered with Menactra, to corresponding immune responses when PCV7 is given without Menactra (study group 3 vs. 4).

Other Objectives

- To describe the safety profile in study groups 1-4.
- To describe SBA-H antibody responses to serogroups A, C, Y and W-135, measured thirty days after each Menactra vaccination (study groups 1A and 1B).
- To describe the IgG antibody responses to pneumococcal vaccine serotypes (study groups 3 and 4).
- To describe the antibody responses to measles, mumps, rubella and varicella antigens thirty days after MMRV (or MMR+V) vaccination(s) in study group 2 participants.

7.2.1.2 Design Overview

This trial was viewed by CBER as an open-label, randomized (study groups 1-3), controlled study. The study groups differed by age of enrollment, the number of administered injections, and blood sampling time points. Also, the study vaccines differed in appearance and routes of administration.

Table 5. MTA-37. Study Design

Study group	Visit 1 (at age 9 months)	Visit 2 (at age 12 months)
Group 1*	Menactra	Menactra
Group 2	Menactra	Menactra + MMRV (or MMR+V [†])
Group 3	Menactra	Menactra + PCV7
Group 4 (ctl grp)		MMRV + PCV7

* Study groups 1A, 1B: blood samples obtained 30-44 days after the 2nd and 1st Menactra vaccinations, respectively

[†] MMR vaccine: M-M-R_{II} (Measles, Mumps, and Rubella Virus Vaccine Live). Varicella vaccine: VARIVAX (Varicella Vaccine [Oka/Merck] Virus Vaccine Live).

The trial was conducted from January 2007 to January 2009, at 92 U.S. study centers. After study initiation, the protocol was amended to defer Hib conjugate immunizations until after the last blood sampling visit.

7.2.1.3 Populations

Inclusion criterion: Aged 9 months (249 to 305 days) for study groups 1-3 or aged 12 months (365 to 400 days) for group 4. The eligibility criteria were otherwise the same as described in study MTA-44 section 7.1.1.3. Children enrolled at 9 months of age were randomized into study groups 1, 2, or 3.

7.2.1.4 Study Products

Product information for Menactra, MMRV, and PCV7 were described in study MTA-44 section 7.1.1.4.

M-M-R_{II} (Merck & Co, Inc., Whitehouse Station, NJ): Each 0.5mL dose contains the following active ingredients: not less than 1,000 TCID₅₀ measles virus, not less than 20,000 TCID₅₀ mumps virus, not less than 1,000 TCID₅₀ rubella virus. No preservative. After reconstitution, the vaccine appears as a clear, yellow solution. Given subcutaneously.

Varivax (Merck & Co, Inc., Whitehouse Station, NJ): Each 0.5mL dose contains a minimum of 1350 PFU of Oka/Merck varicella virus. No preservative. After reconstitution, the vaccine appears as a clear, colorless to pale yellow solution. Given subcutaneously.

7.2.1.5 Endpoints

Primary Endpoints

Study groups 2 and 4

- Anti-measles antibody concentration ≥ 300 mIU/mL (ELISA) or ≥ 120 mIU/mL (neutralization assay)*
- Anti-mumps antibody concentration ≥ 500 U/mL (ELISA) or ≥ 60 (1/dil; neutralization assay)*
- Anti-rubella antibody concentration ≥ 10 IU/mL (ELISA)
- Anti-varicella antibody concentration ≥ 300 mIU/mL (ELISA) or ≥ 4 (1/dil) (fluorescent antibody to membrane antigen [FAMA] assay)*

* the second assay measurement was performed if the ELISA antibody concentration was less than the pre-specified antibody level.

Study groups 3 and 4

- Anti-pneumococcal geometric mean antibody concentrations to vaccine serotypes 4, 6B, 9V, 14, 18C, 19F and 23F (ELISA)

Other endpoints

Study groups 1A and 1B: SBA-H

For each meningococcal serogroup

- Distribution of antibody titers, RCDC, % of subjects with SBA-H titer ≥ 4 , ≥ 8 , with 95%CI, and GMT with 95%CI

Study group 2: MMRV, MMR+V

- Same as the endpoints described above for measles, mumps, rubella and varicella

Study groups 3 and 4

- % of subjects with pneumococcal IgG antibody levels ≥ 0.35 , ≥ 0.5 and ≥ 1.0 ug/mL (ELISA)

7.2.1.6 Surveillance/Monitoring

Safety: Study participants were monitored for immediate reactions (30-minute observation period) after each vaccination. Pre-specified AEs included injection site reactions (erythema, swelling, tenderness) and systemic adverse events (fever, vomiting, inconsolable crying, drowsiness, loss of appetite and irritability). These events were recorded daily on a diary card during the 7 days after each vaccination, and by telephone interview eight days after vaccination. Other non-serious, unexpected AEs, including rash, were obtained by telephone interview eight and twenty-eight days after each vaccination.

Information about medically significant AEs, defined as events that prompted medical advice/attention from a physician's office or emergency room, was obtained by telephone interview for events occurring between 30 days and 6 months after the last vaccination. SAEs were reported and recorded from study start through the 6-months after the last vaccination.

Immunogenicity: Concomitant vaccine evaluations: blood samples were collected 30-44 days after vaccination(s) administered at Visit 2. SBA-H responses: For study group 1A, which constituted a subset of 200 study group 1 participants with an even identification number, blood was drawn 30 days (window:

+12 days) after Visit 2 (second Menactra vaccination). For study group 1B, which constituted a subset of 50 study group 1 participants with an odd identification number, blood was drawn 30 days (window: +12 days) after Visit 1 (first Menactra vaccination).

Measles and mumps -----(b)(4)----- tests, MMRV ELISA, and -----(b)(4)----- were performed by the applicant. The FAMA assay was performed in the laboratory of -----(b)(4)----- . Pneumococcal ELISA and multiplex opsonophagocytic activity (OPA) assay was performed at the -----(b)(4)----- .

7.2.1.7 Statistical Analysis Plan

Primary Hypothesis 1

To demonstrate that, thirty days after MMRV (or MMR+V) vaccination, the proportion of participants achieving a pre-specified antibody concentration to antigens contained in MMRV vaccine(s) in study group 2 is non-inferior to the corresponding proportions of participants in study group 4, for endpoints listed in section 7.2.1.5 (Endpoints).

The hypothesis would be supported by the data if the upper limit of the 2-sided 95% CI of $p_{\text{Group4}} - p_{\text{Group2}}$ is less than 0.05 for measles, mumps, and rubella antigens, and less than 0.10 for varicella antigen. Each antigen was tested separately. With 462 and 384 evaluable subjects in Group 2 and Group 4, respectively, the overall power to achieve the relevant study objectives was 89.9%.

Primary Hypothesis 2

To demonstrate that, thirty days after PCV7 vaccination, the geometric mean IgG concentrations for the seven pneumococcal serotypes among participants receiving PCV7+Menactra (group 3) is non-inferior to corresponding GMCs among participants receiving PCV7+MMRV (group 4).

The hypothesis would be supported by the data if the upper limit of the two-sided 95% CI of the ratio of the GMC ratio ($\text{GMC}_4 / \text{GMC}_3$), was less than 2 for each serotype. With 200 and 384 evaluable subjects in group 3 and group 4 respectively, the overall power to achieve the relevant study objectives was >99%.

The primary analyses were based on the per-protocol population for immunogenicity.

Other immunogenicity analyses

SBA-H: The % of participants with $\text{SBA-H} \geq 4$ and ≥ 8 , GMT, RCDC and distribution of titers, assessed after the second Menactra vaccination, were based on study group 1A and study group 3 participants who had serum available after primary serology testing. SBA-H responses after the first Menactra vaccination were based on study group 1B participants.

MMRV: antibody responses for study group 2 participants were tabulated and presented by vaccine type (combined vs. separate MMR+V).

Pneumococcal OPA: GMT, % with OPA titer ≥ 8 , RCDC and distribution of titers were assessed for study group 3 participants with available sera. A separate protocol was developed post-hoc for this analysis.

A subset of study group 4 subjects were selected from a list of all group 4 subjects, in which a random number was assigned to each subject's ID, and then the random uniform numbers were sorted in ascending order.

Safety analyses: The safety analyses were the same as described in study MTA-44, section 7.1.1.7 (Statistical Analysis Plan)

Populations analyzed

An immunogenicity analysis set for each concomitant vaccine injection included the subset of subjects who received the respective concomitant vaccine and had a valid serology result (i.e. blood sample was obtained and sufficient quantities of sera were available for analysis) for the endpoint being evaluated. The safety and immunogenicity populations analyzed were otherwise the same as described in study MTA-44 section 7.1.17 (Statistical analysis plan).

7.2.2 Results

Pertinent protocol revisions

Version 3.0, dated 02 March 2007

- Per CBER recommendations, the primary criteria and hypotheses for evaluation of PCV7 IgG antibody responses were changed to be based on GMC. Pneumococcal IgG seroresponses at ≥ 0.5 and 1.0 $\mu\text{g/mL}$ were included as observational endpoints.
- Medically significant adverse events were added as a safety endpoint.
- The vaccination window was expanded for visit 2.
- The eligible age of enrollment was expanded and vaccination status requirements for study entry were clarified.

Version 4.0, dated 21 May 2007

Pneumococcal IgG seroresponse at $\geq 0.35 \mu\text{g/mL}$ was included as observational endpoint. The study vaccination schedule was revised to be consistent with the physician prescribing information for ActHIB.

Version 5.0, dated 24 March 2008

An option to administer MMR+V in place of MMRV was added to the protocol procedures. Study objectives were added to describe the safety and immunogenicity of MMR and V vaccines.

Version 6.0, dated 26 September 2008

An evaluation of meningococcal antibody responses was added for study group 3 subjects.

Population

A total of 2289 participants (group 1A, n=201; group 1B, n=50; group 2, n=702; group 3, n=350; group 4, n=1086) were enrolled in the study. Of the enrolled participants, 625 subjects (group 2, n=24, study group 4, n=601) had received concomitant ActHIB vaccine. In this review, Hib participants from this study were excluded from the primary safety and immunogenicity populations, the immunogenicity results were described separately in section 7.2.2.2., and Hib participants reporting a serious adverse event were described in section 7.2.2.1.

Safety analysis set: Eleven participants (group 1A, n=3; group 2, n=3; group 4, n=5) did not receive study vaccines due to ineligibility criteria, (e.g., given antibiotics within 72 hours prior to enrollment, vaccination history), or, study vaccines not given according to protocol (study group 2, n=1). Participants from clinical site 40 (n=9) were excluded due to site non-compliance with study procedures. Ten participants who had been randomized to other study groups were included in the analyses according to the vaccine(s) received: nine participants (randomized to study group 2, n=7; study group 3, n=2) were included in study group 1A analyses. One subject, randomized to study group 3, was included in study group 2 analyses. The safety population therefore consisted of 1643 participants: group 1A, n=207; group 1B, n=50; group 2, n=664 [MMRV n=616, MMR+V n=48]; group 3, n=246; group 4, n=476.

Immunogenicity population: The intent-to-treat population consisted of 1466 participants (group 1A, n=187; group 1B, n=49; group 2, n=579; group 3, n=222; group 4, n=429). Except for study group 1B (98%), the percentage of participants who received vaccination(s) at Visit 2 *and* had a blood sample available ranged between 87.2% (group 2) and 90.5% (group 4). Reasons for not completing the vaccination phase (i.e., visit 2 *or* visit 3) were mainly due to voluntary withdrawal, lost to follow-up and non-compliance with protocol procedures. One participant (group 2) died from blunt head trauma. Four participants (group 1A, n=1; group 2, n=3) withdrew from the study due an SAE. See section 7.2.2.1

(Safety outcomes) for additional details. A total of 185 subjects were excluded from the per-protocol immunogenicity analysis. Reasons for exclusion were mainly due to vaccination or blood sampling visits that were outside the pre-specified window, or, routine childhood vaccinations were not given concomitantly. The per-protocol population therefore included 1281 participants (group 1A, n=148 (71.5%); group 1B, n=45 (90.0%); group 2, n= 498 (75.0%); group 3, n= 191 (77.6%); group 4, n= 399 (83.8%)).

Hib: Of the enrolled population receiving Hib vaccine, seventeen subjects were excluded due to site non-compliance with study procedures (MTA-37, n=15) or receipt of vaccines were inconsistent with the treatment assignment (MTA-44, n=2). One MTA-44 group 3 participant was included in the group 2 analyses, due to the vaccines actually received. The total safety population for subjects in studies MTA-37 and MTA-44 who received Hib vaccine consisted of 739 subjects (n=24 and n=586 subjects in MTA-37 groups 3 and 4, respectively; n=129 in MTA-44 study group 2).

Demographic characteristics

The age distributions were similar among the study groups. Except for study group 2, the percentage of male participants was 6.6% (study group 1B) to 9.4% (study group 1A) higher than enrolled female participants. The percentage of Caucasian (63.2% to 77%), African American (3.7% to 15.6%), Asian (0% to 4.0%), or Hispanic (8.9% to 18.3%) varied among the study groups. Imbalances in gender and ethnicity did not affect the overall study conclusions; please see CBER statistical review for details. Relative to all study group 4 subjects (15.9%), a higher percentage of participants included the subset of used for pneumococcal OPA analyses were Hispanic (n=40/196, 20.4%).

7.2.2.1 Safety Outcomes

The study vaccines administered to groups 1-3 were the same in studies MTA-37 and MTA-44. The safety profile after the first Menactra dose did not differ between studies.

Immediate adverse events (30 minute observation period after Visit 2 vaccination(s))

In study group 4, two adverse events were attributed by the investigator to fussiness and teething pain, respectively, and resolved with antipyretic medication.

Solicited local reactions (within 7 days after Visit 2 vaccination(s))

Local reactions at the MMRV, MMR+V and PCV7 injection sites

The most frequently reported solicited local reaction at the MMRV and PCV7 injection sites was tenderness. The percentage of participants reporting tenderness at the MMRV injection site was 32.2% in group 2, and 41.7% in group 4. The percentage of participants reporting tenderness at the PCV7 injection site was 49.3% in group 3, and 51.9% in group 4.

Local reactions at the Menactra injection site

After the second Menactra dose, administered alone or with an ACIP-recommended childhood vaccine, the percentage of participants with at least one injection site reaction was 43.9% (Menactra only), 45.7% (Menactra+MMRV) and 56.5% (Menactra+PCV7), respectively. Tenderness was the most frequent reaction, and occurred most often when PCV7 was a co-administered vaccine (study group 3, 47.8%). Of the injection site reactions categorized as grade 3, erythema (diameter ≥ 5.0 cm) occurred most often (group 1 n=6; group 2, n=15; group 3, n=7). For >95% of participants, the duration of injection site reactions was 1 to 3 days.

Solicited systemic adverse events

Irritability was the solicited systemic event reported most often in all study groups. The frequency of irritability occurring in participants who received Menactra with MMRV (group 2, 57.8%), with MMR+V (group 2, 60.9%) or PCV7 (group 3, 60.0%) was similar to irritability reported by participants who received MMRV+PCV7 without Menactra (control group, 62.4%). Irritability lasting ≥ 8 days was

reported by 3.7% of participants in study group 2 and in study group 3, and 4.8% in the control group, respectively. The frequency of systemic adverse events occurring in study group 2 participants who received Menactra and MMR+V (n=21/47, 32.6%) or MMRV (n=218/536, 40.7%) varied most for inconsolable crying. The percentage of subjects with at least one solicited systemic reaction was lower in the study group receiving Menactra alone, as expected.

The frequency of fever ($T \geq 38.0^\circ\text{C}$) during Days 0-7 was higher in study groups who received MMRV as a co-administered vaccine (study group 2, 20.6% and control group 4, 24.3% vs. study group 3, 16.4%). In study group 3, the onset of fever peaked between Days 1-3 post-vaccination. In the study group who received Menactra+MMRV, more participants developed fever starting between Days 4 and 7 than between Days 0 and 3. Fever that lasted ≥ 8 days occurred in three participants who received Menactra+MMRV, four participants in the control group, and none in participants who received Menactra+MMR+V. Grade 3 fever ($T \geq 39.5^\circ\text{C}$) occurred in 2.6% and 3.3% of study group 2 and 3 participants, respectively, and in 2.9% of control group participants. Temperatures were measured rectally in 85.3% of all subjects. As expected, the percentage of subjects with fever was lower in the study group receiving Menactra alone.

Unsolicited systemic adverse events (within 30 days after Visit 2 vaccination(s))

Events that occurred at a frequency of $>1\%$, and was higher in study groups 1-3 compared to study group 4, were: conjunctivitis, diarrhea, bronchiolitis, candidiasis, croup infections, nasopharyngitis, gastroenteritis, otitis media, sinusitis, teething, viral infection, cough and rhinorrhea. Urticaria was reported for five participants (study group 3, n=2; control group, n=3). Rash (not otherwise specified) (categorized by preferred term) was reported in 3.4% of participants who received Menactra+MMRV and 3.7% in the control group.

Serious adverse events

During the study period between the first vaccination visit through 6 months after the second vaccination visit, 65 subjects experienced an SAE (group 1, n=14; group 2, n=25 (including participants who received Menactra + MMRV (or MMR+V)); group 3, n=10; group 4, n=17).

Overall, serious adverse events included, in descending frequency and according to MedDRA System Organ Class categories, infections and infestations (n=34); nervous system disorders (n=17); respiratory, thoracic and mediastinal disorders (n=8); injury, poisoning, procedural complications (n=3); gastrointestinal disorders (n=2); metabolism and nutrition disorders (n=2); musculoskeletal and connective tissue disorders (n=1); congenital, familial and genetic disorders (n=1) and eye disorders (n=1).

The SAEs were mainly due to common childhood illnesses such as bronchiolitis, gastroenteritis, acute otitis media, viral infection). Nine subjects experienced a febrile seizure >30 days after vaccination: the event occurred after the 9-month vaccination visit in two subjects, and in seven subjects after the 12-month vaccination visit (group 1, n=2; group 2, n=1; group 4, n=4).

Safety-related study discontinuations, due to an SAE, occurred in four participants:

- Study group 1A (n=1): an 11 month old was hospitalized for methicillin-resistant *Staphylococcus aureus* infection, which started 56 days after the 9-month vaccination.
- Study group 2 (n=3)
 - A 12-month old girl developed a febrile seizure 88 days after the 9-month vaccination.
 - Subject 031-00025: A 10-month old girl was diagnosed with status epilepticus, which started 34 days after the 9-month vaccination. EEG findings were consistent with the clinical symptoms. She continued to have recurrent seizures. Additional laboratory evaluations were consistent with an inborn error of metabolism.

- An 11-month old boy with atypical Kawasaki's disease. The onset of fever (T38.9-39.4°C) and symptoms of viral illness occurred 77 days after the 9-month vaccination. Fever continued for eight days, during which he developed a generalized erythematous, non-blanching, polymorphous rash. At hospital admission, the erythrocyte sedimentation rate (ESR) was 61 mm/hour, and an echocardiogram showed mild prominence of the left coronary artery. After intravenous immunoglobulin treatment, the participant's symptoms improved and fever resolved. At a follow-up appointment, four days after hospital discharge, the participant was noted to have desquamation on the toes. A complete blood cell count showed an elevated platelet count (614,000/mm³), hematocrit 29.8%, white blood cell count of 8,430/mm³ with 69% lymphocytes, and an ESR of 15 mm/hour. The echocardiogram findings remained the same.

Deaths: a 13-month old girl (study group 2) died,----(b)(6)----- the 12-month old vaccinations, from blunt head trauma.

Medically significant adverse events (Day 30 through 6 months after the last vaccination(s))

Bronchiolitis was the most frequently reported event (study group 1, n=1; control group n=5) in all participants. All other types of medically significant AEs (by preferred term) were reported in 3 or fewer subjects.

7.2.2.2 Immunogenicity Outcomes

Measles, Mumps, Rubella, and Varicella Antibody Responses

The non-inferiority criteria were met for each of the vaccine four antigens. The upper limit of the 95%CI for the difference in percentages of participants achieving the pre-specified endpoints was <5% for measles, mumps, and rubella antibody responses, and <10% for varicella antibody responses. The intent-to-treat analysis results were consistent with the per-protocol analysis results.

Table 6. MTA-37. Measles, Mumps, Rubella, and Varicella Antibody Responses After Menactra+MMRV (or MMR+V) or MMRV+PCV7 Vaccinations, Per Protocol population

Vaccine Antigen	Antibody Concentration or Titer (Assay)	MMRV+PCV7		Menactra+MMRV (or MMR + V)		Difference in proportions	
		Group 4		Group 2		(Group 4-Group 2)	
		N=424-425		N=531			
		%	95% CI	%	95% CI	%	95% CI
Measles	≥ 300 mIU/mL (ELISA) or ≥ 120 mIU/mL (neutralization)	97.7	(95.7, 99.0)	98	(97.2, 99.5)	-0.3	(-2.2,1.6)
Mumps	≥ 500 U/mL (ELISA) or ≥ 60 (1/dil) (neutralization)	94.7	(92.0, 96.7)	95.2	(92.6, 96.8)	-0.5	(-3.4,2.4)
Rubella	≥ 10 IU/mL (ELISA)	88.3	(84.7, 91.3)	93	(89.6, 94.7)	-4.6	(-8.5,-0.8)
Varicella	≥ 300 mIU/mL (ELISA) or ≥ 4 (1/dil) (FAMA)	86.6	(82.8, 89.8)	93	(89.8, 94.8)	-6.4	(-10.4,-2.3)

Source: adapted from 125089.395.0, m5.3.5.1, MTA37 report.pdf, Table 5.1.

MMRV vs. MMR + V

Thirty-seven study group 2 participants (per-protocol population) received MMR and varicella vaccines as separate injections. Compared to participants who received MMRV, the percentage of participants who received MMR+V and achieved the pre-specified antibody level/titer was lower for measles (89.2%) and higher for mumps (97.3%), rubella (100%) and varicella (97.3%).

Pneumococcal IgG GMC

The non-inferiority criteria were not met for serotypes 4, 6B, and 18C. For each of the three serotypes, the upper 95% confidence limit of the GMC ratio was >2.00 (2.11 for serotype 4, 2.31 for serotype 6B, and 2.12 for serotype 18C). Statistically lower IgG antibody responses were observed in the study group receiving Menactra+PCV7, compared to the study group receiving PCV7+MMRV (i.e., PCV7 without Menactra).

Table 7. MTA-37. Pneumococcal IgG GMCs (µg/mL) After PCV7 Vaccination in Study Groups 4 and 3, Subset Population

Serotype	MMRV+PCV7		Menactra+PCV7		GMC ratio	
	Study group 4		Study group 3		(Group 4/Group 3)	
	N=399		N=191			
	GMC	95% CI	GMC	95% CI	Ratio	(95% CI)
4	3.33	(3.06, 3.62)	1.82	(1.62, 2.05)	1.83	(1.58, 2.11)
6B	10.8	(9.89, 11.7)	5.40	(4.79, 6.09)	1.99	(1.72, 2.31)
9V	3.57	(3.29, 3.88)	2.06	(1.84, 2.30)	1.74	(1.51, 2.00)
14	10.5	(9.65, 11.3)	6.73	(5.95, 7.60)	1.56	(1.35, 1.80)
18C	2.91	(2.66, 3.18)	1.58	(1.43, 1.75)	1.84	(1.59, 2.12)
19F	4.03	(3.74, 4.34)	2.50	(2.24, 2.78)	1.61	(1.42, 1.84)
23F	7.03	(6.39, 7.73)	4.62	(4.06, 5.25)	1.52	(1.29, 1.79)

Source: adapted from 125089.395.0, m5.3.5.1, MTA37 report.pdf, Table 5.3.

Pneumococcal OPA GMT

For serotypes 4, 6B, and 18C, statistically lower OPA GMTs were observed in the study group receiving Menactra+PCV7, compared to the study group receiving PCV7+MMRV (i.e., PCV7 without Menactra).

Table 8. MTA-37. Pneumococcal OPA GMTs After PCV7 Vaccination in Study Groups 4 and 3, Subset Population

Serotype	PCV7 + MMRV	PCV7 + Menactra	GMT Ratio	
	Study group 4	Study group 3	Group 4/Group 3	
	N=193-196	N=195-196		
	GMT	GMT	Ratio	95% CI
4	1271	617	2.06	(1.73, 2.46)
6B	5141	2760	1.86	(1.52, 2.29)
9V	2214	1406	1.57	(1.29, 1.92)
14	2072	1298	1.60	(1.30, 1.96)
18C	1156	645	1.79	(1.49, 2.16)
19F	662	469	1.41	(1.15, 1.73)
23F	5308	3694	1.44	(1.14, 1.81)

Source: adapted from 125089.395.0, m5.3.5.1, MTA37 PnOPA report.pdf, Table 7.1.

Hib antibody responses

The percentage of participants who achieved an anti-PRP antibody concentration $\geq 1.0\mu\text{g/mL}$ was 99.3% (n=438/441) in MTA-37 group 4 and 95.9% (n=94/98) in MTA-44 study group 2. The 95% CIs for each of the estimates was (98.0, 99.9) and (89.9, 98.9), respectively. The GMCs, described in the same order, were 68.7% (95% CI 60.6, 77.8) and 59.8% (95% CI 44.1, 81.2).

Meningococcal SBA-H antibody responses: post-dose 1 and 2 antibody responses, measured after each Menactra vaccination, were similar to results from participants receiving the same dosing regimen in study MTA-26 (see section 7.4).

7.2.3 Summary and Conclusions

Study MTA-37 was designed to evaluate the safety and immunogenicity of childhood vaccines (MMRV or PCV7), when concomitantly administered with a second Menactra dose (study group 2 and group 3, respectively). Study group 1 participants received a second dose Menactra alone, and children in study group 4 received MMRV+PCV7 without Menactra. The second Menactra dose (groups 1-3) and study group 4 vaccines (control group) were administered at 12 months of age.

Safety

The study vaccines administered to groups 1-3 in MTA-37 and MTA-44 were the same. The solicited adverse event data after first Menactra dose in MTA-37 participants were consistent with the safety data summarized in study MTA-44.

The reactogenicity of MMRV and of PCV7 did not increase when each of the vaccines was administered concomitantly with the second dose of Menactra (study group 2 and group 3, respectively), compared to when the vaccines were administered concomitantly without Menactra (study group 4). The most frequent reaction at the Menactra injection site was tenderness, which occurred most often when PCV7 was a co-administered vaccine. The frequency of fever ($T \geq 38.0^\circ\text{C}$) was higher in study groups who received concomitant MMRV (study groups 2 and 4), particularly for temperatures ranging from $>38.5^\circ\text{C}$ to $<39.5^\circ\text{C}$. Irritability was the systemic adverse event reported most often by all participants. As expected, the percentage of subjects with any systemic adverse event was lower in the group receiving Menactra alone.

Medically significant AEs reported from Day 30 to 6 months after the last vaccination(s) and SAEs reported during the course of the study (between Visit 1 through the 6-month follow-up after the 12-month vaccination(s)) did not reveal safety concerns. Serious adverse events generally occurred in similar proportions of subjects in each study group. The SAEs reported were primarily illnesses that were common in young children (e.g., bronchiolitis, gastroenteritis, acute otitis media). One death occurred due to blunt head trauma.

Immunogenicity

Co-administration of Menactra and MMRV did not adversely affect antibody responses to measles mumps, rubella and varicella vaccine antigens. The non-inferiority criteria were met for each of the pre-specified endpoints.

Lower pneumococcal antibody responses to serotypes 4, 6B and 18C were observed following co-administration of Menactra, which contains a diphtheria toxoid carrier protein, and a CRM₁₉₇-based 7-valent pneumococcal conjugate vaccine. The primary hypotheses were to demonstrate non-inferiority of pneumococcal IgG antibody responses to each serotype when Menactra was given with PCV7, compared to corresponding antibody responses when PCV7 was given with MMRV. The upper 95% confidence limit for the GMC ratio exceeded 2.00 for serotypes 6B, 4 and 18C (2.31, 2.11 and 2.12, respectively). Pneumococcal OPA responses, measured in a subset, were consistent with IgG responses. Carrier protein-related interference is one possible explanation for the observed findings. Differences in pneumococcal antigen-specific immunogenicity suggest that, in addition to competition for a limited number of T-cells, variations in carrier-induced T-cell help might contribute to differences in pneumococcal antibody responses.[5-7] At present, the incidence of invasive pneumococcal disease due to PCV7 serotypes is low in the U.S. Reduced antibody responses to serotypes contained in PCV7 may not have a population effect, due to protection afforded by indirect effects of routine pneumococcal infant immunization. Assessment of the effectiveness of pneumococcal vaccines routinely given to infants through continued post-licensure surveillance is important, particularly since immunological interference was observed following the last administered dose of the primary series. The effect of lowered pneumococcal antibody responses on an individual basis is not known.

In study group two and group three, 10-12% of participants/per group did not complete the vaccination phase (non-safety reasons) and another 12% of participants/per group were excluded from the per-protocol immunogenicity population (blood sampling reasons). Immunogenicity results from the primary intent-to-treat analyses were consistent with the per-protocol analyses.

7.3 Study MTA-48: Safety Study of Menactra when Administered with Other Pediatric Vaccines to Healthy Toddlers

7.3.1 NCT#00483574

7.3.1.1 Objectives

Safety

To describe the Menactra safety profile, as assessed by the frequency of immediate adverse events, solicited local and systemic AEs; non-serious unexpected AEs; medically significant AEs; and serious adverse events.

Immunogenicity

To describe the SBA-BR response to each serogroup, measured 30 days after the second Menactra vaccination, a subset of study group 1 Chilean participants.

7.3.1.2 Design Overview

This trial was an open-label, non-randomized, controlled study in the U.S. and Chile.

Table 9. MTA-48. Study Design

Study group	Visit 1 (at age 9 months)	Visit 2 (at age 12 months)
Group 1	Menactra	Menactra + PCV7 + MMRV [†] + HepA
Group 2 (ctl grp)		PCV7 + MMRV* + HepA

[†] Vaccines permitted in place of MMRV: U.S.: MMR vaccine: M-M-R_{II} (Measles, Mumps, and Rubella Virus Vaccine Live). Varicella vaccine: VARIVAX (Varicella Vaccine [Oka/Merck] Virus Vaccine Live). Chile: TRIMOVAX MERIEUX (Measles [Schwarz Strain], Mumps [Urabe AM-9 Strain] and Rubella [Wistar RA 27/3M Strain] Vaccine Live).

The protocol was amended during the study to permit administration of MMR+V in place of MMRV in the U.S., due to preliminary information available about increased rates of febrile seizures following MMRV (ProQuad) vaccination. In Chile, TRIMOVAX MERIEUX (a licensed MMR vaccine in Chile) would be permitted in place of MMRV. Varicella vaccine was not a routine childhood vaccination in Chile. At the time of the protocol amendment, study group 2 participants in Chile had completed the vaccination phase, and approximately 85% of group 1 subjects withdrew from the study due to concerns about ProQuad safety. The study was therefore terminated in Chile, the timing which occurred before the protocol changes were implemented.

The overall study period occurred from May 2007 (first visit of the first participant) to January 2009 (last contact of the last subject).

7.3.1.3 Population

The study was conducted at 82 centers in the United States and 11 centers in Chile.

Children were eligible for study enrollment if (s)he was aged 9 months (249 to 305 days) for study group 1 or aged 12 months (365 to 400 days) for group 2, and ineligible if (s)he had received a 4th dose of PCV7, one dose of MMR, Varicella or HepA vaccines. The eligibility criteria were otherwise the same as described in study MTA-44, section 7.1.1.3.

7.3.1.4 Study Products

Product information for Menactra/MMRV/PCV7 vaccines were described MTA-44, section 7.1.1.4. Descriptions of MMR and varicella vaccines were described in study MTA-37, section 7.1.1.4.

Hepatitis A (Vaqta, Merck & Co., Inc., Whitehouse Station, NJ): Each 0.5 mL dose contains approximately 25 U of hepatitis A virus antigen adsorbed onto approximately 0.225 mg of aluminum (AlPO₄). The vaccine is a liquid formulation given IM.

7.3.1.5 Endpoints

Safety: Occurrence of solicited local and systemic AEs, occurrence of unsolicited AEs, SAEs, occurrence of medically significant AEs

Immunogenicity: % with SBA-BR titer \geq 1:8, SBA-BR titer

7.3.1.6 Surveillance/Monitoring

Safety: Study participants were monitored for immediate reactions (30-minute observation period) after each vaccination. Pre-specified AEs included injection site reactions (erythema, swelling, tenderness) and systemic adverse events (fever, vomiting, inconsolable crying, drowsiness, loss of appetite and irritability). These events were recorded daily on a diary card during the 7 days after each vaccination, and by telephone interview eight days after vaccination. Other non-serious, unexpected AEs, including rash, were obtained by telephone interview eight and twenty-eight days after each vaccination.

Information about medically significant AEs, defined as events that prompted medical advice/attention from a physician's office or emergency room, was obtained by telephone interview for events occurring between 30 days and 6 months after the last vaccination. SAEs were reported and recorded from study start through the 6-months after the last vaccination.

Immunogenicity: Approximately 50 Chilean study group 1 participants were planned to have blood drawn at baseline (prior to the first Menactra vaccination) and 30 days after the second Menactra vaccination. Laboratory testing would be performed at Sanofi Pasteur, Inc. See study MTA-44 section 7.1.1.6 for additional details.

7.3.1.7 Statistical Analysis Plan

Enrollment of 1200 subjects receiving Menactra vaccine would provide a sample size to detect, with a 95% chance, an adverse event that occurred at a frequency of 1:400.

Safety analyses

Immediate unsolicited systemic AEs, occurring within 30 minutes after each vaccination, were summarized by study group and severity. For solicited local reaction and systemic adverse events, the number and percentage of participants were tabulated by reaction/AE, severity, onset and duration of the event. Unsolicited adverse events were described using MedDRA preferred terms and system organ class (SOC). The number and percentage of subjects reporting any of these AEs were tabulated by study group and severity. Medically significant events and SAEs were described separately. Analyses were provided by country and by study group, according to the vaccines received. Also, safety analyses were provided for subjects who received MMR+V vaccines.

Populations analyzed

The safety analysis set included all subjects who received at least one injection of any study vaccine(s) and had any safety data available.

The immunogenicity analysis set for each concomitant vaccine injection included the subset of subjects who received Menactra and had a valid serology result (i.e. blood sample was obtained and sufficient quantities of sera were available for analysis).

7.3.2 Results

Pertinent protocol revisions

Version 2.0 of the Protocol, Dated 23 May 2007

- The protocol and informed consent were updated to be consistent with Guillain Barre Syndrome information available in the Menactra U.S. package insert.

Version 3.0 of the Protocol, Dated 03 April 2008

- An option was included to offer MMR+V in place of MMRV (ProQuad) for U.S. study group 1 subjects, and replace MMRV with TRIMOVAX MÉRIEUX for Chilean participants.
- The sample size of Chilean study group 1 was updated to reflect the number of subjects actually enrolled, and accordingly, the power calculations.
- Analyses categorized by country and vaccines received were included in the study report
- Since blood samples were obtained for only four participants, baseline and post-vaccination bactericidal antibody titers would be presented as line listings. A separate report containing the immunogenicity data would be provided at a later date.

Only the sections of this study that relate to safety evaluations are covered in this review.

A total of 1778 (study group 1 (Menactra) n=1256, study group 2 (control group) n=522) children were enrolled in the study. Twenty-three U.S. study group 1 participants received MMR+V. The remaining study participants in U.S. and Chile received MMRV.

The safety population, defined as participants who received *at least one injection* and for whom safety data was available, consisted of 1774 participants (study group 1, N=1253 [U.S. n= 1053, Chile n=200]; study group 2, N=521 [U.S. n= 321, Chile n=200]). However, 85% (n=171/200) of study group 1 participants in Chile withdrew before receiving the 12-month study vaccinations (see section 7.3.1.2 for details).

US: Four subjects were excluded before receiving any study vaccines (group 1, n=3; group 2, n=1), due to voluntary withdrawal or protocol non-compliance. The percentage of participants who did not complete the vaccination phase was 9.7% and 4.0% in study groups 1 and 2, respectively. Reasons for not completing the vaccination phase (i.e. did not complete ≥ 1 scheduled visits or the safety follow-up 30 days after the 12-month vaccinations) were voluntary withdrawal (group 1, 4.9%, group 2, 0%), non-compliance with protocol procedures (group 1, 2.7%; group 2, 2.8%), and lost to follow-up (group 1, 1.5%; group 2, 1.2%).

Chile: In addition to the 86% of study group 1 participants who did not complete the vaccination phase, seven study group 1 participants voluntarily withdrew for non-safety related reasons or were lost-to follow-up.

Safety-related discontinuations

An additional seven participants withdrew from the study for safety-related reasons (U.S study group 1: n= 3 due to an SAE, n=3 due to non-serious AE; Chile study group 1: n=1 due to an SAE). See section 7.3.2.1 (Safety outcomes) for additional details.

Demographic characteristics

US: There were no substantive gender differences between study group 1 and 2 participants. The population included participants who were Caucasian (69.1%), African American (12.8%), Hispanic (11.9%), Asian (2.1%), and individuals with other ethnic backgrounds (2.7%).

Chile: 52% of Study group 1 participants were male and 48% were female; study group 2 included 40.0% male and 60.0% female participants. The population was comprised of 99.8% Hispanic participants.

There were no substantive differences between the ages of U.S. and Chilean participants in study groups 1 or 2.

7.3.2.1 Safety Outcomes

Immediate adverse events (30 minute observation period after each vaccination visit)

U.S. study group 1 (n=5): Three participants developed teething pain and one participant experienced mild diarrhea after first Menactra dose. The fifth participant developed a rash (not otherwise specified) in the left cheek and neck after the 12-month vaccinations (Menactra, MMRV, HepA, and PCV7). The subject recovered within 4 days following treatment with an unspecified medication.

Solicited Local Reactions

Local reactions at the Menactra injection site

The percentage of U.S. subjects with at least one solicited reaction at the Menactra injection site was 52.1% after the first dose, and 57.5% after the second dose (administered concomitantly with childhood vaccines). In all participants, solicited local reactions mainly lasted 1-3 days.

Table 10. MTA-48. Solicited Local Reactions at the Menactra Injection Site Within 7 Days After Each Vaccination, Study Group 1 (Safety Population – US Sites)

Menactra Injection Site Reactions	Intensity	After 9-month vaccination: Menactra		After 12-month vaccinations: Menactra + MMRV + PCV7 + HepA	
		N=998*		N=903-904*	
		%	95% CI	%	95% CI
Tenderness [†]	Any	37.4	(34.4, 40.5)	48.5	(45.2, 51.8)
	Grade 1	32.5	(29.6, 35.5)	39.6	(36.4, 42.9)
	Grade 2	4.3	(3.1, 5.8)	7.5	(5.9, 9.5)
	Grade 3	0.6	(0.2, 1.3)	1.3	(0.7, 2.3)
Erythema	Any	30.2	(27.3, 33.1)	30.1	(27.1, 33.2)
< 2.5 cm	Grade 1	27.2	(24.4, 30.0)	28.5	(25.6, 31.6)
>2.5 to <5 cm	Grade 2	2.5	(1.6, 3.7)	1.3	(0.7, 2.3)
≥ 5 cm	Grade 3	0.3	(0.1, 0.9)	0.1	(0.0, 0.6)
Swelling	Any	16.8	(14.6, 19.3)	16.2	(13.8, 18.7)
< 2.5 cm	Grade 1	15.7	(13.5, 18.1)	15.0	(12.8, 17.5)
>2.5 to <5 cm	Grade 2	0.9	(0.4, 1.7)	0.9	(0.4, 1.7)
≥ 5 cm	Grade 3	0.2	(0.0, 0.7)	0.1	(0.0, 0.6)

*N: number of vaccinated subjects with at least one safety record for the reported solicited reaction.

† Grade 1: minor reaction when injection site is touched; Grade 2: cries and protests when injection site is touched;

Grade 3: cries when injected limb is moved, or the movement of the injected limb is reduced.

Source: adapted from 125089.395.0, m5.3.5.1, MTA48 report.pdf, Table 6.5, and m2.7.4, Summary of clinical safety.pdf, Tables 7.3A and 7.3B.

In Chile, the incidence of any solicited Menactra injection site reaction after the first dose was 40%. Menactra injection site erythema (15%; n=30/200) and swelling (7%; n=14/200) occurred less frequently in Chilean participants than in the U.S. participants. Of the 21 participants who received a second Menactra dose (administered concomitantly with childhood vaccines) in Chile, 16 participants (76.2%) reported at least one solicited reaction at the Menactra injection site.

Solicited Systemic Adverse Events

Table 11. MTA-48. Solicited Systemic Adverse Events Within 7 Days After Each Vaccination, by Intensity (Safety Population - US Sites)

Adverse Event	Intensity	After 9-month vaccination		After 12-month vaccinations			
		Menactra only (Study group 1)		Menactra + PCV7 + MMRV + HepA (Study group 1)		PCV7 + MMRV + HepA (Study group 2)	
		N=999-1002		N=898-908		N=303-307	
		%	95% CI	%	95% CI	%	95% CI
Irritability^a	Any	56.8	(53.7, 59.9)	62.1	(58.9; 65.3)	64.8	(59.2; 70.2)
	Grade 1	30.8	(28.0, 33.8)	32.7	(29.7, 35.9)	31.9	(26.7, 37.5)
	Grade 2	23.1	(20.5, 25.8)	25.7	(22.9, 28.6)	28.7	(23.7, 34.1)
	Grade 3	2.9	(1.9, 4.1)	3.7	(2.6; 5.2)	4.2	(2.3; 7.1)
Fever - Any Route 38.0°C-38.5°C >38.5°C-39.5°C >39.5°C	Any	12.2	(10.2, 14.4)	24.5	(21.7, 27.4)	21.8	(17.3, 26.9)
	Grade 1	6.5	(5.1, 8.2)	10.0	(8.1, 12.2)	11.6	(8.2, 15.7)
	Grade 2	4.5	(3.3, 6.0)	11.9	(9.9, 14.2)	7.3	(4.6, 10.8)
	Grade 3	1.1	(0.6, 2.0)	2.2	(1.4, 3.4)	2.6	(1.1, 5.1)
- Rectal 38.0°C-38.5°C >38.5°C-39.5°C >39.5°C	Any	9.4	(7.7, 11.4)	19.5	(16.9, 22.2)	15.2	(11.3, 19.7)
	Grade 1	5.4	(4.1, 7.0)	8.2	(6.5, 10.2)	8.3	(5.4, 11.9)
	Grade 2	3.2	(2.2, 4.5)	9.8	(7.9, 11.9)	5.3	(3.1, 8.4)
	Grade 3	0.7	(0.3, 1.4)	1.3	(0.7, 2.3)	1.7	(0.5, 3.8)
Abnormal Crying^b	Any	33.3	(30.4, 36.3)	40.0	(36.8, 43.2)	39.4	(33.9, 45.1)
	Grade 1	23.1	(20.5, 25.8)	26.1	(23.3, 29.1)	28.7	(23.7, 34.1)
	Grade 2	8.3	(6.7, 10.2)	11.5	(9.5, 13.7)	10.1	(7.0, 14.0)
	Grade 3	2.0	(1.2, 3.1)	2.4	(1.5, 3.6)	0.7	(0.1, 2.3)
Drowsiness^c	Any	30.2	(27.4, 33.2)	39.8	(36.6, 43.0)	39.1	(33.6, 44.8)
	Grade 1	26.0	(23.4, 28.9)	33.4	(30.3, 36.5)	33.2	(28.0, 38.8)
	Grade 2	3.5	(2.4, 4.8)	5.3	(3.9, 7.0)	5.2	(3.0, 8.3)
	Grade 3	0.7	(0.3, 1.4)	1.1	(0.5, 2.0)	0.7	(0.1, 2.3)
Vomiting^d	Any	14.1	(12.0, 16.4)	11.0	(9.1, 13.2)	9.8	(6.7, 13.7)
	Grade 1	9.2	(7.5, 11.1)	6.4	(4.9, 8.2)	7.8	(5.1, 11.4)
	Grade 2	4.6	(3.4, 6.1)	4.4	(3.2, 6.0)	2.0	(0.7, 4.2)
	Grade 3	0.3	(0.1, 0.9)	0.2	(0.0, 0.8)	0.0	(0.0, 1.2)
Loss of Appetite^e	Any	30.2	(27.4, 33.2)	35.7	(32.6, 38.9)	31.9	(26.7, 37.5)
	Grade 1	21.9	(19.3, 24.6)	25.4	(22.6, 28.4)	24.8	(20.0, 30.0)
	Grade 2	7.1	(5.9, 8.9)	7.6	(6.0, 9.5)	6.5	(4.0, 9.9)
	Grade 3	1.2	(0.6, 2.1)	2.6	(1.7; 3.9)	0.7	(0.1; 2.3)

^a Grade 1: easily consolable; Grade 2: requiring increased attention; Grade 3: inconsolable.

^b Grade 1: <1 hour; Grade 2: 1-3 hours; Grade 3: >3 hours.

^c Grade 1: Sleeper than usual or less interested in surroundings. Grade 2: not interested in surroundings or did not wake up for a feed/ meal; Grade 3: Sleeping most of the time or difficult to wake up.

^d Episodes/per 24hours: Grade 1: 1 episode; Grade 2: 2-5 episodes; Grade 3: ≥6 episodes or requiring parenteral hydration.

^e Grade 1: eating less than usual; Grade 2: missed 1 or 2 feeds/meals completely; Grade 3: refuses ≥ 3 feeds/meals or refuses most feeds/meals.

Source: adapted from 125089.395.0, m5.3.5.1, MTA48 report.pdf, Table 6.6, and m2.7.4, Summary of clinical safety.pdf, Tables 7.22A and 7.22B.

The occurrence of fever, when categorized by country, was similar when MMRV, PCV7 and HepA vaccines were given with a second Menactra dose (study group 1) compared to when the childhood vaccines were given without Menactra (study group 2; control group). The overall rate of fever, however, in Chilean participants (group 1, 24.5%; group 2, 21.8%) was 2 times lower than in U.S. participants (group 1, 42.9%; group 2, 47.5%). Among Chilean participants, all temperatures at the 12-month old visit were measured by the rectal route.

Unsolicited systemic adverse events (within 30 days after each vaccination visit)

Unsolicited systemic adverse events most frequently reported were events included in the ‘infections and infestations’ system organ class.

- U.S.: Commonly reported unsolicited adverse events were otitis media (OM) and upper respiratory tract infection (URI). The frequency of OM reported after vaccination visit 2 (12-months of age) was 9.7% (n=89/921) in study group 1 (Menactra +MMRV+PCV7 +HepA), compared with 8.2% (n=26/319) in study group 2; upper respiratory tract infections were reported in 6.4% (59/921) and 5.0% (16/319) of subjects, respectively. Unsolicited adverse events commonly reported were cough, rhinorrhea and diarrhea.
- In Chile, frequently reported unsolicited adverse events included gastroenteritis, diarrhea, nasopharyngitis, bronchitis and cough. One participant developed urticaria after the first Menactra vaccination.

The occurrence of urticaria was similar in 12-month old U.S. participants who received MMRV, PCV7 and HepA vaccines with or without Menactra (0.7% vs. 0.6%, respectively). In Chile, urticaria occurred in three control group participants and none of the Menactra vaccinated participants.

Serious Adverse Events

Of the U.S. (including participants who received Menactra + MMR+V) and Chilean populations, 50/1030 participants in study group 1 and 12/321 participants in the control group (group 2) reported at least one SAE was reported.

Overall, serious adverse events included, in descending frequency and according to MedDRA System Organ Class categories, infections and infestations (n=31); nervous system disorders (n=11); respiratory, thoracic and mediastinal disorders (n=7); injury, poisoning, procedural complications (n=5); metabolism and nutrition disorders (n=4); gastrointestinal disorders (n=2); congenital, familial and genetic disorders (n=1); neoplasms benign, malignant and unspecified (n=1); immune system disorder (n=1) and psychiatric disorder (n=1); general disorders and administration site conditions (n=1).

The events that were typical for the age of the study population: infection (e.g. bronchiolitis, croup, gastroenteritis, viral infection), respiratory (e.g. reactive airways disease), and neurological (e.g. febrile convulsion).

Safety-related study discontinuations

Four group 1 participants withdrew from the study:

- A 10-month old Chilean boy experienced a febrile seizure 2 days after the first Menactra vaccination. He had a 2-day history of URI symptoms, and developed a T40.1°C on the morning of the event. After the event occurred, the participant was brought to the emergency room for further evaluation. Information about the seizure characteristics (e.g., generalized vs. local, duration) and initial physical examination were not provided. The laboratory work-up was notable for an ESR of 40 mm/hour (normal 1-15), and C-reactive protein of 21 mg/L (normal: less than 5). WBC count and CSF results were within normal limits. No further seizures occurred during a 3-4 hour observation period.
- A participant experienced a night terror 2 days after the first Menactra vaccination.
- A participant developed fever >30 days after the first Menactra vaccination.

- A participant developed inconsolable (grade 3 irritability) for >3 hours (grade 3 abnormal crying) 5 days after the first Menactra vaccination, and coincided with the onset of URI symptoms.

Deaths (n=2, study group 1): One participant died from asphyxia. The other participant was newly diagnosed with epilepsy and experienced frequent seizure episodes. He withdrew from the study, and two months later, had a seizure associated with cardiopulmonary arrest.

7.3.3 Summary and Conclusions

Study MTA-48 was primarily designed to evaluate the safety of two doses of Menactra when administered alone (at 9 months of age) and when the second dose was administered concomitantly with routine pediatric vaccines (MMRV, PCV7, and HepA vaccines) recommended at 12 months of age.

Participants were enrolled from study sites in the U.S. and Chile. In Chile, study group 2 included 60% female participants and 40% male participants. There were no substantive gender differences in the other study groups (U.S. and Chile). The U.S. population was mostly Caucasian (69.1%), but also included African American, Hispanic and Asian participants, and individuals with other ethnic backgrounds. The Chilean population was 99.8% Hispanic. While the study was ongoing, available safety data in an updated MMRV (ProQuad) package insert indicated a possible increased risk of febrile seizures following vaccination. As a result, 86% (171/200) of Chilean group 1 subjects withdrew from the study during the amendment process to include alternatives to MMRV vaccination; 21 Chilean group 1 subjects completed the vaccination phase of the study. Two percent (n=23/1053) of U.S. study group 1 participants received MMR+V. All group 2 participants had already completed the vaccination phase before the protocol was amended.

Tenderness was the most frequently reported Menactra injection site reactions after the first Menactra dose and after the second vaccination visit (group 1, 51.9%; group 2, 60.7%; group 3, 57.4%). Most of the solicited local reactions at the Menactra injection site lasted 1-3 days. In all participants, irritability was the most frequently reported solicited systemic adverse event, and occurred similarly between groups after vaccinations given at Visit 2. The overall rate of fever in Chilean participants (42.9%-47.5%) was two times lower following Visit 2 vaccinations, compared to corresponding fever rates in U.S. participants (21.8%-24.5%); when categorized by country, between group comparisons of fever rates were similar.

Unsolicited adverse events reported after each vaccination visit were events that were common to the age and location of the study population. Medically significant AEs reported from Day 30 to 6 months after the last vaccination(s) and SAEs reported during the course of the study (between Visit 1 through the 6-month follow-up after the 12-month vaccination(s)) did not reveal significant safety concerns. Two deaths occurred during the study (asphyxia, epilepsy with frequent recurrent seizures).

7.4 Additional Studies

7.4.1 Study MTA-26: Safety and Immunogenicity of Menactra (Meningococcal [Groups A, C, Y and W-135] Polysaccharide Diphtheria Toxoid Conjugate Vaccine) in Toddlers 9 to 18 Months of Age

Study Design: This supportive study was an open-label, dose-ranging trial in the U.S. The primary objective was to describe Menactra immunogenicity when administered to children at 9 and 12 months, 9 and 15 months, 12 and 15 months, 15 months or 18 months of age. A sixth group of children, aged 3 to 6 years, were enrolled and received one dose of a tetravalent polysaccharide vaccine (Menomune), manufactured by Sanofi Pasteur, Inc. In all study groups, meningococcal vaccines were not administered concomitantly with routine childhood vaccines. Sera were collected prior to the first vaccination (baseline) and 28 days after the last vaccination. Evaluation of solicited local and systemic AEs,

unsolicited AEs, and SAEs were the same as described in MTA-48 (section 7.3.1.5). The study period occurred from December 2004 to March 2006.

Results: A total of 378 children were enrolled into six study groups (in the order described above), 322 participants were included in the per-protocol population for immunogenicity: group 1, n=42; group 2, n=51; group 3, n=54; group 4, n=57; group 5, n=52; group 6, n=66.

Safety

Except for mild (grade 1) drowsiness and fever, the reactogenicity after the 2nd Menactra dose was generally similar for 2-dose regimens given at 9 and 12 months (study group 1) or 12 and 15 months (study group 3). In study group 1, 15 of 48 (31.3%) participants were sleepier than usual or less interesting in surroundings, compared to 6 of 62 (9.7%) participants in study group 2. Fevers between T38.0°C and T38.5°C occurred in 9 of 47 (19.1%) study group 1 participants and 6 of 62 (9.7%) study group 2 participants. Except for moderate erythema (>2.5 cm to <5 cm), the reactogenicity after 2nd Menactra dose (n=7/59; 11.9%) in study group 3 participants was comparable to study groups 1 (n=48, 4.2%) or group 3 (n=1/62, 1.6%). Among the three 2-dose regimens, there were no substantive differences in occurrence of unsolicited adverse events.

In total, 16 Menactra participants reported at least one SAE (2-dose regimens, n=7; 1-dose regimens, n=6). All SAEs occurred >30 days after the last vaccination, and included viral illnesses, bacterial infection (e.g., superficial abscess), seizures (febrile and non-febrile), or injuries.

Immunogenicity

2-dose Menactra regimens

For any regimen, the percentage of participants who achieved a SBA-H titer ≥8 after two Menactra doses was higher than responses after a single dose, especially for serogroups Y and W135.

Table 12. MTA-26. Percentage of Children with SBA-H Antibody Titers ≥1:8, by Timepoint Prior to-and Following Menactra Vaccination, Per-Protocol Population

Serogroup	Timepoint	Age at vaccination (first dose/ second dose)					
		9months/ 12months (study group 1)		9 months/ 15 months (study group 2)		12 months/ 15 months (study group 3)	
		N=33-40		N=41-50		N=48-54	
		% ≥1:8	95% CI	% ≥1:8	95% CI	% ≥1:8	95% CI
A	Baseline	37.8	(22.5, 55.2)	43.9	(28.5, 60.3)	33.3	(20.4, 48.4)
	Post Dose 1	75.8	(57.7, 88.9)	66.7	(51.0, 80.0)	51.9	(37.6, 66.0)
	Post Dose 2	88.9	(73.9, 96.9)	89.4	(76.9, 96.5)	85.2	(72.9, 93.4)
C	Baseline	5.0	(0.6, 16.9)	2.2	(0.1, 11.5)	0	(0.0, 6.8)
	Post Dose 1	82.9	(66.4, 93.4)	85.4	(72.2, 93.9)	84.6	(71.9, 93.1)
	Post Dose 2	100	(90.5, 100.0)	100	(92.9, 100.0)	100	(93.4, 100.0)
Y	Baseline	2.6	(0.1, 13.5)	0	(0.0, 8.2)	2.0	(0.0, 10.4)
	Post Dose 1	20.6	(8.7, 37.9)	24.4	(12.9, 39.5)	34.6	(22.0, 49.1)
	Post Dose 2	94.6	(82.8, 99.3)	94.0	(83.5, 98.7)	96.3	(87.3, 99.5)
W-135	Baseline	2.8	0.1, 14.5)	0	(0.0, 8.6)	0	(0.0, 7.1)
	Post Dose 1	23.5	(10.7, 41.2)	26.7	(14.6, 41.9)	17.6	(8.4, 30.9)
	Post Dose 2	91.7	(77.5, 98.2)	92.0	(80.8, 97.8)	96.2	(86.8, 99.5)

Source: adapted from 125089.395.0, m5.3.5.1, MTA26 report.pdf, Table 5.8.

At baseline (pre-dose 1), SBA-H GMTs for serogroup A were 5, 6, and 6 for study group 1, 2, and 3 respectively. For the remaining serogroups, the baseline GMT was 2 for all participants.

Serogroup A: After Dose 1, the GMTs were 15, 9 and 8 for Groups 1, 2 and 3, respectively.

After Dose 2 (described in the same order), the GMTs were 35, 86, and 25.

Serogroup C: After Dose 1, the GMTs were 20, 24 and 29 for Groups 1, 2 and 3, respectively.

After Dose 2 (described in the same order), the GMTs were 204, 252, and 183.

Serogroup Y: After Dose 1, the GMTs were 4 for each of Groups 1, 2 and 3.

After Dose 2 (described in the same order), the GMTs were 47, 82, and 75.

Serogroup W-135: After Dose 1, GMTs were 4, 4 and 3 for Groups 1, 2 and 3, respectively.

After Dose 2 (described in the same order), the GMTs were 31, 56, and 41.

In children 3-6 years old, who received a single Menomune dose, the post-vaccination SBA-H GMTs were 14, 8, 12 and 11 for serogroups A, C, Y and W135, respectively.

1-dose Menactra regimens: For serogroups A, W135 and Y, children who received a single Menactra dose at 15 months or 18 months of age had lower SBA-H antibody responses ($\geq 1:8$, GMTs), compared to corresponding responses in older children who received a single Menomune dose.

Summary:

After any of the 2-dose regimens, SBA-H antibody responses to each serotype were higher than corresponding responses in children 3-6 years old, who received a single Menomune dose. The safety and immunogenicity data support the 2-dose regimen selected for phase 3 studies.

8.0 Overview of Efficacy Across Trials

Effectiveness against systemic meningococcal infection was inferred from an immunological measure of protection, serum bactericidal antibody.

Study MTA-44 was the pivotal immunogenicity trial for inferring effectiveness after a 2-dose Menactra series, when administered to children at 9 and 12 months old. The first dose was given alone; the second dose was administered either alone or concomitantly with a childhood vaccine (MMRV or PCV7). The primary immunogenicity endpoint was the proportion of participants achieving a SBA-H titer $\geq 1:8$, measured thirty days after the 2nd Menactra vaccination, for each serogroup. In study group 1, when two of doses of Menactra were given alone, more than 95% of participants achieved a SBA-H titer $\geq 1:8$ for serogroups A, C, and Y, and 86.4% for serogroup W135. The percentage of participants who achieved an SBA-H $\geq 1:8$ to serogroup W-135 was similar to seroresponses in children 4-10 years old (85%), after a single Menactra dose.[4]

MTA-26 was a supportive study designed to evaluate other Menactra dosing regimens. Immunogenicity data available in children, who received Menactra at 12 months and 15 months of age, supported bridging of immunogenicity data from children 9 and 12 months of age to children 13 months through 23 months of age. Please see section 7.4 for a summary of the study design and immunogenicity outcomes.

8.1 Advisory Committee Meeting

An approach to demonstrating effectiveness of meningococcal conjugate vaccines in young children was a discussion topic at a VRBPAC meeting held April 6-7, 2011. The meeting outcomes were included in section 4.1.

8.2 Drug-Drug Interactions

Study MTA-37 was a trial with primary objectives to evaluate the safety and immunogenicity of routine pediatric vaccines (MMRV or PCV7), when concomitantly administered with a second Menactra dose. A control group received MMRV+PCV7 without Menactra. The non-inferiority criteria for measles, mumps, rubella, varicella, and 4 of 7 pneumococcal vaccine serotypes were met. Please see section 7.2 for a description of the study design, immunogenicity outcomes, and conclusions.

In study MTA-48, participants received Menactra, MMRV (or MMR+V), PCV7 and Hep A vaccines (study group 1) or MMRV, PCV7 and HepA vaccines without Menactra (study group 2). No adverse safety outcomes occurred following co-administration of childhood vaccines (recommended in the U.S. at 12 months old) with a second Menactra dose.

9.0 Overview of Safety Across Trials

Across the 4 studies in the BLA supplement, a total of 3993 children received at least one dose Menactra, 2582 children received a second Menactra dose concomitantly with ≥ 1 U.S. licensed childhood vaccine, and 1583 children received concomitant childhood vaccines without Menactra. There no substantive age differences among children enrolled in Menactra study groups, or among children enrolled in study groups who received childhood vaccines without Menactra. The male to female ratio varied among the studies, but gender imbalances did not affect overall study conclusions; please see CBER statistical review of MTA-44 and MTA-37 for details.

The safety monitoring was similar in the 4 trials. Study participants were monitored for immediate reactions 30 minutes after each vaccination. Pre-specified adverse events included injection site reactions (erythema, swelling, tenderness) and systemic adverse events (fever, vomiting, inconsolable crying, drowsiness, loss of appetite and irritability). The events were recorded daily on a diary card during the 7 days after each vaccination, and by telephone interview eight days after vaccination. Other non-serious, unexpected adverse events, including rash, were obtained by telephone interview eight and twenty-eight days after each vaccination. Medically significant AEs were defined as events that prompted medical advice/attention from a physician's office or emergency room between Day 30 and 6 months after the last vaccination. Information was obtained by scripted telephone interview. Serious adverse events (SAEs) reported were recorded through the 6-month study period following the last vaccination.

9.1 Deaths

In total, three deaths occurred in the four trials. Two deaths were due to closed head injury and asphyxia, respectively. The third participant (MTA-48, group 1 [Menactra+MMRV+PCV7+HepA]) was newly diagnosed with epilepsy, and had frequent seizure episodes thereafter. Two months after withdrawing from the study, he experienced a seizure with subsequent cardiopulmonary arrest. The deaths were viewed by this reviewer as unrelated to vaccination.

9.2 Serious Adverse Events

Three pivotal trials (MTA-44, -37, -48)

During the study period between the first and second Menactra dose, 71/3691 (1.9%) of subjects reported at least one SAE. Of the 71 SAEs, 20 SAEs occurred within the first 30 days after the first Menactra dose. Six of the SAEs occurred in the first 7 days after the 1st dose (respiratory distress, head injury, two febrile convulsions, and fatty filum terminale [congenital spinal cord anomaly], contact dermatitis).

At least one SAE during the study period between second Menactra dose and the subsequent 6-month follow-up was reported in 70/2582 (2.7%) of study participants who received a second dose with concomitant childhood vaccines, 16/632 (2.5%) of subjects who received a second dose alone, and 45/1583 (2.8%) of participants receiving childhood vaccines alone. During the first 30 days after the second Menactra dose (at 12 months old), 17 SAEs were reported in study groups who received a second dose with concomitant childhood vaccines, 3 SAEs occurred in study groups who received a second dose alone, and 5 SAEs occurred in study groups who received childhood vaccines alone. Among children who received Menactra with or without childhood vaccines, seven SAEs occurred in the first 7 days after the second dose (insulin-dependent diabetes mellitus, two febrile convulsions, acute otitis media, pyrexia, diarrhea, viral pneumonia); 1 SAE occurred in a participant who received childhood vaccines alone (lobar pneumonia).

Across the different vaccination groups, febrile seizure was the most frequently reported SAE.

- Febrile seizures occurring <5 days after vaccination was reported by in two participants: a 12-month old who received Menactra+PCV7 and a 10-month old who received Menactra+MMRV+PCV7 +HepA developed a febrile seizure 1 and 2 days after vaccination, respectively.
- Two of 33 participants, a 10-month and a 12-month old participant (MTA-37: n=1 study group 2, n=1 study group 4, respectively) experienced a febrile seizure within 5-12 days after vaccination. Febrile seizures for the remaining participants occurred between 19-188 days after vaccination; three participants withdrew from the study due to the event.

Thirty three of 3198 participants who received MMRV vaccine experienced a febrile seizure for the first time. None of the 71 participants who received MMR+V reported a febrile seizure.

After febrile seizures, the next most frequently reported SAEs in the U.S. population were in the MedDRA System Organ Class infections and infestations. Of events in this category, bronchiolitis (n=14), gastroenteritis (n=12) and pneumonia (n=12) were most common.

9.3 Study Discontinuations Due to a SAE

Three pivotal trials (MTA-44, -37, -48)

Six participants had safety-related study discontinuations due to an SAE:

- Disseminated staphylococcal infection (MTA-37, Menactra only [study group 1]) 58 days after vaccination at 9 month of age;
- Epilepsy (MTA-37 Menactra+MMRV [study group 2]) 34 days after vaccination at 9 month of age,
- Three febrile seizures occurring 45-88 days after vaccination (as described above).
- MTA-37 (Menactra+MMRV): An 11-month old boy was diagnosed with incomplete Kawasaki's disease 77 days after vaccination at 9 month of age. He developed symptoms of viral illness (nasal congestion, cough), concurrent fever (T38.2-40.0C) for >5 days, then generalized erythematous rash, unilateral cervical lymphadenopathy. ESR was 61mm/hr. Echocardiogram, chest x-ray, and complete blood count with differential were unremarkable. Following IGIV treatment, the participant became afebrile. He recovered without sequelae.

9.4 Medically Significant Adverse Events

During the study period between 30 days and 6 months after the last vaccination, 2.3% (n=56/2083) of Menactra participants (received routine childhood vaccines) and 3.5% (n=70/2013) of control group participants (given childhood vaccines without Menactra) reported a medically significant AE. Of participants who received two doses of Menactra alone (no concomitant childhood vaccines), 2.6% reported a medically significant AE.

Other than bronchiolitis (n=8), otitis media (n=8) and asthma (n=5), medically significant AEs (by preferred term) were reported in 3 or fewer subjects.

9.5 Safety Conclusions

Overall, the safety profile of a 2-dose Menactra series given three months apart was similar to other licensed vaccine for this age range. In the pivotal safety trial, Menactra was given at 9 months and at 12 months of age. The second dose of Menactra was given with three childhood vaccines, recommended by the Advisory Committee on Immunization Practices (ACIP), for routine immunization at 12 months old. Other than increased frequency and intensity of tenderness at the Menactra injection site, local reactogenicity after the first dose (given alone) was similar to the reactogenicity after the second Menactra dose (given with MMRV, PCV7 and HepA vaccines). The frequencies of systemic adverse events after a second Menactra dose when given concomitantly with routine childhood vaccines (group 1) were generally similar to systemic adverse event frequencies when routine childhood vaccines were administered without Menactra (group 2). Comparisons of solicited local and systemic adverse events across trials were limited because the number of concomitantly administered childhood vaccines differed amongst the study groups. Also, the percentage of Chilean participants who completed the vaccination phase was 14% (21/200), due to

their concerns about new safety data in an updated MMRV (ProQuad) package insert, which indicated an increased frequency of febrile seizures following MMRV vaccination. Second, protocols for studies MTA-44 and -37 were amended such that concomitant vaccination schedules were consistent with physician prescribing information. Participants who received concomitantly administered ActHIB vaccine at 12 months of age were provided as separate analyses.

Analyses of serious adverse events did not reveal imbalances in distribution between study groups who received Menactra (with or without childhood vaccines) or childhood vaccines alone. The SAEs reported in the first month after the 9 month and 12 month vaccination(s) were similar to SAEs reported during subsequent months. Rates of serious adverse events leading to discontinuation represented less than 1% of each study group. The medically significant AEs and SAEs were events that were common to the age of the study population (e.g., bronchiolitis, gastroenteritis, otitis media). In this clinical reviewer's opinion, no safety signals were identified in the review of this BLA supplement.

10.0 Pharmacovigilance Plan

Please see CBER pharmacovigilance review for additional details.

Safety data from routine post-marketing surveillance were available during a 5-year time period (January 2005 to January 2010). Menactra was licensed in January 2005 for use in individuals 11-55 years of age, and was recommended in the U.S. for routine adolescent immunization in May 2005. Also, in October 2007, Menactra was approved for use in children 2-10 years of age, and was recommended by ACIP for use in children in this age group who are at increased risk to develop invasive meningococcal disease.

A total of ---(b)(4)--- doses were distributed (worldwide) through the end of December 2009. Ninety-five percent of the doses were administered to pre-/adolescents 11 through 18 years of age. The most commonly reported SAEs included Guillain-Barre Syndrome (GBS), syncope, convulsion, acute disseminated encephalomyelitis, meningococcal disease, paresthesia, facial palsy, vaccination failure, headache, and hypersensitivity/ anaphylactic reaction. The most commonly reported AEs regardless of seriousness included pyrexia, injection site reaction, headache, vomiting/nausea, GBS, fatigue, paresthesia, syncope, myalgia, and dizziness/vertigo. Post-licensure observational safety surveillance studies in the U.S. are being conducted in the two age cohorts described above. Surveillance for the first study, initiated following ACIP recommendations for routine Menactra vaccination of adolescents, is complete. The second study is ongoing.

Relevant to the proposed population, no safety signals were identified in pre-licensure trials. The applicant has included plans for submitting 30-day reports, for events as follows: all allergic events, including anaphylaxis and urticaria, not reported as a 15-day report; all neurological events not reported as a 15-day report; and new-onset autoimmune disease, including idiopathic thrombocytopenic purpura, diabetes, arthritis, hemolytic anemia, myositis, Kawaski's disease, Henoch-Schonlein purpura, and collagen-vascular disease not reported as a 15-day report. The time frame for expedited reporting is one year following FDA approval of Menactra use in the proposed population. A post-marketing agreement for expedited reports, in this reviewer's opinion, was not necessary given the absence of pre-licensure safety signals, and the accumulated post-licensure surveillance data in individuals 2-55 years of age. The applicant plans to conduct a descriptive, epidemiological surveillance study as a continued assessment of Menactra safety in children 9-23 months of age. -----(b)(4)-----

11.0 Other Regulatory Requirements

11.1 Pediatric Research Equity Act (PREA)

The Pediatric Review Committee (PeRC) review committee concluded that the assessment of Menactra safety and effectiveness for the claimed indication satisfied PREA requirements.

A waiver was granted for children from birth through 8 months of age. Supportive data included safety and immunogenicity evaluations of a 3-dose Menactra series (2, 4 and 6 months of age) in 19 children. After the third dose, 47%, 47%, 53%, and 68% of children achieved an SBA-H titer $\geq 1:8$ to serogroups C, W-135, Y and A, respectively. Studies MTA-44 and MTA-48 supported the safety and immunogenicity (inferred effectiveness) of Menactra in children 9 months through 12 months of age. Immunogenicity data available in older children, who received two doses of Menactra at 12 months and 15 months of age, supported use of a 2-dose Menactra schedule (given 3 months apart) in children through 23 months of age. Menactra is appropriately labeled for use in children 24 months through 17 years of age.

11.2 Previous Post-Marketing Requirements

Studies MTA-44 and MTA-48 fulfill the pediatric requirement to evaluate the safety and immunogenicity of Menactra when administered to children less than 2 years of age, as stated in requirement #2 of the January 14, 2005, approval letter.

12.0 Conclusions - Overall

The clinical data from studies included in this supplemental application support Menactra safety and immunogenicity for use in children as young as 9 months of age.

Immunogenicity data from a concomitant vaccine study indicated reduced pneumococcal antibody responses following co-administration of a CRM₁₉₇-based pneumococcal vaccine with Menactra. An evaluation of possible immunological interactions between DTaP-containing vaccines and Menactra, which contains a diphtheria toxoid carrier protein, would be important to study.

Immunogenicity data provided by the applicant supported use of a 2-dose Menactra regimen through the second year of life. However, the safety data available in children 13 months through 23 months of age were limited. A continued assessment of Menactra safety in children 9 months through 23 months in the post-licensure setting would be acceptable, given that safety concerns were not identified in pre-licensure studies.

13.0 Recommendations

13.1 Approval or Non-approval Recommendation

The immunogenicity and safety data from the submitted clinical studies support the approval of Menactra for use in children 9 months through 23 months of age. The vaccination schedule consists of a 2-dose series administered three months apart.

13.2 Postmarketing Actions

The applicant agreed to fulfill two post-licensure commitments:

1. To conduct a study to evaluate the safety and immunogenicity of two doses of Menactra, when administered alone at 9 months and concomitantly with Pentacel[®] (DTaP-IPV/PRP-T) at 15 to 18 months of age. The final report for the study will be submitted by November 2014.
2. To conduct a descriptive, epidemiological, safety surveillance study of Menactra vaccine when administered as a 2-dose schedule to children 9 months through 23 months of age. The final report for the study will be submitted by March 2016.

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